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***“Mapping the genetic architecture of brain metabolism across neurodegenerative
diseases: Shared and Disease-Specific Pathways”***

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Abstract

Background

Alzheimer's disease (AD), Parkinson's disease (PD), dementia with Lewy bodies (DLB) and REM sleep behaviour disorder (iRBD) show distinct regional glucose hypometabolism on 18F-FDG-PET and frequently co-occur. The biological mechanisms and genetic determinants of this vulnerability, and their overlap, remain incompletely understood.

Objective

To identify gene pathways whose regional expression is associated with hypometabolism in each condition, and to characterise shared and disease-specific pathways.

Methods

FDG-PET scans from 327 subjects (86 AD, 83 PD, 61 DLB, 56 iRBD, 41 healthy controls [HC]) were analysed. Preprocessed values from 116 regions generated disease-versus-HC subtraction maps. Brain expression of 226 genome-wide association study risk genes, derived from the Allen Human Brain Atlas, was spatially correlated with these maps. Significant genes underwent Gene Ontology enrichment analysis.

Results

Of 192 significant genes, most were shared. Genes common to all four disorders (LRRK2, ANK3, ADD1) converged on cytoskeletal anchoring and neurite development. AD-PD-DLB genes were enriched in APP catabolism (e.g. APP, ADAM10) and synapse organisation, and DLB-PD genes (APOE, PICALM) in clathrin-mediated endocytosis and amyloid- β clearance. The 45 AD-specific genes (e.g. DLG2, CD2AP, ABCA7) implicated endocytosis and lipid handling. Immune pathways characterised the synucleinopathy spectrum: PD-iRBD

genes (CD33, PTPRC) were enriched in immune receptor signaling and TNF production, and DLB-PD-iRBD genes in MHC binding. AD-iRBD genes (CLU, SNCA) were enriched in chaperone binding and microglial activation.

Conclusion

Hypometabolism follows risk-gene expression converging on few mechanisms: APP processing, synaptic organisation and endocytic trafficking across AD and synucleinopathies, immune and antigen-presentation pathways spanning the α -synuclein spectrum from prodromal iRBD onward.

Neurodegeneration may share a partly common genetic architecture.

Abstract

Italiano

Background

La malattia di Alzheimer (AD), la malattia di Parkinson (PD), la demenza a corpi di Lewy (DLB) e il disturbo comportamentale del sonno REM isolato (iRBD) presentano distinti pattern regionali di ipometabolismo glucidico alla 18F-FDG-PET e spesso coesistono. I meccanismi biologici e genetici dietro tale vulnerabilità metabolica e la loro coesistenza rimangono in parte non chiari.

Obiettivo

Identificare le vie geniche la cui espressione regionale si associa all'ipometabolismo in ogni patologia e distinguere quelle condivise e le specifiche di malattia.

Metodi

Sono state analizzate FDG-PET di 327 soggetti (86 AD, 83 PD, 61 DLB, 56 iRBD, 41 controlli). Le mappe di ipometabolismo, divise in 116 regioni, sono state correlate all'espressione di 226 geni di rischio GWAS dell'Allen Human Brain Atlas; i geni significativi sono stati sottoposti ad analisi Gene Ontology.

Risultati

Di 192 geni significativamente associati ai pattern metabolici la maggior parte era condivisa tra le diverse condizioni. I geni comuni a tutte le patologie (LRRK2, ANK3, ADD1) erano associati all'ancoraggio del citoscheletro e allo sviluppo neuritico. I geni condivisi tra AD, PD e DLB risultavano arricchiti nei processi di metabolismo dell'APP e organizzazione sinaptica, mentre quelli comuni a DLB e PD nell'endocitosi mediata da clatrina e nella clearance della β -amiloide. Nell'AD, 45 geni specifici erano coinvolti nell'endocitosi e nel

metabolismo lipidico. Le sinucleinopatie mostravano un arricchimento di pathway immunitari, inclusi segnalazione immunitaria, produzione di TNF e legame al complesso maggiore di istocompatibilità.

Conclusioni

L'ipometabolismo segue l'espressione di geni di rischio convergenti su pochi meccanismi: processamento di APP, organizzazione sinaptica e traffico endocitico in AD e sinucleinopatie; vie immunitarie e di presentazione antigenica nelle α -sinucleinopatie, dell'iRBD in poi. Le malattie neurodegenerative sembrano condividere in parte l'architettura genetica.

CHAPTER 1 – Introduction

1. Neurodegenerative diseases: overview

Progressive cognitive deterioration attributable to neurodegenerative or vascular disease represents a major cause of disability and loss of independence in older adults. Once cognitive decline becomes sufficiently severe to interfere with everyday functioning, it constitutes the clinical syndrome of dementia. Although impairment of cognition is central, dementia frequently also involves alterations in mood, behaviour and motivation (*Dementia*, n.d.). According to the underlying disorder, additional manifestations may include motor signs such as parkinsonism, postural instability and falls, as well as sleep disorders and autonomic dysfunction (McKeith et al., 2017). In 2021, an estimated 57 million people worldwide were living with dementia, more than 60% of whom were in low- and middle-income countries, with almost 10 million new cases arising annually. Dementia ranks as the seventh leading global cause of death, while its economic burden was estimated at US\$1.3 trillion in 2019, approximately half of this cost being related to informal care (*Dementia*, n.d.). The burden is disproportionately greater among women, who experience higher mortality and disability-adjusted life years attributable to dementia and provide 70% of informal care hours (*Dementia*, n.d.). Increasing age remains the strongest established risk factor (*Dementia*, n.d.). Nevertheless, the 2024 Lancet Commission reported that age-specific incidence has declined in several countries, probably as a consequence of advances in education, nutrition, health care and lifestyle. The Commission identified 14 potentially modifiable risk factors - including hypertension, diabetes, obesity, smoking, depression, infrequent social contact, air pollution, less education, head injury, excessive alcohol

consumption, physical inactivity, hearing impairment, untreated vision loss and high LDL cholesterol - which collectively account for approximately 45% of dementia cases worldwide (Livingston et al., 2024).

Dementia encompasses aetiologically diverse disorders. Alzheimer's disease (AD) is the predominant cause, responsible for approximately 60–70% of cases (*Dementia*, n.d.), and is neuropathologically characterised by extracellular amyloid- β plaques and intracellular tau neurofibrillary tangles. Under the recently revised Alzheimer's Association criteria, AD is conceptualised as a biological disease that can be identified using fluid and imaging biomarkers (Jack Jr. et al., 2024). Vascular cognitive impairment and dementia, arising from cerebral small vessel disease, strategic infarction or chronic hypoperfusion, represents the second most common form and commonly occurs alongside neurodegenerative pathology. Lewy body dementias, comprising dementia with Lewy bodies (DLB) and Parkinson's disease dementia, are defined by α -synuclein accumulation as Lewy bodies and Lewy neurites (Chia et al., 2021). Their clinical presentation is characterised by fluctuating cognition, visual hallucinations, parkinsonism and REM sleep behaviour disorder (RBD) (McKeith et al., 2017). Other aetiologies encompass frontotemporal lobar degeneration, limbic-predominant age-related TDP-43 encephalopathy (LATE), prion diseases, normal pressure hydrocephalus, and toxic, metabolic or infectious disorders. In older individuals, coexistence of multiple pathological processes is frequent (*Dementia*, n.d.; McKeith et al., 2017).

The diagnostic process remains predominantly clinical and relies on the medical history, preferably supported by an informant or caregiver, neurological examination and neuropsychological evaluation. Laboratory investigations are used to identify potentially

reversible causes, whereas structural MRI or CT can reveal alternative pathology and provide information regarding cerebral atrophy and cerebrovascular burden (Chételat et al., 2020). Increasingly, biomarkers contribute to the determination of aetiology, including amyloid and tau measures obtained from cerebrospinal fluid, plasma or PET in AD (Jack Jr. et al., 2024); dopamine transporter SPECT, cardiac MIBG scintigraphy and polysomnography in Lewy body diseases (McKeith et al., 2017); and ^{18}F -FDG-PET for differentiating neurodegenerative dementias (Chételat et al., 2020).

Parkinson's disease (PD), DLB and isolated RBD are increasingly conceptualised as manifestations within a common α -synucleinopathy spectrum. Whereas many prodromal markers have limited specificity, RBD represents a particularly strong early indicator of PD, DLB and multiple system atrophy. In a multicentre cohort comprising 1,280 patients, progression from RBD to an overt neurodegenerative syndrome occurred at a rate of 6.3% per year, with 73.5% of participants converting after 12 years (Postuma et al., 2019). This makes RBD a distinctive model in which neurodegenerative processes can be investigated before the emergence of established clinical disease. The study itself describes idiopathic RBD as a powerful early sign of Parkinson's disease, DLB and multiple system atrophy and emphasises its value for observing prodromal neurodegeneration.

FDG-PET provides a measure of regional glucose consumption that is closely associated with synaptic activity (Chételat et al., 2020). It can identify disease-specific metabolic patterns, including temporoparietal and posterior cingulate hypometabolism in AD (Chételat et al., 2020) and occipital hypometabolism accompanied by the cingulate island sign in DLB (McKeith et al., 2017); however, the molecular determinants of this regional vulnerability remain incompletely understood. Genetic findings suggest that some of the underlying

mechanisms may be shared across neurodegenerative disorders. Brain-wide transcriptomic atlases registered to MRI coordinate space (Hawrylycz et al., 2012) therefore provide a framework for relating regional gene expression to neuroimaging phenotypes.

2. Alzheimer's disease

Alzheimer's disease (AD) represents the leading cause of dementia and is increasingly recognised as one of the most costly, fatal, and burdensome diseases of the 21st century. Its most common clinical phenotype is characterised by progressive impairment of memory, although atypical presentations, including the language variant, can instead be dominated by deficits in other cognitive domains. With progression to the dementia stage, individuals progressively lose functional autonomy and require increasing assistance from others, thereby imposing a substantial burden on caregivers (Scheltens et al., 2021).

2.1. Epidemiology and risk factors

It is estimated that tens of millions of people worldwide are living with AD dementia, while a substantially greater number are considered to be in the prodromal or preclinical phases of the disease, although the precision of these estimates remains limited (Gustavsson et al., 2023). Among the most established risk factors for AD are advanced age and possession of at least one *APOE* $\epsilon 4$ allele. The incidence of the disease is also higher in women than in men, with this difference becoming particularly pronounced after 80 years of age. Genetic susceptibility represents a major component of AD risk, as demonstrated by twin studies attributing 60–80% of the risk to heritable factors. Moreover, rare pathogenic variants in

APP, *PSEN1*, and *PSEN2* underlie autosomal dominant familial forms of AD (ADAD), which may manifest as early as 40 years of age (Scheltens et al., 2021). Alongside these non-modifiable determinants, a number of potentially modifiable factors have been linked to AD. A comprehensive systematic review and meta-analysis reported strong evidence concerning education, cognitive activity, late-life body mass index, hyperhomocysteinaemia, depression, stress, diabetes, head trauma, midlife hypertension, and orthostatic hypotension, whereas the evidence was weaker for midlife obesity, late-life weight loss, physical exercise, smoking, sleep, cerebrovascular disease, frailty, atrial fibrillation, and vitamin C (Yu et al., 2020).

2.2. Clinical manifestations and phenotypic heterogeneity

The clinical course of AD spans a continuum of approximately 15–25 years, with pathological changes potentially preceding the emergence of symptoms by many years. The initial preclinical phase, which may last around 10 years in a 70-year-old individual, is characterised by preserved cognition, although some individuals experience subjective cognitive complaints whose predictive value for dementia remains uncertain. This phase is followed by a prodromal period characterised by mild cognitive impairment (MCI), lasting approximately 4 years, during which measurable cognitive impairment develops despite preservation of functional independence. Progression may subsequently lead to dementia, at which point impairment involves multiple cognitive domains (Scheltens et al., 2021). Although the majority of patients exhibit the typical amnesic phenotype, atypical clinical presentations account for a substantial proportion of cases and are particularly over-represented among individuals with young-onset disease. These presentations include the logopenic variant of primary progressive aphasia, posterior cortical atrophy, behavioural and dysexecutive variants, and corticobasal syndrome. Increasing availability of cerebrospinal

fluid and PET biomarkers has facilitated earlier and more confident identification of these atypical forms (Graff-Radford et al., 2021).

2.3. Glucose Metabolism and FDG-PET Findings

By providing an assessment of cerebral glucose metabolism, ^{18}F -FDG-PET complements amyloid-PET in the diagnostic evaluation of AD (Chételat et al., 2020). FDG-PET evidence of posterior cingulate and temporoparietal hypometabolism, which reflects neurodegeneration, constitutes one of the three most extensively validated neuroimaging biomarkers of AD, alongside medial temporal lobe atrophy assessed by MRI and cortical amyloid deposition detected by amyloid-PET. Whereas amyloid-PET has particular value for ruling out AD, FDG-PET contributes to the differential diagnosis of neurodegenerative disorders, prediction of short-term clinical outcome, and characterisation of the extent and anatomical distribution of neurodegeneration (Scheltens et al., 2021). Patterns of hypometabolism show a close relationship with both the nature and severity of cognitive impairment and are comparatively distinct among different neurodegenerative diseases and their clinical variants. On this basis, recent recommendations have proposed diagnostic algorithms in which amyloid-PET and FDG-PET are incorporated at different stages of the diagnostic work-up according to the presenting clinical phenotype (Chételat et al., 2020). Evidence of amyloid pathology by biomarkers was likewise a prerequisite for inclusion in phase 3 trials investigating the newer anti-amyloid antibodies (Sims et al., 2023; van Dyck et al., 2023).

2.4. Treatment and Prognosis

Among patients attending European memory clinics, the median survival following a diagnosis of AD dementia has been estimated at approximately 6 years (Scheltens et al., 2021). For many patients, treatment is based on cholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist memantine (Scheltens et al., 2021), although these agents provide only modest attenuation of cognitive decline (Livingston et al., 2024). More recently, anti-amyloid monoclonal antibodies have been investigated in early AD, defined as mild cognitive impairment or mild dementia attributable to AD in the presence of amyloid pathology. In the phase 3 Clarity AD trial, treatment with Lecanemab (brand name: Leqembi) reduced amyloid biomarkers and was associated with moderately less deterioration in cognition and functional abilities than placebo over 18 months, although adverse events occurred (van Dyck et al., 2023). Similarly, the TRAILBLAZER-ALZ 2 trial showed that Donanemab (brand name: Kisunla) significantly slowed clinical progression at 76 weeks. Nevertheless, amyloid-related imaging abnormalities characterised by oedema or effusion were observed in 24.0% of participants receiving treatment (Sims et al., 2023). These therapeutic agents have been evaluated in populations with mild disease and relatively few comorbid illnesses, while evidence regarding their long-term effects remains limited (Livingston et al., 2024).

2.5. Multidisciplinary management, comorbidities and quality of life

For patients with atypical AD, management based on a multidisciplinary strategy tailored to the individual clinical phenotype and specific symptoms may contribute to better functional outcomes and quality of life (Graff-Radford et al., 2021). According to the clinical

presentation, this may encompass speech therapy, involvement of a case manager responsible for organising and overseeing care in the home environment, and management of vascular risk factors.

More generally, among people living with dementia, interventions delivered after diagnosis may contribute to maintaining physical health, enhancing quality of life, reducing hospital admissions, and facilitating planning for the future. Such interventions should be individually tailored and should include family members and other carers. In particular, person-centred multicomponent interventions addressing coping in carers, together with appropriate management of neuropsychiatric symptoms, are important components of care. Interventions promoting activity may additionally alleviate these symptoms while supporting the preservation of enjoyment and a sense of purpose among people with dementia (Livingston et al., 2024).

3. REM Sleep Behaviour Disorder: Disease or Prodrome

3.1. Introduction

REM sleep behaviour disorder (RBD) is a parasomnia resulting from the absence of the normal muscle atonia that accompanies REM (Rapid Eye Movement) sleep, thereby allowing patients to physically enact their dreams. In its idiopathic form, RBD is considered the most specific prodromal marker of α -synucleinopathies, given that the majority of affected individuals ultimately develop Parkinson's disease, dementia with Lewy bodies or multiple system atrophy. Accordingly, RBD represents an important model for investigating the

earliest phases of neurodegeneration and constitutes a target population for future neuroprotective trials (Postuma et al., 2019).

3.2. RBD as a Standalone Condition

RBD may occur in an idiopathic form or as a secondary condition related to antidepressant and antipsychotic use or with neurological pathologies such as narcolepsy type 1 (Dauvilliers et al., 2018). In a population-based investigation involving 1,997 adults who underwent polysomnography, RBD was identified in 1.06% of participants, without a significant difference between men and women. Relative to unaffected individuals, those with RBD more commonly reported the use of antidepressants or antipsychotics and were more frequently current or former smokers. Polysomnographic assessment further revealed a distinctive sleep architecture, characterised by higher proportion of stage N2 sleep, reduced REM sleep, and a lower apnoea–hypopnoea index during REM sleep (Haba-Rubio et al., 2018). Dream-enactment behaviours may result in injuries and negatively influence the quality of life of bed partners. A definite diagnosis requires both a clinical history of dream enactment or complex motor behaviours and the objective demonstration of REM sleep without atonia (RSWA) on video-polysomnography. Treatment includes clonazepam and/or melatonin, together with appropriate counselling (Dauvilliers et al., 2018). In addition to these clinical manifestations, both RSWA and RBD are currently considered early manifestations of α -synucleinopathies such as Parkinson's disease, dementia with Lewy bodies and multiple system atrophy, and most older individuals with idiopathic RBD will ultimately develop an overt neurodegenerative syndrome (Dauvilliers et al., 2018).

3.3. RBD as a Prodromal Synucleinopathy

Synucleinopathies are characterised by a prolonged prodromal phase, frequently lasting more than a decade, during which neurodegenerative processes and related signs are already present despite the absence of the fully developed clinical syndrome. A broad range of prodromal markers has been described, encompassing subtle motor signs, autonomic dysfunction, olfactory impairment, cognitive changes, depression and anxiety. Most of these features are relatively non-specific, meaning that the majority of individuals who test positive for an individual marker will not ultimately develop the corresponding disease; idiopathic RBD is a notable exception. Its occurrence is likely associated with neurodegeneration affecting pontine or medullary regions involved in the regulation of REM atonia (Postuma et al., 2019). In a prospective cohort of 1,280 patients recruited across 24 centres of the International RBD Study Group, the estimated risk of phenoconversion to an overt neurodegenerative syndrome reached 31.3% at 5 years, 60.2% at 10 years and 73.5% at 12 years. Of those who converted, 56.5% presented with parkinsonism as the initial manifestation, whereas 43.5% developed dementia first. Several features were associated with an increased risk of phenoconversion, including motor abnormalities, olfactory deficit (hyposmia) assessed using standardised smell identification tests like the UPSIT (12/40 item University of Pennsylvania Smell Identification Test) or the Sniffin' Sticks Olfactory Test (ODOFIN), mild cognitive impairment (MCI), erectile dysfunction, abnormal DAT-SPECT, colour vision abnormalities, constipation and loss of REM atonia. Most markers showed similar predictive values regardless of the clinical phenotype that subsequently emerged. Cognitive measures were the main exception, with variables including colour vision testing showing a preferential association with conversion to dementia rather than parkinsonism.

Accordingly, Postuma et al. noted that few patients are truly "idiopathic" and that terms such as "clinically isolated" RBD may be more appropriate (Postuma et al., 2019). The term isolated (formerly idiopathic) RBD is now used to indicate RBD occurring in the absence of a clinically manifest neurological disease (Stefani et al., 2025). Consequently, idiopathic RBD represents a unique setting in which prodromal neurodegenerative states can be directly investigated, with potential relevance to strategies aimed at preventing or treating synucleinopathies at an early stage (Postuma et al., 2019).

3.4. Clinical Implications

From a clinical perspective, diagnostic accessibility remains a significant limitation, as video-polysomnography requires specialized training, entails substantial costs, and is not broadly available. Although screening questionnaires can be useful, their specificity is low, while home-based approaches such as wrist actigraphy are not yet capable of substituting for video-polysomnography (Stefani et al., 2025). Biomarkers could contribute to patient stratification, as greater abnormalities in cerebral glucose metabolism assessed by ^{18}F -FDG-PET have been associated with a higher risk of short-term phenoconversion. In a study of 148 patients with isolated RBD, CSF α -synuclein positivity was the only marker associated with short-term overall phenoconversion (Stefani et al., 2025). Patients with isolated RBD are regarded as an ideal population for neuroprotective trials, since they are not receiving symptomatic treatment and 60–70% continue to show normal dopamine transporter scans, leaving a potential window for intervention (Stefani et al., 2025). Finally, RBD represents a prodromal manifestation in 30–50% of patients with Parkinson's disease (PD). Compared with patients without RBD, those with PD and RBD more frequently exhibit the rigid-akinetic phenotype, a greater burden of non-motor manifestations and hallucinations, and a

faster progression toward dementia, motor disability and falls, consistent with a more severe form of Parkinson's disease (Stefani et al., 2025).

4. Parkinson's disease

Parkinson's disease (PD) is a common progressive neurodegenerative disorder in which both motor and non-motor manifestations occur. It is principally characterised by the degeneration of dopaminergic neurons within the substantia nigra and by the accumulation of α -synuclein in Lewy bodies and Lewy neurites.

4.1. Epidemiology and risk factors

PD is characterised by considerable clinical and biological heterogeneity, with its development reflecting the interplay of ageing, genetic susceptibility, and environmental exposures (Morris et al., 2024).

Age represents a major determinant of PD risk, as both incidence and prevalence rise substantially in older populations. A higher frequency of the disease is also observed in men compared with women. Over recent decades, the global prevalence of PD has risen markedly, a trend attributable in part to population ageing, although modifications in environmental exposures may also have a role (Ben-Shlomo et al., 2024).

The causes of PD are multifactorial. A minority of patients carry pathogenic variants in genes including *LRRK2*, *SNCA*, *PRKN*, *PINK1*, and *PARK7*, whereas additional genetic variants may confer increased susceptibility to the disease. Environmental exposures have likewise

been implicated in PD risk: pesticides, certain industrial chemicals, and air pollution have been associated with increased risk, while physical activity, female hormones, and coffee or tea consumption have been associated with reduced risk. The complexity of risk-factor research is further compounded by the prolonged prodromal period of PD, which can extend for years before the clinical diagnosis is established (Ben-Shlomo et al., 2024).

4.2. Clinical manifestations and phenotypic heterogeneity

The clinical phenotype of Parkinson's disease is broad and heterogeneous, with patients differing substantially in both symptoms and disease trajectories. Diagnosis is predominantly clinical and relies on the medical history and neurological examination. Parkinsonism is defined by the presence of bradykinesia together with either rest tremor, rigidity, or both; the diagnosis of PD is then supported by the broader clinical picture and by the absence of findings indicative of alternative causes of parkinsonism (Bloem et al., 2021).

The manifestations of PD, however, extend considerably beyond its characteristic motor syndrome. Non-motor features such as cognitive decline, depression, and pain may make an important contribution to disability. A number of symptoms can already be present during the early or prodromal phases, including constipation, REM sleep behaviour disorder, hyposmia, depression, and nonspecific musculoskeletal complaints. Because none of these manifestations is specific to PD, their isolated presence does not establish the diagnosis (Bloem et al., 2021).

Marked differences can also be observed between individuals in the combination and severity of motor and non-motor symptoms. On this basis, several clinically recognizable subtypes have been described, reflecting symptom clusters that commonly occur together. Such

phenotypic variation is relevant both to the way the disease presents and to its subsequent progression and prognosis. Certain phenotypic profiles, for instance, have been linked to more rapid progression towards clinically relevant endpoints and to reduced survival. Nevertheless, existing subtype classifications have limited capacity to predict the disease trajectory of individual patients.

Recognizing this heterogeneity therefore offers a framework for interpreting differences in clinical evolution and may contribute to the development of more individualized strategies for disease characterization and management (Bloem et al., 2021).

4.3. Glucose Metabolism and FDG-PET Findings

In addition to its clinical features, Parkinson's disease is accompanied by functional changes within the brain that can be assessed through alterations in cerebral glucose metabolism. Because regional glucose metabolism is closely linked to neuronal and synaptic activity, differences in metabolism provide a functional representation of cerebral abnormalities associated with the disease. Fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) enables these alterations to be examined in vivo, providing an index of regional cerebral glucose metabolism and allowing metabolic activity to be compared across brain regions.

Early FDG-PET investigations focused on metabolic abnormalities at the level of individual brain regions by comparing tracer uptake between patients with PD and healthy controls. However, because metabolic activity is correlated among functionally interconnected areas, PD-related abnormalities can also be examined as alterations affecting distributed brain networks. Multivariate spatial covariance methods have consequently been used to derive reproducible disease-associated metabolic patterns from FDG-PET data. One such pattern,

the Parkinson's disease-related pattern (PDRP), is defined by relative hypermetabolism involving the thalamus, putamen and globus pallidus, pons, cerebellum, and motor cortex, accompanied by relative hypometabolism in frontal, posterior parietal, temporal, and occipital cortical areas. The degree to which this spatial pattern is expressed can additionally be quantified in individual PET scans through a single subject score (Meles et al., 2020).

Meles and colleagues subsequently showed that the PDRP could be independently identified in PD cohorts from the Netherlands, Italy, and Spain and across different PET scans. While regional differences in pattern expression were present between cohorts - with less marked frontal hypometabolism among de novo patients and greater occipital hypometabolism in those with more advanced disease - the overall metabolic topography remained highly consistent. These observations indicate that the metabolic abnormalities associated with PD extend beyond isolated anatomical regions and instead constitute reproducible, spatially distributed patterns involving functionally connected brain areas (Meles et al., 2020).

4.4. Treatment and Prognosis

Management of Parkinson's disease is predominantly symptomatic and is tailored according to disease stage, functional impairment, therapeutic response, and individual patient characteristics. Levodopa, dopamine receptor agonists, and monoamine oxidase-B (MAO-B) inhibitors represent the principal initial pharmacological options for motor manifestations. Levodopa generally achieves the greatest degree of motor improvement and is better tolerated, especially among older patients, although prolonged treatment is commonly associated with motor fluctuations and dyskinesias. Dopamine agonists, in contrast, are more frequently associated with adverse effects such as nausea, orthostatic hypotension, sleep

attacks, and impulse-control disorders. In patients whose disabling motor fluctuations are no longer adequately managed with oral therapies, device-aided approaches may be considered, including deep brain stimulation, continuous levodopa-carbidopa intestinal infusion, and subcutaneous apomorphine infusion (Bloem et al., 2021).

PD follows a progressive course, although the rate and nature of progression differ considerably between individuals. Overall life expectancy is reduced, despite the fact that many patients live with the disease for several decades. As the disease advances, clinically important milestones may emerge, including falls, fractures, cognitive decline, and progressively greater treatment requirements; nevertheless, predicting the trajectory for an individual patient remains challenging (Bloem et al., 2021).

4.5. Multidisciplinary management, comorbidities and quality of life

The burden associated with PD cannot be explained by motor dysfunction alone. Non-motor manifestations - including cognitive and psychiatric symptoms, pain, autonomic dysfunction, and sleep disturbances - may contribute substantially to overall disease burden and therefore require dedicated management in addition to dopaminergic therapy (Bloem et al., 2021). Accordingly, treatment may encompass both pharmacological and non-pharmacological measures within a multidisciplinary model involving neurologists, specialised nurses, physiotherapists, occupational and speech therapists, and other healthcare professionals (Rajan et al., 2020).

This comprehensive model is particularly pertinent to health-related quality of life (HRQoL), which encompasses the combined impact of motor and non-motor manifestations on physical, psychological, and social functioning. Integrated-care approaches seek to

coordinate the contributions of different professional disciplines while incorporating patients and caregivers into care delivery and self-management. In their systematic review and meta-analysis, Rajan and colleagues reported substantial heterogeneity across existing models; however, outpatient integrated-care programmes with longer-term follow-up were associated with a modest but significant improvement in health-related quality of life compared with standard care. These results support the relevance of quality of life as a clinically meaningful outcome and underscore the value of management strategies that consider the multidimensional burden of Parkinson's disease rather than focusing exclusively on motor manifestations (Rajan et al., 2020).

5. Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is an age-associated neurodegenerative disorder characterised by the accumulation of α -synuclein within Lewy bodies and Lewy neurites and is considered the second most common form of dementia after Alzheimer's disease. Its substantial neuropsychiatric burden adversely affects both patients' quality of life and caregivers, while the lack of disease-modifying therapies contributes to the increasing socio-economic impact of Lewy body disorders (Erskine & Taylor, 2025; Outeiro et al., 2019).

5.1. Epidemiology and risk factors

Although clinically diagnosed DLB is relatively uncommon at the population level, population-based studies estimate a pooled incidence of 4.79 cases per 100,000 person-years (Urso et al., 2026). Age represents the principal determinant, with incidence increasing from

0.34 per 100,000 person-years before 65 to 46.85 thereafter, and prevalence rising from 2.52 to 352.26 per 100,000. A modest excess among males has likewise been observed (5.45 vs 4.32), although the corresponding confidence intervals overlap. Most available evidence derives from high-income countries, with greater consistency among European than Asian studies (Urso et al., 2026). These estimates are likely to underestimate the actual burden because DLB is frequently unrecognised, while disparities in access to diagnosis may disproportionately affect women and older individuals (Urso et al., 2026). In addition to advanced age and male sex, APOE ε4 and GBA variants represent the risk factors most consistently associated with Lewy body dementia. For DLB specifically, higher risk has been linked to REM sleep behaviour disorder, herpes simplex infection and adult ADHD. By contrast, cardiovascular risk factors were not associated with risk in RBD cohorts.

5.2. Clinical manifestations and phenotypic heterogeneity

The clinical definition of DLB centres on progressive dementia characterised by early impairment of attention, executive functions and visuoperceptual abilities, whereas memory and naming are relatively preserved (McKeith et al., 2017).

Four core clinical features contribute to the diagnosis: cognitive fluctuations, visual hallucinations, parkinsonism and RBD.

Cognitive fluctuations exhibit a delirium-like pattern and may manifest as drowsiness, staring episodes and periods of incoherent speech.

Recurrent, well-formed *visual hallucinations*, most commonly involving people or animals, occur in up to 80% of patients.

Spontaneous parkinsonism ultimately occurs in more than 85% of patients, frequently presenting in an incomplete form.

REM sleep behaviour disorder (RBD) is present in 76% of autopsy-confirmed cases compared with 4% of non-DLB cases and can precede cognitive decline by many years.

Additional supportive manifestations comprise marked sensitivity to antipsychotics, falls, syncope, autonomic dysfunction, hypersomnia, hyposmia, delusions, apathy, anxiety and depression (McKeith et al., 2017). The clinical phenotype is highly heterogeneous, reflecting the fact that Lewy pathology seldom occurs in isolation and commonly coexists with Alzheimer-type and vascular lesions (Urso et al., 2026). When Alzheimer co-pathology is extensive, the resulting clinical presentation may more closely resemble Alzheimer disease than DLB (McKeith et al., 2017). Considerable variability is also evident during the prodromal stage. Among patients with RBD, deficits affecting attention, executive function, memory and visuospatial abilities are associated with subsequent conversion to DLB, whereas in mild cognitive impairment, fluctuations, parkinsonism, RBD and visuospatial impairment are predictive features (Ratnavel et al., 2025).

5.3. Glucose Metabolism and FDG-PET Findings

On FDG-PET, DLB is characterised by hypometabolism involving the lateral and medial occipital cortices, with extension into temporo-parietal and frontal areas (Caminiti et al., 2019). Among these metabolic abnormalities, occipital hypometabolism represents the most characteristic feature and is not attributable to cerebral atrophy (Caminiti et al., 2019). Another distinctive pattern is the cingulate island sign (CIS), defined by relative preservation of posterior cingulate cortex metabolism in the context of reduced uptake involving the precuneus, cuneus, and occipital cortex; AD exhibits the opposite metabolic pattern (McKeith et al., 2017). Both occipital hypometabolism and the CIS are considered supportive biomarkers of DLB (McKeith et al., 2017). However, the CIS becomes progressively less

evident with increasing concomitant Alzheimer-type tangle pathology (Graff-Radford et al., 2020). More extensive occipital involvement has also been associated with the presence of visual hallucinations (Caminiti et al., 2019). In larger cohorts and at earlier disease stages, FDG-PET ability to distinguish DLB from Alzheimer's disease (AD) was limited to approximately 70% sensitivity and 74% specificity (McKeith et al., 2017). Occipital involvement provided the greatest discriminatory value, outperforming the CIS (Caminiti et al., 2019).

5.4. Treatment and Prognosis

Because no disease-modifying treatment is currently available for DLB, therapeutic management is directed toward individual symptom domains (Erskine & Taylor, 2025). Cholinesterase inhibitors, including donepezil, rivastigmine and galantamine, constitute first-line therapy and provide modest, yet meaningful, improvements in cognition and hallucinations, with possible sustained effects and an association with longer survival. Although memantine is generally well tolerated, its clinical benefits are limited. Antipsychotic treatment can provoke severe and potentially fatal reactions and is therefore reserved for cautious second-line use; risperidone, olanzapine and aripiprazole are generally avoided. Because parkinsonism tends to respond poorly to dopaminergic treatment, low-dose levodopa is preferred to dopamine agonists, while zonisamide may be used as an adjunct (Erskine & Taylor, 2025). Physical therapy and cognitive rehabilitation have demonstrated beneficial effects, predominantly in Parkinson's disease dementia, whereas evidence in DLB remains limited (Erskine & Taylor, 2025). Management should involve a multidisciplinary team, with active education and support for caregivers (McKeith et al., 2017). Prognosis remains poor, as Lewy body dementia is associated with the highest mortality risk among

dementias relative to people without dementia, with mean survival of approximately 4.7 years following diagnosis, and DLB carries a greater risk of death than Alzheimer's disease (Liang et al., 2021).

5.5. Multidisciplinary management, comorbidities and quality of life

Dementia with Lewy bodies (DLB) is associated with a poorer prognosis than Alzheimer's disease (AD). Across pooled data from eleven longitudinal studies, survival after diagnosis is approximately 4.7 years in people with DLB, about a year and a half shorter than in those with AD, with a 35% higher risk of death. This difference is not accounted for by age, sex or cognitive level (Mueller et al., 2019). Quality of life is similarly compromised. In a multicentre cohort undergoing annual assessments, individuals with DLB reported poorer self-rated health than those with AD from the initial assessment onward, and their quality of life was influenced more strongly by non-cognitive than cognitive symptoms (van de Beek et al., n.d.). This burden is further compounded by the simultaneous occurrence of cognitive, psychiatric, motor, sleep and autonomic disturbances. In particular, autonomic dysfunction is associated with more rapid progression and shorter survival (Taylor et al., 2020). Therapeutic management is consequently complex, as an intervention targeting one symptom may exacerbate another, while care is frequently distributed across specialists without adequate coordination (Taylor et al., 2020). Accordingly, an interdisciplinary model that considers symptoms collectively rather than treating each manifestation in isolation is thought to provide the greatest benefit (Taylor et al., 2020).

6. Diagnostic Framework and Biomarkers

6.1. Clinical Assessment and Neuropsychological Evaluation

Clinical assessment integrates neurological examination, informant-based interviewing, and cognitive testing within the framework of consensus diagnostic criteria. In Parkinson's disease (PD), diagnosis is primarily established through the clinical history and neurological examination. The presence of parkinsonism - defined by bradykinesia accompanied by rest tremor, rigidity, or both - is first established and subsequently differentiated from alternative causes. A favourable response to dopaminergic therapy supports a diagnosis of PD, whereas red flags, including a wide-based gait and impaired tandem walking, may indicate atypical parkinsonism (Bloem et al., 2021). For dementia with Lewy bodies (DLB), the identification of a single cardinal parkinsonian sign is sufficient, provided that manifestations attributable to comorbid conditions, such as arthritis, are excluded in older individuals. Assessment of cognitive fluctuations requires at least one documented measure, while REM sleep behavior disorder (RBD) should be evaluated using scales based on reports from the patient or bed partner, following exclusion of mimics such as obstructive sleep apnoea. Although global screening instruments such as the MMSE (Mini-Mental State Examination) and MoCA (Montreal Cognitive Assessment) provide an initial assessment, neuropsychological evaluation should encompass all major cognitive domains. In DLB, deficits in attention, executive functioning, and visuoperceptual abilities typically emerge early and can be evaluated through tasks including trail-making, phonemic fluency, and pentagon copying, whereas memory and naming are comparatively preserved (McKeith et al., 2017). In Alzheimer's disease (AD), biological criteria provide additional diagnostic support but do not

supersede clinical assessment in patients presenting with cognitive impairment (Jack Jr. et al., 2024).

6.2. Biomarkers of Cerebral Metabolism: general overview

Following definition of the clinical phenotype, biomarker selection and interpretation are guided by the underlying condition under consideration.

Alzheimer's disease. AD is currently defined on a biological basis. The presence of an abnormal Core 1 biomarker, including amyloid PET or validated CSF and plasma assays, is sufficient to establish the diagnosis. In contrast, FDG-PET represents a non-specific biomarker of neurodegeneration and is therefore primarily employed for disease staging and prognostic assessment rather than diagnosis (Jack Jr. et al., 2024). At present, biomarker testing is recommended exclusively for symptomatic patients (Jack Jr. et al., 2024).

Dementia with Lewy bodies. DLB continues to be diagnosed clinically, since biomarkers alone cannot establish the diagnosis (McKeith et al., 2017). Reduced striatal dopamine transporter uptake constitutes an indicative biomarker, showing a sensitivity of 78% and a specificity of 90% when compared with AD. By comparison, occipital hypometabolism detected by FDG-PET, either with or without the cingulate island sign, is considered only a supportive biomarker (McKeith et al., 2017). The diagnostic utility of amyloid PET is limited because abnormalities are present in more than half of patients (McKeith et al., 2017).

REM sleep behaviour disorder. RBD represents a core feature of DLB and can precede the development of cognitive impairment by many years. In individuals with dementia who

report a history of RBD, polysomnographic demonstration of REM sleep without atonia is indicative of a synucleinopathy with a likelihood of at least 90% (McKeith et al., 2017).

Parkinson's disease. Establishing a definitive diagnosis remains difficult, and the detection of disease at its earliest stages continues to be an unmet clinical need (Tolosa et al., 2021). By demonstrating the depletion of striatal dopaminergic terminals, DAT-SPECT can differentiate neurodegenerative parkinsonism from non-degenerative conditions that may mimic it, including essential tremor. Nevertheless, this imaging technique cannot be used to discriminate PD from other forms of degenerative parkinsonism (Tolosa et al., 2021). In cases where dementia develops before or concurrently with parkinsonism, the appropriate diagnosis is DLB rather than PD (McKeith et al., 2017).

The following sections provide a detailed examination of these biomarkers, beginning with FDG-PET.

6.3. Imaging Biomarkers: FDG-PET and glucose metabolism

Regional cerebral glucose metabolism can be evaluated using ^{18}F -FDG-PET, whose clinical application is recommended by the EANM–EAN consensus as an adjunct to the diagnosis of MCI due to AD or DLB, for distinguishing AD from DLB and PD from PSP, and for identifying cortical dysfunction in PD. Conversely, its use in pre-clinical stages of neurodegenerative disorders is not supported (Nobili et al., 2018). In AD, the characteristic metabolic pattern is predominantly one of hypometabolism affecting temporal, parietal and frontal areas, accompanied by reduced uptake in the posterior cingulate and relative preservation of occipital metabolism. DLB shows a different distribution, characterised by occipital hypometabolism together with relative preservation of posterior cingulate

metabolism, known as the “cingulate island sign (CIS)”. This pattern is considered a supportive rather than an indicative biomarker, since its sensitivity (70%) and specificity (74%) are slightly below the thresholds reported for an indicative biomarker such as dopamine transporter imaging (McKeith et al., 2017). Accordingly, FDG-PET is used in conjunction with the more specific biomarkers addressed in the subsequent sections.

6.4. Other Molecular Imaging Biomarkers (Amy, Tau, Dat spect, MIBG)

Beyond the assessment of glucose metabolism, molecular imaging can also target disease-specific pathological substrates. In AD, an abnormal amyloid PET finding is sufficient to establish the diagnosis, whereas tau PET abnormalities emerge at a later stage and primarily provide prognostic information (Jack Jr. et al., 2024). In DLB, by contrast, cerebral amyloid deposition is present in more than half of patients. Accordingly, amyloid and tau PET are principally informative for identifying concomitant AD pathology rather than for distinguishing DLB from AD (McKeith et al., 2017). The DLB consensus criteria therefore incorporate three indicative biomarkers. The first consists of reduced striatal dopamine transporter uptake on SPECT/PET, with 78% sensitivity and 90% specificity compared with AD. The second is decreased myocardial ^{123}I -MIBG uptake, whose interpretation requires consideration of cardiac disease, diabetes, and potentially interfering medications. The third is polysomnographic evidence of REM sleep without atonia, which confirms RBD; in patients with dementia and a history of RBD, this finding is indicative of a synucleinopathy in at least 90% of cases. Nevertheless, none of these biomarkers is sufficient to establish a probable diagnosis in the absence of core clinical features (McKeith et al., 2017). Likewise,

in PD, a normal presynaptic dopaminergic scan excludes the diagnosis, while evidence of cardiac denervation on MIBG scintigraphy provides supportive evidence. If uncertainty regarding concomitant AD pathology remains, CSF measures of amyloid and tau can also be considered, as addressed in the following section (Jack Jr. et al., 2024; McKeith et al., 2017).

6.5. Cerebrospinal Fluid (CSF) and Peripheral Biomarkers

Whereas imaging reflects the cumulative burden of protein deposition, fluid biomarkers provide a snapshot of the equilibrium between analyte production and clearance at the time of specimen collection (Jack Jr. et al., 2024).

Amyloid and tau markers (AD). CSF A β 42 represents the soluble, aggregation-prone peptide that gives rise to amyloid plaques. Its sequestration within plaques consequently leads to a reduction in its level relative to A β 40. Phosphorylated tau species, including p-tau181, p-tau217, and p-tau231, are released at an early stage, probably reflecting a neuronal response to amyloid. Within CSF, these markers are therefore interpreted in relation to A β 42 rather than as isolated measures (Jack Jr. et al., 2024). In plasma, the A β 42/40 ratio exhibits a substantially smaller change than that observed in CSF, making p-tau217 the most reliable blood-based marker. Given the uncertainty surrounding diagnostic cut-offs, a "grey zone" between two thresholds is recommended, with additional testing for borderline results (Jack Jr. et al., 2024).

Non-specific markers. Neurofilament light chain serves as an indicator of axonal injury, whereas GFAP reflects astrocytic activation. Although both biomarkers can be quantified in CSF and plasma, neither is specific to a particular disease (Jack Jr. et al., 2024).

α -Synuclein seed amplification assays (DLB, PD, RBD). Misfolded α -synuclein is present in CSF at concentrations below the detection threshold of conventional analytical techniques. Seed amplification assays, including RT-QuIC, address this limitation by amplifying the pathological protein in vitro. In this approach, patient CSF is incubated with recombinant α -synuclein, allowing pathological "seeds," if present, to induce its misfolding through intermittent shaking. Formation of fibrils is subsequently monitored in real time using thioflavin T fluorescence (Rossi et al., 2020). The assay therefore yields an essentially positive or negative result. It detects Lewy pathology in DLB, PD, and prodromal syndromes such as isolated RBD, but cannot differentiate among these conditions. Conversely, it largely fails to detect multiple system atrophy, which is thought to be associated with a distinct α -synuclein strain (Rossi et al., 2020). In patients with dementia, the assay may additionally identify Lewy co-pathology occurring alongside AD (Jack Jr. et al., 2024). Its sensitivity is reduced when the pathological process is restricted to the amygdala (Quadalti et al., 2023).

Invasiveness and alternatives. Because α Syn-SAA presently requires lumbar puncture, skin biopsy has been investigated as a potential alternative, whereas blood-based seeding assays are still under development (Quadalti et al., 2023).

7. Genetic Architecture of Neurodegenerative Diseases

Genetic information provides an important complement to clinical and biomarker-based diagnosis, since inherited variants may reveal the biological mechanisms underlying neurodegeneration (Bellenguez et al., 2022). The majority of genetic evidence derives from

two main approaches: family-based investigations of multigenerational pedigrees, which have led to the identification of rare mutations with high penetrance, and genome-wide association studies (GWAS), which examine large patient and control populations to identify common genetic variants associated with disease risk (Bellenguez et al., 2022; Reitz et al., 2023).

7.1. Genetic risk factors in Alzheimer's disease

Alzheimer's disease (AD) has a substantial genetic component, with heritability estimates ranging from 60–80% (Bellenguez et al., 2022). Mid-life onset forms can result from rare autosomal dominant mutations affecting *APP*, *PSEN1* and *PSEN2*, whereas the majority of AD cases have a later onset. Among these late-onset forms, *APOE* represents the principal genetic risk gene, with the $\epsilon 4$ allele associated with increased risk and $\epsilon 2$ regarded as protective (Reitz et al., 2023). In a GWAS including 111,326 cases and 677,663 controls, 75 risk loci were identified, highlighting the involvement of amyloid and tau pathways, lipid metabolism, endocytosis and microglial immunity (Bellenguez et al., 2022). Several of these loci, including *GRN* and *TMEM106B*, are also implicated in frontotemporal lobar degeneration, suggesting that some underlying biological mechanisms are shared across neurodegenerative disorders (Bellenguez et al., 2022).

7.2. Genetic risk factors in synucleinopathies

The genetic architecture of synucleinopathies comprises loci that are disease-specific as well as variants that partially overlap with Alzheimer's disease (AD). For Parkinson's disease (PD), the largest GWAS meta-analysis conducted in populations of European ancestry, comprising 37,688 cases and 1.4 million controls, identified 90 independent risk signals

distributed across 78 genomic regions and accounting for 16–36% of heritable risk. Integration of gene-expression and DNA-methylation data enabled the nomination of candidate genes for 70 of these signals, while the identified risk loci showed strong enrichment in brain tissue (Nalls et al., 2019). In Lewy body dementia (LBD), whole-genome sequencing performed in 2,981 patients revealed five independent risk loci. Three corresponded to previously established loci (*GBA*, *SNCA-AS1*, *APOE*), whereas two, *BINI* and *TMEM175*, were newly identified; analyses of rare variants further highlighted *GBA* as a key gene. At the *SNCA-AS1* and *TMEM175* loci, colocalization of the risk signal with expression QTLs suggests that altered gene expression may contribute to the observed genetic risk. Moreover, genetic risk scores for AD and PD each independently predicted DLB (Chia et al., 2021). Given that several of these genetic signals appear to exert their effects through gene expression in the brain, integrating genotype with brain transcriptomic and imaging measures represents a logical subsequent step.

7.3. Imaging genetics and transcriptomic approaches in neurodegeneration

Identifying risk loci alone does not fully explain how genetic susceptibility is translated into brain pathology; this requires the integration of genomic information with molecular and imaging phenotypes. Paired bulk-tissue and single-nucleus RNA-sequencing of the anterior cingulate cortex from 28 donors, including controls, PD, PDD and DLB cases ($n = 7$ per group), demonstrated transcriptional alterations involving multiple cell types, with the most prominent changes observed in excitatory neurons and oligodendrocytes, as well as widespread alterations in RNA splicing, particularly in PDD and DLB. The two Lewy body

dementias displayed largely comparable transcriptomic profiles, whereas PD showed a distinct pattern (Feleke et al., 2021). An in vivo dimension is provided by imaging transcriptomics. In a cohort of 164 DLB patients and 164 matched controls, regional grey matter atrophy measured by MRI was related to normative gene-expression patterns derived from the Allen Human Brain Atlas. Within the more homogeneous Mayo Clinic sub-cohort, regional expressions of *APP*, *BINI*, *GBA*, *MAPT*, *PINK1*, *SNCA* and *TMEM175* significantly predicted the observed pattern of atrophy. These findings suggest that regional vulnerability in DLB encompasses both α -synuclein-related and amyloid/tau-related pathways, although gene expression explains only a proportion of the spatial variance (Habich et al., 2026). Ultimately, the integration of genetic, transcriptomic and neuroimaging information represents a promising approach to investigating the heterogeneity of dementias.

CHAPTER 2 – Objectives

This study seeks to integrate genetic and neuroimaging data across several neurodegenerative disorders, specifically Alzheimer's disease (AD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), and REM sleep behavior disorder (RBD). At first, we assess the relationship between regional gene expression and disease-specific patterns of altered glucose metabolism derived from FDG-PET. We then compare the genes significantly associated with the metabolic pattern of each disorder to distinguish disease-specific genes from those shared across pathologies.

In the end, we investigate the biological pathways involving these genes and their protein products, with the aim of discriminating between “disease-specific pathways” and “shared pathways” and exploring their potential contribution to the pathogenesis of these diseases.

CHAPTER 3 - Materials and Methods

1. Sample selection and clinical data

1.1. Study population

Patients were recruited at the IRCCS Ospedale Policlinico San Martino in Genoa (Italy) between 2008 and 2026. Inclusion criteria were based on the most recent guidelines based on the following articles: for Alzheimer's disease: “Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup” (Jack Jr. et al., 2024); for REM sleep behavior disorder: “International Classification of Sleep Disorders-Third Edition” (Sateia, 2014); for Parkinson's disease: “MDS clinical diagnostic criteria for Parkinson's disease” (Postuma et al., 2015); for Dementia with Lewy Bodies: “Diagnosis and management of dementia with Lewy bodies; Fourth consensus report of the DLB Consortium” (McKeith et al., 2017).

Alzheimer's disease

A total of 86 patients with Alzheimer's disease (AD) were enrolled, with a mean age of 72.7 ± 6.9 years; 47 of them were female (54.7%).

Patients had a mean Mini-Mental State Examination (MMSE) score of 25.4 ± 4.2 . Clinical severity, assessed with the Clinical Dementia Rating (CDR), was 0.5 ± 0.29 . Notably, most of the analysed sample (81%) had a CDR of 0.5 (Jack Jr. et al., 2024). This places the cohort in the early and prodromal phases of the disease, corresponding to biological stages 3 and 4

of the recently revised NIA-AA criteria (Jack Jr. et al., 2024), and makes the sample well suited to identifying early transcriptomic determinants of metabolic damage. Motor assessment with the Unified Parkinson's Disease Rating Scale (UPDRS-III) was not performed, as parkinsonism is not a feature of the AD phenotype and the scale is not part of the routine diagnostic work-up for AD.

REM sleep behavior disorder

A total of 56 patients with REM sleep behavior disorder (RBD) were enrolled, with a mean age of 70 ± 7 years; 14 of them were female (25%).

Patients had a mean Mini-Mental State Examination (MMSE) score of 28.3 ± 1.7 , indicating preserved cognitive function. The mean duration of RBD symptoms prior to diagnosis was 40.8 ± 42.3 months. CDR data were not collected in this group: the CDR is designed to stage the severity of dementia, and it is therefore not routinely administered to cognitively unimpaired subjects. UPDRS-III scores were quite low (1.5 ± 1.9), since patients with iRBD do not typically manifest parkinsonism. This makes the RBD cohort well suited to identifying early transcriptomic changes that precede the clinical onset of α -synucleinopathies.

Parkinson's disease

A total of 83 patients with Parkinson's disease (PD) were enrolled, with a mean age of 70.8 ± 8.6 years; 37 of them were female (44.6%).

Patients had a mean Mini-Mental State Examination (MMSE) score of 28.1 ± 2.2 indicating no cognitive decline. Motor symptoms evaluation, assessed with the UPDRS-III (Postuma 2015), had a mean score of 17.3 ± 10.2 . CDR data were not collected in this group, since the CDR is a dementia staging instrument and is not routinely administered to PD patients without cognitive impairment. The preserved cognitive profile of this cohort allows the study

of synuclein-related transcriptomic alterations without the confounding effect of an overt dementia.

Dementia with Lewy Bodies

A total of 61 patients with Dementia with Lewy Bodies (DLB) were enrolled, with a mean age of 75.3 ± 5.6 years; 18 of them were female (29.5%).

Patients had a mean Mini-Mental State Examination (MMSE) score of 24.6 ± 4.2 , consistent with a mild stage of dementia. Since parkinsonism is one of the core clinical features of DLB (McKeith et al., 2017), motor severity was assessed with the UPDRS-III, with a mean score of 13.4 ± 12.8 . CDR data were not collected in this cohort, as these patients were evaluated within a clinical pathway in which disease severity is primarily rated with motor scales. The combination of mild cognitive impairment and motor involvement makes this cohort suitable for investigating transcriptomic signatures shared with, and distinct from, both AD and PD.

Healthy controls

For comparison, a control group of 41 healthy subjects (HC) was also included, with a mean age of 69.6 ± 8.7 years, a mean MMSE score of 29.2 ± 0.8 , and a female prevalence of 63.4% (26 subjects). All subjects in the control group had a CDR score of 0 (100%). All subsets of the different pathologies showed similar levels of education, with mean scores of 10.5 ± 4 for AD, 10.9 ± 4.2 for RBD, 11.3 ± 3.9 for PD, 9.7 ± 4.3 for DLB, 10.5 ± 3.8 for HC, respectively, indicating good comparability across the study cohorts.

1.2. Acquisition and pre-processing of ^{18}F - FDG-PET images

All patients underwent ^{18}F -FDG-PET to assess cerebral glucose metabolism, following the guidelines of the European Association of Nuclear Medicine and the Society of Nuclear

Medicine and Molecular Imaging in use at the time of acquisition (Arbizu et al., 2025; Guedj et al., 2022; Orso et al., 2026). Scans were acquired on a Siemens Biograph 16 hybrid PET/CT system, with a total axial field of view (FOV) of 15 cm and no inter-plane gaps (Orso et al., 2026). To ensure blood glucose levels remained below 7.8 mmol/L, patients were asked to fast for at least 6 hours before the scan. Once blood glucose was confirmed, patients rested for 10 minutes in a quiet, dimly lit room, with eyes closed and ears unplugged. Subsequently, 185–250 MBq of ^{18}F FDG were administered intravenously (Orso et al., 2026).

A low-dose CT scan was also performed for attenuation correction. Data were reconstructed with the iterative OSEM (Ordered Subset Expectation Maximization) algorithm, using 16 subsets and 6 iterations, yielding a voxel size of $1.33 \times 1.33 \times 2.00$ mm (Orso et al., 2026).

All ^{18}F -FDG-PET images were acquired in static mode and then spatially normalised, with both affine and non-linear transformations, to MNI (Montreal Neurological Institute) space using SPM12 (Wellcome Department of Cognitive Neurology, London, UK). Default software settings were applied, using an ^{18}F -FDG-PET-specific brain template as reference. Finally, the normalised images were smoothed with a 10 mm isotropic Gaussian filter to compensate for individual anatomical variability and improve the signal-to-noise ratio (Orso et al., 2026).

1.3. SUVR extraction (AAL3)

Semi-quantitative analysis of glucose metabolism was performed by calculating the SUVR (Standardized Uptake Value Ratio). To this end, regions of interest, hereafter referred to as ROIs, were defined automatically by applying the AAL3 atlas to the images previously normalised to MNI space.

The SUVR of each ROI was calculated as the ratio between the mean metabolic activity of the target region and the mean activity of a reference region (the cerebellar white matter), chosen as an area spared by the disease process:

$$SUVR = \frac{\text{mean activity in the ROI}}{\text{mean activity in the cerebellar}}$$

1.4. Mapping of brain gene expression data (AHBA)

Baseline brain gene expression profiles were reconstructed using data from the Allen Human Brain Atlas (AHBA; Allen Reference Atlases :: Atlas Viewer, n.d.). Expression profiles of thousands of genes were extracted and mapped onto the same 116 ROIs defined by the AAL3 atlas, ensuring full anatomical consistency with the PET imaging data (Martins et al., 2021).

Gene selection was initially based on 226 genes available in the Allen Human Brain Atlas (AHBA). Among these, 192 genes could be assigned to one of 11 distinct spatial expression patterns, whereas the remaining 34 lacked a corresponding pattern and were therefore excluded from subsequent analyses. For each expression pattern, Gene Ontology (GO) enrichment analysis was subsequently conducted, encompassing a total of 8,091 GO terms, 666 of which showed significant enrichment following correction for multiple testing (FDR < 0.05).

These 192 genes were chosen based on the most recent epidemiological genome-wide association studies (GWAS), which have robustly associated them with the risk of developing Alzheimer's disease (AD), Parkinson's disease (PD), Dementia with Lewy bodies

(DLB), and REM sleep behavior disorder (RBD) in the general population (Andrews et al., 2023; Bellenguez et al., 2022). For each of the 192 selected genes and each pathology, a vector was generated containing its expression value across the 116 ROIs of the AAL3 atlas.

2. Statistical analysis

2.1. Analysis of clinical variables

Demographic and clinical characteristics of patients and healthy controls were compared using parametric and non-parametric statistical tests. Specifically, the Kruskal-Wallis test for independent samples was used for continuous variables (such as age, CDR, UPDRS, MMSE), while the categorical variable “sex” was analysed with the Chi-square test.

All results and the demographic overview are summarized here in Figure 1.

Variable	HC	AD	PD	DLB	RBD	p
N	41	86	83	61	56	
Age	69.6 ± 8.7	72.7 ± 6.9	70.8 ± 8.6	75.3 ± 5.6	70 ± 7	<0.001
Female	63.4%	54.7%	44.6%	29.5%	25%	<0.001
Education	10.5 ± 3.8	10.5 ± 4	11.3 ± 3.9	9.7 ± 4.3	10.9 ± 4.2	0.198
MMSE	29.2 ± 0.8	25.4 ± 4.2	28.1 ± 2.2	24.6 ± 4.2	28.3 ± 1.7	<0.001
CDR	0 ± 0	0.5 ± 0.29	-	-	-	
UPDRSIII	-	-	17.3 ± 10.2	13.4 ± 12.8	1.5 ± 1.9	
RBD_duration_ (months) prior diagnosis	-	-	-	-	40.8 ± 42.3	

Data are presented as mean ± SD or n (%). Group comparisons were performed using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. P-values <0.05 were considered statistically significant.

Figure 1 - Demographic data of all the subsets

2.2. MMSE and correlation with imaging

For the subset of patients with a diagnosis of AD, we further examined whether baseline regional brain metabolism was related to the subsequent rate of cognitive decline. The analysis comprised 69 patients (38 females, 31 males; mean age at FDG-PET 73.7 ± 7.0 years) (Figure 2).

Table AD patients - MMSE slope characteristics

Characteristics	N = 69 ¹
Age at FDG-PET (years)	73.7 ± 7.0
Sex	
Male	31 (45%)
Female	38 (55%)
MMSE basal	26 [25; 28]
MMSE slope (points/year)	-2.18 ± 2.86

¹Mean $\pm$ SD; n (%); Median [Q1; Q3]

Figure 2 - AD patients with calculated MMSE slope characteristics

At baseline, the median MMSE score was 26, while the mean annual change in MMSE was -2.18 ± 2.86 points (Figure 3).

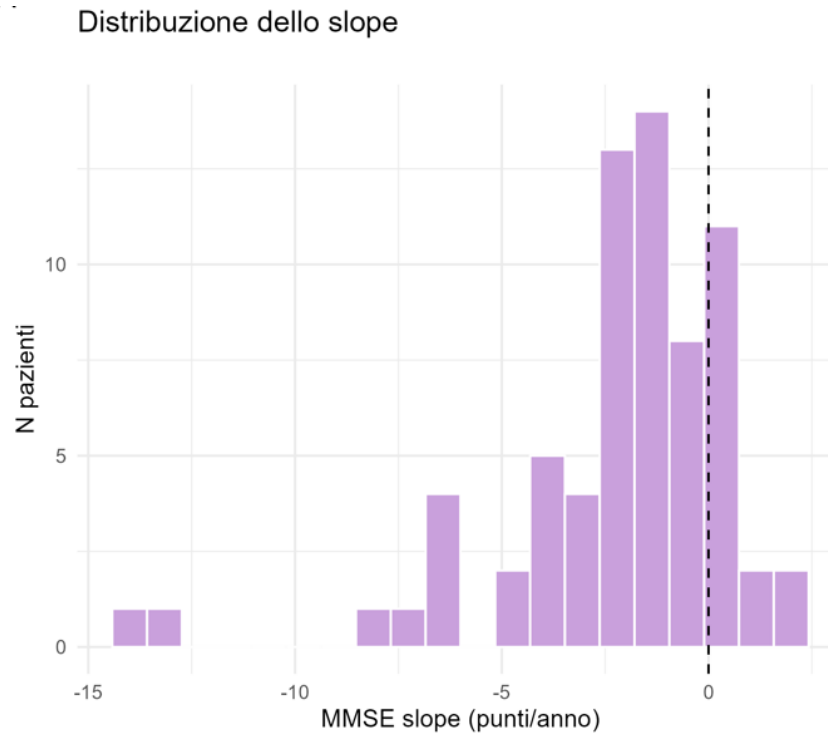


Figure 3 - MMSE slope of AD patients' distribution

The relationship between FDG uptake across the 116 ROIs and MMSE slope was assessed using linear regression models controlling for age, sex, and baseline MMSE. To account for multiple testing, P-values were adjusted using the Benjamini-Hochberg false discovery rate (FDR) test.

None of the ROIs remained significant after FDR correction (all $p \text{ FDR} \geq 0.803$). At the uncorrected significance threshold ($p < 0.05$), associations were identified in five ROIs. In three regions of the left hemisphere, greater metabolic activity was associated with a slower rate of cognitive decline:

- left inferior parietal gyrus ($\beta = 0.34$, $p = 0.025$)
- left superior temporal gyrus ($\beta = 0.31$, $p = 0.028$)
- left postcentral gyrus ($\beta = 0.31$, $p = 0.038$)

All results for the 116 ROIs are reported in *Supplementary Materials* (Table S1 - MMSE slope).

2.3. CSF and correlation with imaging

For the subgroup of patients with AD for whom CSF measurements were available, we additionally investigated the association between CSF biomarkers and regional cerebral metabolism. The analysis comprised 40 patients (23 females, 17 males), with a mean age at FDG-PET of 74.4 ± 6.4 years (Figure 4).

Median CSF T-tau concentration was 630 pg/mL. The mean A β 42/40 ratio was 0.046 ± 0.011 (Figure 5).

AD patients with CSF data	
Characteristics	N = 40¹
Age at FDG-PET (years)	74.4 ± 6.4
Sex	
Male	17 (43%)
Female	23 (58%)
T-tau (pg/mL)	630 [415; 804]
Aβ42/40 ratio	0.046 ± 0.011

¹Mean $\pm$ SD; n (%); Median [Q1; Q3]

Figure 4 - AD patients with CSF data characteristics

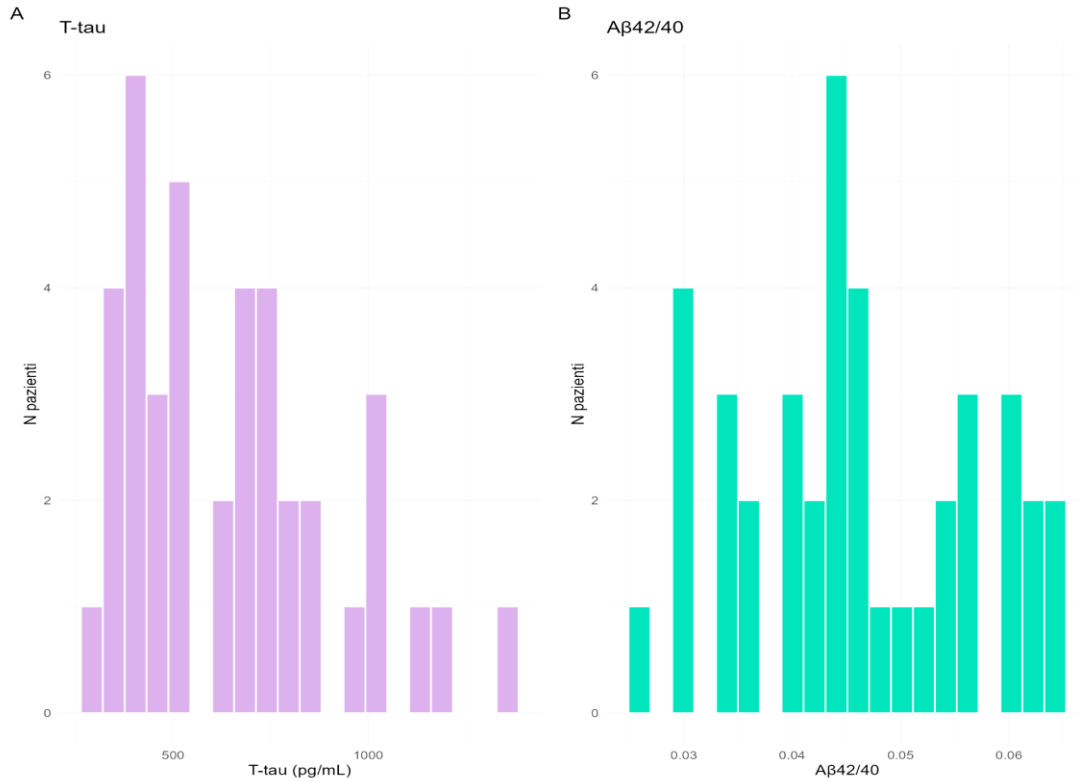


Figure 5 - CSF biomarkers distribution

For each biomarker, its relationship with FDG uptake was assessed across 116 ROIs by means of linear regression models controlling for age and sex. To account for multiple testing, P-values were adjusted using the Benjamini-Hochberg (FDR) test.

The analysis of T-tau yielded no ROI that remained significant after FDR correction (all $p \geq 0.588$). At the uncorrected threshold of $p < 0.05$, however, seven ROIs exhibited a positive association. These comprised the bilateral olfactory cortex, bilateral lateral orbitofrontal cortex, bilateral precuneus and left pallidum, with standardized β coefficients ranging from 0.31 to 0.37. Among these, the association was strongest in the left olfactory cortex ($\beta = 0.37$, $p = 0.019$).

Similarly, none of the ROIs assessed for A β 42/40 remained significant following FDR correction (all p FDR ≥ 0.113). At the uncorrected level ($p < 0.05$), 24 ROIs displayed a negative association, 19 of which were located in the left hemisphere. The most pronounced associations involved the left putamen ($\beta = -0.46$, $p = 0.003$), left inferior frontal gyrus, orbital part ($\beta = -0.44$, $p = 0.002$), left superior parietal gyrus ($\beta = -0.41$, $p = 0.005$), left insula ($\beta = -0.40$, $p = 0.004$) and left superior temporal gyrus ($\beta = -0.39$, $p = 0.004$).

All results for the 116 ROIs are reported in the *Supplementary Materials* (Table S2 - A β 42/40 ratio; Table S3 - T-tau).

2.4. Transcriptomic analysis and correlation with imaging

To isolate the hypometabolic pattern specific to the patient group, a subtraction procedure was performed relative to the control group as follows. Firstly, the mean SUVR of each set of patients was calculated for each region; the same was done for healthy controls.

Finally, the two mean maps were subtracted. This was repeated for each set of patients based on the pathology.

This yielded a mean map of the difference of each subset of patients (AD, PD, DLB, RBD) from healthy controls, in which negative values indicate hypometabolism and positive values indicate hypermetabolism. This made it possible to highlight areas with significant metabolic deficits.

A spatial transcriptomic analysis was then performed to investigate the topographic association between gene expression and FDG-PET hypometabolic patterns.

We used Allen Human Brain Atlas (AHBA) data to extract the expression profiles of thousands of genes for the same ROIs analysed in the imaging data. This step was necessary to ensure anatomical consistency between molecular and neuroimaging data. The spatial correlation between gene expression levels and the SUVR values from the subtraction (SUB) images was then calculated using Pearson's correlation coefficient, in order to identify genes whose topographic expression was significantly correlated with the hypometabolic pattern.

Statistical significance was then rigorously assessed through a permutation test (spin test; Alexander-Bloch et al., 2018). For each gene map, 1,000 null correlations were computed against spatially permuted FDG-PET subtraction maps, and significance was defined as the fraction of permuted correlation values exceeding the original spatial correlation value.

2.5. Functional enrichment analysis (Gene Ontology – GO)

To investigate the biological significance of the genes identified through the spatial correlation analysis, we conducted a functional enrichment analysis using the Gene Ontology (GO) platform. This analysis was used to determine whether the genes whose expression was associated with the metabolic deficit observed in each condition showed significant enrichment for specific biological pathways (Gene Ontology Consortium et al., 2023).

The findings for the individual diseases were subsequently compared with the corresponding gene subsets cross-referenced to identify pathways shared across conditions. Such common pathways could potentially contribute to understanding the clinical co-occurrence of these conditions. Indeed, mixed pathology is common in neurodegenerative diseases: AD co-

pathology is often found in DLB, and RBD is widely recognised as a prodromal stage of α -synucleinopathies such as PD and DLB. We therefore evaluated every possible combination of the four conditions, yielding a total of 15 subsets comprising genes specific to individual diseases as well as genes shared by two, three, or all four conditions. The resulting overlaps among the gene sets are illustrated in Figure 6.

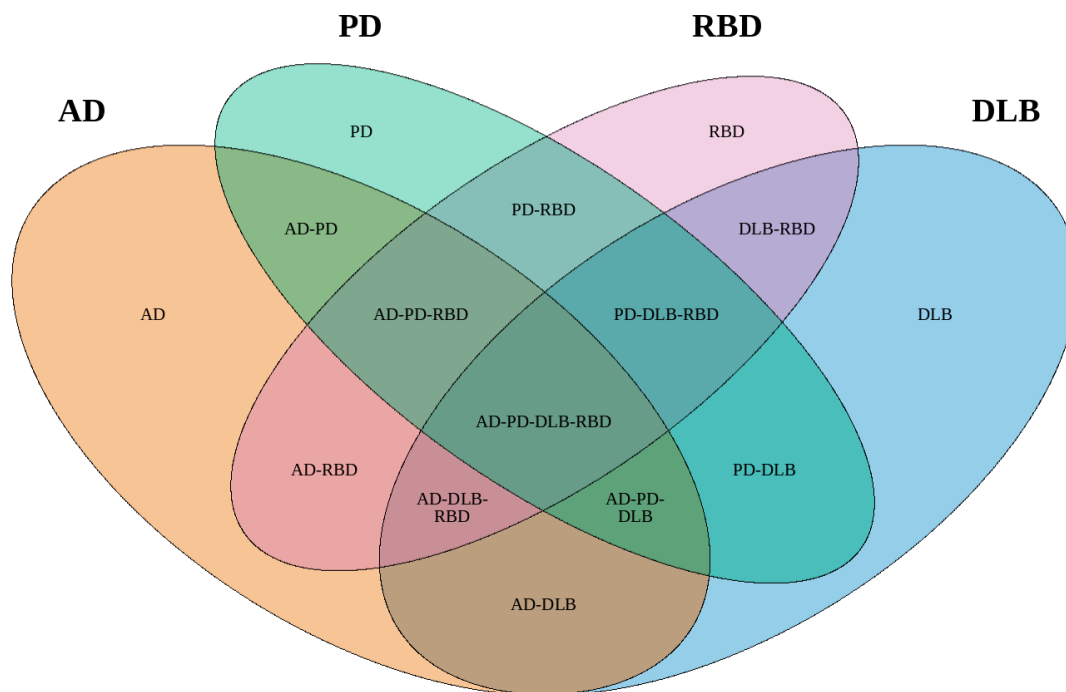


Figure 6 - Overlapping of all four pathologies

CHAPTER 4 - Results

1. Patterns of FDG-PET alterations

Regional SUVR was assessed in each patient group relative to HC across 116 AAL3 regions, with FDR correction applied separately to each contrast. Hypometabolism was detected in all groups, following a severity gradient of: DLB > AD > PD > RBD.

In **DLB** was observed the most extensive hypometabolic pattern, with maximal reductions in the *inferior parietal lobule* ($t = -10.90$) and *lingual gyrus* ($t = -9.15$). Relative hypermetabolism was additionally observed in the posterior cingulate gyrus, hippocampus and cerebellar vermis.

In **AD**, the metabolic reductions showed a predominantly temporoparietal distribution, with the largest effects observed in the *left inferior parietal lobule* ($t = -8.18$) and *left middle temporal gyrus* ($t = -6.90$), whereas the hippocampus was spared.

In **PD**, the abnormalities were predominantly posterior: *parietal, occipital and amygdalar regions* ($t = 4.0-5.0$).

Finally, **RBD** was characterised by mild, diffused reductions, with just *four parietal and orbitofrontal regions* remaining significant after correction ($p_{\text{FDR}} = 0.049$).

2. Results of imaging–transcriptomic spatial correlation analysis

Spatial correlations between the expression of 226 GWAS risk genes and the four subtraction maps were evaluated using the spin test with 1,000 permutations. Of these genes, 192 (85%)

reached significance in at least one disease and the remaining 34 showed no significant association across any condition and were excluded from analyses.

The number of significant genes varied between conditions: 173 in AD, 123 in DLB, 99 in PD and 56 in RBD.

Disease-specific signatures were heterogeneous: AD included 45 specific genes (26%), compared with 2 (2%) in PD, 1 (2%) in RBD and none in DLB.

All genes associated with DLB were also significant in AD, PD, or both.

An important portion of the significant genes, 75%, was shared across conditions, with 144 genes occurring in at least two conditions. The most extensive overlaps comprised the AD + DLB + PD combination (51 genes), AD + DLB (31 genes), and the four-condition overlap (29 genes). Four of the 15 possible combinations contained no genes. Across the remaining 11 overlap patterns, 8,091 GO terms were evaluated, of which 666 reached significance (FDR < 0.05) (Figure 7; Table 1).

3. Shared biological pathways (AD, PD, DLB, RBD)

Of the 226 genes available in the AHBA, 192 were significant in at least one disease and were grouped according to the pathologies in which they were found (Figure 7). The remaining 34 genes were not assigned to any pattern and therefore they were excluded. With four diseases, there are 15 possible combinations. Eleven of them contained at least one gene and were analysed; the other four were empty (AD + PD, DLB + RBD, AD + DLB + RBD, and DLB only).

Overlap of significant genes across disease contrasts

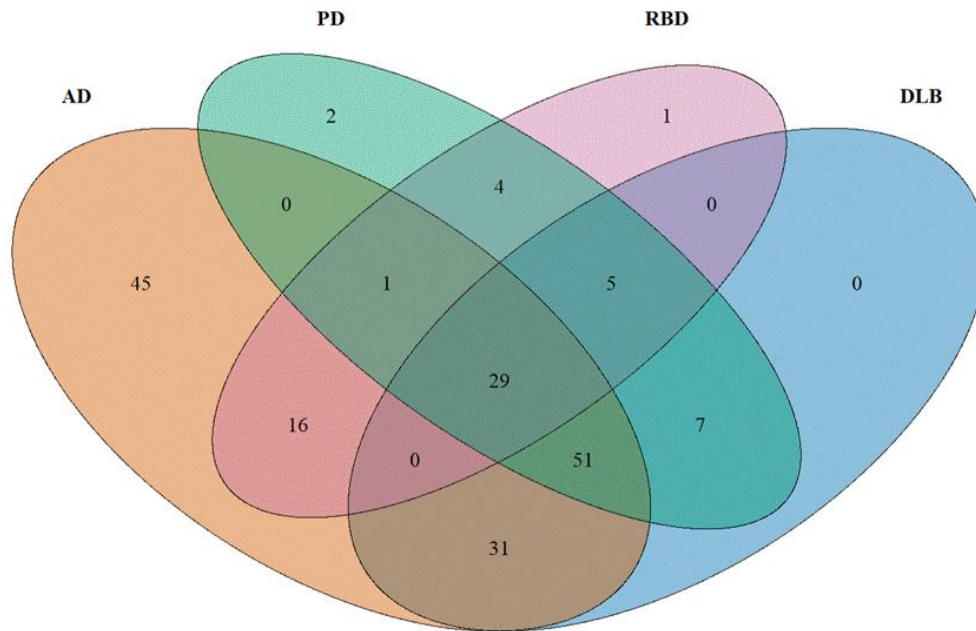


Figure 7 - Overlap of significant genes across the four disease contrasts (AD, PD, RBD, DLB). Numbers indicate the genes in each combination.

Across the 11 patterns, 8,091 GO terms were tested and 666 were significant ($FDR < 0.05$) (Table 1). Before GO enrichment, gene symbols were converted to Entrez IDs: 189 of 192 genes (98%) were mapped, while three genes were not (*GBAP1*, *MFSD10*, *GBA*) (Table 2).

General study parameters

Overview of the genes analysed and of the GO enrichment results

PARAMETER	VALUE
Initial genes available in the AHBA	226
Genes in analysed patterns	192
Excluded genes	34
Patterns analysed	11
Total GO terms	8,091
Significant GO terms ($FDR < 0.05$)	666

Table 1 - General study parameters.

Quality control of gene identifier mapping

Mapping of gene symbols to Entrez IDs for each pattern

PATTERN	INPUT GENES	MAPPED SYMBOLS	UNMAPPED	UNIQUE ENTREZ IDS	UNMAPPED GENES
AD + DLB	31	30	1	30	<i>GBAP1</i>
AD + DLB + PD	51	51	0	51	—
AD + DLB + PD + RBD	29	28	1	28	<i>MFSD10</i>
AD + PD + RBD	1	1	0	1	—
AD + RBD	16	16	0	16	—
AD only	45	44	1	44	<i>GBA</i>
DLB + PD	7	7	0	7	—
DLB + PD + RBD	5	5	0	5	—
PD + RBD	4	4	0	4	—
PD only	2	2	0	2	—
RBD only	1	1	0	1	—
Total	192	189	3	189	

Table 2 - Quality control of the mapping of gene symbols to Entrez IDs for each pattern.

Eight of the 11 patterns were shared by two or more diseases and included 144 genes (75% of the analysed genes). The largest pattern was AD + DLB + PD (51 genes), followed by AD + DLB (31) and the pattern common to all four diseases (29). The table below (Table 3) summarises the number of genes and significant GO terms per pattern, and in Table 4 are listed the genes in each pattern. The number of significant terms did not follow the number of genes: the small patterns DLB + PD (7 genes) and PD + RBD (4 genes) gave the most terms (236 and 226), while AD + DLB (31 genes) gave only one.

Summary of shared patterns

Number of genes and significant GO terms (FDR < 0.05) for each pattern

PATTERN	DISEASES	NO. OF GENES	SIGNIFICANT GO TERMS
AD + DLB		31	1
AD + DLB + PD		51	53
AD + DLB + PD + RBD		29	3
AD + PD + RBD		1	0
AD + RBD		16	24
AD only		45	4
DLB + PD		7	236
DLB + PD + RBD		5	80
PD + RBD		4	226
PD only		2	39
RBD only		1	0
Total		192	666

AD = Alzheimer's disease · DLB = dementia with Lewy bodies · PD = Parkinson's disease · RBD = REM sleep behavior disorder

Table 3 - Number of genes and significant GO terms (FDR < 0.05) for each pattern.

Gene composition of patterns

Genes assigned to each pattern of sharing across diseases

PATTERN	NO.	GENES
AD + DLB	31	ADAMTS1, AKR1D1, BIN3, BRIP1, C16orf95, CHRN1, CTSE, DDX46, DGKQ, ERCC3, GBAP1, HCAR1, HCN3, IGSF9B, IP6K2, IPMK, KAT8, KPNA1, LILRB1, MAPT, MEX3C, MGAT5, MSTO1, NMD3, PDLIM2, PITPNM2, PRSS3, SETD1A, SH3GL2, SLC24A4, SNAI1
AD + DLB + PD	51	ABI3, ACE, ADAM10, ADAM15, ADAMTS4, AGRN, APH1B, APP, AXIN1, BAG3, BST1, CAB39L, CAMK2D, CLCN3, DMPK, DOCK4, DPM3, DYRK1A, EFNA1, FCGR2B, HBEGF, ICA1L, IDUA, IGF2BP3, IRS2, KCNIP3, KTN1, LAMP3, LINC00174, LMNA, LRRC25, MAF, MAP4K4, MCCC1, MED13, MEX3A, MIPOL1, MTF2, MYO15A, NSF, PAM, PKP2, PLEKHA1, RHOF, RPS12, SATB1, SCARB2, SHARPIN, SLC25A44, SLC26A1, SLC2A13
AD + DLB + PD + RBD	29	ADAM17, ADD1, ANK3, ANO5, ATP8B4, CC2D2A, CCT3, CEP89, ECHDC3, EIF4G3, EML2, HS3ST5, INPP5F, KNTC1, LCORL, LRRK2, MED12L, MFSD10, MLX, MMRN1, NYAP1, PAQR6, PGS1, RASGEF1C, RBCK1, RIT2, SCIMP, SEC23IP, SIPA1L2
AD + PD + RBD	1	C1S
AD + RBD	16	ANKH, CLU, DDRGK1, DOC2A, ELOVL7, EPHA1, FAM47E, FDFT1, GPNMB, IL34, LAMTOR2, NOD2, RILPL2, SEC61G, SEMA4A, SNCA
AD only	45	ABCA7, ADGRL3, APOC1, AREL1, ARHGAP27, ASXL3, BIN1, CCSER1, CD2AP, CELF1, CTSH, CYLD, DCST1, DLG2, FAM193B, FAM200B, FASN, FERMT2, FGFR1, GBA, HIP1R, ITPKB, JAZF1, KPNA3, MAP3K14, MUC19, NCK2, NEK1, NFATC2IP, PARP9, PBXIP1, PCGF3, PMVK, POLR2D, PPP2R3A, PPP6R2, PRDM7, PSMG1, RICB8, RIMST1, RITA1, RNF141, RPS6KL1, SIGLEC11, SLC50A1
DLB + PD	7	APOE, ASH1L, GAK, GON4L, KRTCAP2, PICALM, RIPOR3
DLB + PD + RBD	5	CNTN1, HLA-DRB5, ICA1, LILRB2, PIK3CA
PD + RBD	4	BLNK, CD33, FCGR2A, PTPRC
PD only	2	IQCK, MYLK2
RBD only	1	CCDC62
Total	192	

Table 4 - Genes assigned to each pattern of sharing across diseases.

Pathways shared by all four diseases: AD + DLB + PD + RBD.

Twenty-nine genes were significant in all four diseases, including *LRRK2*. Three GO terms were enriched (Table 5). The top term was negative regulation of neuron projection

development (*ADAM17*, *INPP5F*, *LRRK2*, *RIT2*). The other two terms, cytoskeletal anchor activity and spectrin binding, were driven by *ADD1* and *ANK3*.

GO enrichment – AD + DLB + PD + RBD AD DLB PD RBD

Genes in pattern: 29 · Significant GO terms (FDR < 0.05): 3

ONT.	GO ID	GO TERM	GENE RATIO	FDR	GENES
BP	GO:0010977	negative regulation of neuron projection development	4/27	0.032	<i>ADAM17</i> , <i>INPP5F</i> , <i>LRRK2</i> , <i>RIT2</i>
MF	GO:0008093	cytoskeletal anchor activity	2/26	0.038	<i>ADD1</i> , <i>ANK3</i>
MF	GO:0030507	spectrin binding	2/26	0.038	<i>ADD1</i> , <i>ANK3</i>

BP = biological process · MF = molecular function · CC = cellular component · FDR = p-value adjusted for multiple testing

Table 5 - GO enrichment for genes shared by AD, DLB, PD and RBD.

Alzheimer's disease and the other diseases

Four patterns combined AD with one or more of the other diseases.

1. AD + DLB. This pattern included 31 genes but only one GO term was significant: inositol phosphate kinase activity (*IP6K2*, *IPMK*; FDR = 0.023) (Table 6).

GO enrichment – AD + DLB AD DLB

Genes in pattern: 31 · Significant GO terms (FDR < 0.05): 1

ONT.	GO ID	GO TERM	GENE RATIO	FDR	GENES
MF	GO:0180030	inositol phosphate kinase activity	2/28	0.023	<i>IP6K2</i> , <i>IPMK</i>

BP = biological process · MF = molecular function · CC = cellular component · FDR = p-value adjusted for multiple testing

Table 6 - GO enrichment for genes shared by AD and DLB.

2. AD + DLB + PD. This was the largest pattern (51 genes) and gave 53 significant terms (Table 7). The strongest terms were related to amyloid precursor protein (APP) processing and amyloid-beta metabolism (*ADAM10*, *APH1B*, *APP*, *DYRK1A*, *EFNA1*, *SLC2A13*). Other enriched terms involved the regulation of synapse organisation (8 genes), regulation of blood circulation and metalloendopeptidase activity.

GO enrichment – AD + DLB + PD

Genes in pattern: 51 · Significant GO terms (FDR < 0.05): 53

ONT.	GO ID	GO TERM	GENE RATIO	FDR	GENES
BP	GO:0042987	amyloid precursor protein catabolic process	6/47	4.54×10^{-5}	ADAM10, APOB, APP, DYRK1A, EFNA1, SLC2A13
BP	GO:0042982	amyloid precursor protein metabolic process	6/47	1.57×10^{-4}	ADAM10, APOB, APP, DYRK1A, EFNA1, SLC2A13
BP	GO:0050435	amyloid-beta metabolic process	5/47	4.33×10^{-4}	ACE, APOB, DYRK1A, EFNA1, SLC2A13
BP	GO:0050807	regulation of synapse organization	8/47	4.33×10^{-4}	ABI3, ADAM10, AGRN, APP, DMPK, DOCK4, EFNA1, FCGR2B
BP	GO:0050803	regulation of synapse structure or activity	8/47	4.33×10^{-4}	ABI3, ADAM10, AGRN, APP, DMPK, DOCK4, EFNA1, FCGR2B
BP	GO:0099175	regulation of postsynapse organization	6/47	4.33×10^{-4}	ABI3, ADAM10, APP, DOCK4, EFNA1, FCGR2B
BP	GO:1903522	regulation of blood circulation	7/47	0.001	ACE, APP, CAMK2D, DMPK, DOCK4, HBEGF, PKP2
BP	GO:0034205	amyloid-beta formation	4/47	0.003	APH1B, DYRK1A, EFNA1, SLC2A13
BP	GO:1902991	regulation of amyloid precursor protein catabolic process	4/47	0.003	APP, DYRK1A, EFNA1, SLC2A13
MF	GO:0030165	PDZ domain binding	4/49	0.018	CLCN3, DOCK4, NSF, PLEKHA1
MF	GO:0004222	metalloendopeptidase activity	4/49	0.025	ACE, ADAM10, ADAM15, ADAMTS4
CC	GO:0043198	dendritic shaft	3/50	0.029	ABI3, APP, NSF
MF	GO:0019207	kinase regulator activity	5/49	0.046	AXIN1, CAB39L, HBEGF, IRS2, RHOH
MF	GO:0043395	heparan sulfate proteoglycan binding	2/49	0.046	AGRN, APP
MF	GO:0016805	dipeptidase activity	2/49	0.046	ACE, ADAM10

Showing the 15 most significant of 53 terms (max 5 per ontology; full breakdown: BP 42 · MF 10 · CC 1).
BP = biological process · MF = molecular function · CC = cellular component FDR = p-value adjusted for multiple testing

Table 7 - GO enrichment for genes shared by AD, DLB and PD (15 most significant of 53 terms).

3. AD + RBD. This pattern included 16 genes and gave 24 significant terms (Table 8). Two main patterns emerged: 1) protein folding and handling: protein-folding chaperone binding, tau protein binding, protein sequestering activity and chaperone-mediated autophagy, mainly driven by *CLU* and *SNCA*; 2) inflammation: positive regulation of NF-κB activity, tumor necrosis factor (TNF) production and macrophage proliferation (*CLU*, *NOD2*, *GPNMB*, *IL34*, *DDRGKI*).

GO enrichment – AD + RBD

Genes in pattern: 16 · Significant GO terms (FDR < 0.05): 24

ONT.	GO ID	GO TERM	GENE RATIO	FDR	GENES
MF	GO:0051087	protein-folding chaperone binding	3/16	0.020	CLU, NOD2, SNCA
MF	GO:0048156	tau protein binding	2/16	0.022	CLU, SNCA
MF	GO:0140311	protein sequestering activity	2/16	0.022	CLU, SNCA
MF	GO:0030544	Hsp70 protein binding	2/16	0.022	NOD2, SNCA
BP	GO:0051092	positive regulation of NF-kappaB transcription factor activity	3/16	0.023	CLU, DDRGK1, NOD2
BP	GO:0061517	macrophage proliferation	2/16	0.023	CLU, IL34
BP	GO:0061684	chaperone-mediated autophagy	2/16	0.023	CLU, SNCA
BP	GO:0051091	positive regulation of DNA-binding transcription factor activity	3/16	0.024	CLU, DDRGK1, NOD2
BP	GO:0031340	positive regulation of vesicle fusion	2/16	0.030	DOC2A, SNCA
MF	GO:0140313	molecular sequestering activity	2/16	0.037	CLU, SNCA
BP	GO:0031338	regulation of vesicle fusion	2/16	0.044	DOC2A, SNCA
BP	GO:0051090	regulation of DNA-binding transcription factor activity	3/16	0.044	CLU, DDRGK1, NOD2
BP	GO:0032640	tumor necrosis factor production	3/16	0.044	CLU, GPNMB, NOD2
BP	GO:0032680	regulation of tumor necrosis factor production	3/16	0.044	CLU, GPNMB, NOD2
BP	GO:0043410	positive regulation of MAPK cascade	4/16	0.044	GPNMB, IL34, LAMTOR2, NOD2

Showing the 15 most significant of 24 terms (max 5 per ontology; full breakdown: BP 19 · MF 5 · CC 0).
BP = biological process · MF = molecular function · CC = cellular component · FDR = p-value adjusted for multiple testing

Table 8 - GO enrichment for genes shared by AD and RBD (15 most significant of 24 terms).

4. AD + PD + RBD. This pattern contained a single gene (*CIS*), and no GO term was significant (Table 9).

GO enrichment – AD + PD + RBD

Genes in pattern: 1 · Significant GO terms (FDR < 0.05): 0 · Genes: CIS

ONT.	GO ID	GO TERM	GENE RATIO	FDR	GENES
No significant GO terms (FDR < 0.05)					

Table 9 - GO enrichment for genes shared by AD, PD and RBD.

Alpha-synucleinopathies

Three patterns involved only alpha-synucleinopathies (DLB, PD, RBD). These patterns contained few genes (4–7) but gave many significant terms. Because many terms were driven

by the same one or two genes, the high number of terms mainly reflects the nested structure of GO rather than many independent pathways.

1. DLB + PD + RBD. Five genes were shared by the three alpha-synucleinopathies (*CNTN1*, *HLA-DRB5*, *ICA1*, *LILRB2*, *PIK3CA*), giving 80 significant terms (57 BP, 17 MF, 6 CC) (Table 10). The main theme was the immune response: MHC protein complex binding, antigen processing and presentation, and positive regulation of T cell activation (*HLA-DRB5*, *LILRB2*). Phosphatidylinositol 3-kinase activity (*PIK3CA*) and vesicle-related components (*HLA-DRB5*, *ICA1*) were also enriched.

GO enrichment – DLB + PD + RBD DLB PD RBD

Genes in pattern: 5 · Significant GO terms (FDR < 0.05): 80 · Genes: *CNTN1*, *HLA-DRB5*, *ICA1*, *LILRB2*, *PIK3CA*

ONT.	GO ID	GO TERM	GENE RATIO	FDR	GENES
MF	GO:0023023	MHC protein complex binding	2/5	0.001	<i>HLA-DRB5</i> , <i>LILRB2</i>
MF	GO:0042277	peptide binding	2/5	0.020	<i>HLA-DRB5</i> , <i>LILRB2</i>
MF	GO:0016303	1-phosphatidylinositol-3-kinase activity	1/5	0.020	<i>PIK3CA</i>
MF	GO:0032396	inhibitory MHC class I receptor activity	1/5	0.020	<i>LILRB2</i>
MF	GO:0043560	insulin receptor substrate binding	1/5	0.020	<i>PIK3CA</i>
CC	GO:0030658	transport vesicle membrane	2/5	0.041	<i>HLA-DRB5</i> , <i>ICA1</i>
CC	GO:0030667	secretory granule membrane	2/5	0.041	<i>ICA1</i> , <i>LILRB2</i>
CC	GO:0005942	phosphatidylinositol 3-kinase complex	1/5	0.041	<i>PIK3CA</i>
CC	GO:0042613	MHC class II protein complex	1/5	0.041	<i>HLA-DRB5</i>
CC	GO:0030133	transport vesicle	2/5	0.041	<i>HLA-DRB5</i> , <i>ICA1</i>
BP	GO:0019882	antigen processing and presentation	2/5	0.044	<i>HLA-DRB5</i> , <i>LILRB2</i>
BP	GO:0050870	positive regulation of T cell activation	2/5	0.044	<i>HLA-DRB5</i> , <i>LILRB2</i>
BP	GO:1903039	positive regulation of leukocyte cell-cell adhesion	2/5	0.044	<i>HLA-DRB5</i> , <i>LILRB2</i>
BP	GO:0002666	positive regulation of T cell tolerance induction	1/5	0.044	<i>LILRB2</i>
BP	GO:0002765	immune response-inhibiting signal transduction	1/5	0.044	<i>LILRB2</i>

Showing the 15 most significant of 80 terms (max 5 per ontology; full breakdown: BP 57 · MF 17 · CC 6).
BP = biological process · MF = molecular function · CC = cellular component FDR = p-value adjusted for multiple testing

Table 10 - GO enrichment for genes shared by DLB, PD and RBD (15 most significant of 80 terms).

2. DLB + PD. Seven genes were shared by DLB and PD (*APOE*, *ASH1L*, *GAK*, *GON4L*, *KRTCAP2*, *PICALM*, *RIPOR3*), giving 236 significant terms (188 BP, 24 MF, 24 CC), the highest number of all patterns (Table 11). Most terms were driven by *APOE*, *PICALM* and

GAK and concerned lipoprotein receptor binding, clathrin-coated vesicles and receptor-mediated endocytosis. Terms related to amyloid-beta and tau protein binding were also enriched.

GO enrichment – DLB + PD DLB PD

Genes in pattern: 7 · Significant GO terms (FDR < 0.05): 236 · Genes: *APOE*, *ASH1L*, *GAK*, *GON4L*, *KRTCAP2*, *PICALM*, *RIPOR3*

ONT.	GO ID	GO TERM	GENE RATIO	FDR	GENES
MF	GO:0050750	low-density lipoprotein particle receptor binding	2/7	0.001	<i>APOE</i> , <i>PICALM</i>
MF	GO:0070325	lipoprotein particle receptor binding	2/7	0.001	<i>APOE</i> , <i>PICALM</i>
CC	GO:0030136	clathrin-coated vesicle	3/6	0.001	<i>APOE</i> , <i>GAK</i> , <i>PICALM</i>
MF	GO:0048156	tau protein binding	2/7	0.002	<i>APOE</i> , <i>PICALM</i>
MF	GO:0030276	clathrin binding	2/7	0.002	<i>GAK</i> , <i>PICALM</i>
CC	GO:0030135	coated vesicle	3/6	0.002	<i>APOE</i> , <i>GAK</i> , <i>PICALM</i>
BP	GO:0048268	clathrin coat assembly	2/6	0.004	<i>GAK</i> , <i>PICALM</i>
BP	GO:1902004	positive regulation of amyloid-beta formation	2/6	0.004	<i>APOE</i> , <i>PICALM</i>
MF	GO:0001540	amyloid-beta binding	2/7	0.004	<i>APOE</i> , <i>PICALM</i>
BP	GO:1902993	positive regulation of amyloid precursor protein catabolic process	2/6	0.004	<i>APOE</i> , <i>PICALM</i>
BP	GO:0034250	positive regulation of amide metabolic process	2/6	0.004	<i>APOE</i> , <i>PICALM</i>
BP	GO:0006898	receptor-mediated endocytosis	3/6	0.005	<i>APOE</i> , <i>GAK</i> , <i>PICALM</i>
CC	GO:0045334	clathrin-coated endocytic vesicle	2/6	0.005	<i>APOE</i> , <i>PICALM</i>
CC	GO:0042627	chylomicron	1/6	0.026	<i>APOE</i>
CC	GO:0008250	oligosaccharyltransferase complex	1/6	0.026	<i>KRTCAP2</i>

Showing the 15 most significant of 236 terms (max 5 per ontology; full breakdown: BP 188 · MF 24 · CC 24).
BP = biological process · MF = molecular function · CC = cellular component · FDR = p-value adjusted for multiple testing

Table 11 - GO enrichment for genes shared by DLB and PD (15 most significant of 236 terms).

3. PD + RBD. Four genes were shared by PD and RBD (*BLNK*, *CD33*, *FCGR2A*, *PTPRC*), giving 226 significant terms (196 BP, 28 MF, 2 CC) (Table 12). All terms were related to the immune system. The top term, immune response-regulating cell surface receptor signalling pathway, included all four genes. Other terms included TNF production, Fc-gamma receptor signalling and B cell receptor signalling.

GO enrichment – PD + RBD

Genes in pattern: 4 · Significant GO terms (FDR < 0.05): 226 · Genes: *BLNK*, *CD33*, *FCGR2A*, *PTPRC*

ONT.	GO ID	GO TERM	GENE RATIO	FDR	GENES
BP	GO:0002768	immune response-regulating cell surface receptor signaling pathway	4/4	5.15×10^{-5}	<i>BLNK</i> , <i>CD33</i> , <i>FCGR2A</i> , <i>PTPRC</i>
CC	GO:0030667	secretory granule membrane	3/4	2.10×10^{-4}	<i>CD33</i> , <i>FCGR2A</i> , <i>PTPRC</i>
CC	GO:0009897	external side of plasma membrane	3/4	2.10×10^{-4}	<i>CD33</i> , <i>FCGR2A</i> , <i>PTPRC</i>
BP	GO:0032640	tumor necrosis factor production	3/4	2.85×10^{-4}	<i>CD33</i> , <i>FCGR2A</i> , <i>PTPRC</i>
BP	GO:0032680	regulation of tumor necrosis factor production	3/4	2.85×10^{-4}	<i>CD33</i> , <i>FCGR2A</i> , <i>PTPRC</i>
BP	GO:0071706	tumor necrosis factor superfamily cytokine production	3/4	2.85×10^{-4}	<i>CD33</i> , <i>FCGR2A</i> , <i>PTPRC</i>
BP	GO:1903555	regulation of tumor necrosis factor superfamily cytokine production	3/4	2.85×10^{-4}	<i>CD33</i> , <i>FCGR2A</i> , <i>PTPRC</i>
BP	GO:0038094	Fc-gamma receptor signaling pathway	2/4	0.001	<i>CD33</i> , <i>FCGR2A</i>
BP	GO:0038093	Fc receptor signaling pathway	2/4	0.003	<i>CD33</i> , <i>FCGR2A</i>
BP	GO:0050853	B cell receptor signaling pathway	2/4	0.003	<i>BLNK</i> , <i>PTPRC</i>
MF	GO:0030292	protein tyrosine kinase inhibitor activity	1/4	0.019	<i>PTPRC</i>
MF	GO:0019763	immunoglobulin receptor activity	1/4	0.019	<i>FCGR2A</i>
MF	GO:0005068	transmembrane receptor protein tyrosine kinase adaptor activity	1/4	0.019	<i>BLNK</i>
MF	GO:0005001	transmembrane receptor protein tyrosine phosphatase activity	1/4	0.019	<i>PTPRC</i>
MF	GO:0019864	IgG binding	1/4	0.019	<i>FCGR2A</i>

Showing the 15 most significant of 226 terms (max 5 per ontology; full breakdown: BP 196 · MF 28 · CC 2).
BP = biological process · MF = molecular function · CC = cellular component · FDR = p-value adjusted for multiple testing

Table 12 - GO enrichment for genes shared by PD and RBD (15 most significant of 226 terms).

All these GO enrichment analysis results are also summarized in *Supplementary materials* because of the length of some of these tables (Table S1 - S11 GO enrichment analysis).

4. Disease-specific biological pathways

Three of the 11 patterns contained genes significant in a single disease: AD only (45 genes), PD only (2 genes) and RBD only (1 gene). No DLB-specific pattern was analysed, because every gene significant in DLB was also significant in at least one other disease (Figure 7).

1. AD only. This was the largest disease-specific pattern (45 genes; 44 mapped, as *GBA* could not be mapped). Four GO terms were significant (Table 13): actin filament binding (*ARHGAP27*, *BINI*, *CD2AP*, *FERMT2*, *HIP1R*), clathrin binding (*BINI*, *CD2AP*, *HIP1R*),

phosphotransferase activity with a phosphate group as acceptor (*DLG2*, *ITPKB*, *PMVK*) and protein-lipid complex assembly (*ABCA7*, *APOC1*, *BIN1*). Numerous of these genes (*BIN1*, *CD2AP*, *ABCA7*, *FERMT2*) are known AD risk genes.

GO enrichment – AD only AD

Genes in pattern: **45** · Significant GO terms (FDR < 0.05): **4**

ONT.	GO ID	GO TERM	GENE RATIO	FDR	GENES
MF	GO:0016776	phosphotransferase activity, phosphate group as acceptor	3/42	0.009	<i>DLG2</i> , <i>ITPKB</i> , <i>PMVK</i>
MF	GO:0051015	actin filament binding	5/42	0.009	<i>ARHGAP27</i> , <i>BIN1</i> , <i>CD2AP</i> , <i>FERMT2</i> , <i>HIP1R</i>
MF	GO:0030276	clathrin binding	3/42	0.010	<i>BIN1</i> , <i>CD2AP</i> , <i>HIP1R</i>
BP	GO:0065005	protein-lipid complex assembly	3/39	0.033	<i>ABCA7</i> , <i>APOC1</i> , <i>BIN1</i>

BP = biological process · MF = molecular function · CC = cellular component · FDR = p-value adjusted for multiple testing

Table 13 - GO enrichment for genes specific to AD.

2. PD only. Two genes were specific to PD (*IQCK*, *MYLK2*). Thirty-nine terms were significant (32 BP, 4 MF, 3 CC) (Table 14), but all were driven by *MYLK2* alone (gene ratio 1/1). These terms concerned calcium/calmodulin-dependent kinase activity and muscle contraction.

GO enrichment – PD only PD

Genes in pattern: 2 · Significant GO terms (FDR < 0.05): 39 · Genes: *IQCK*, *MYLK2*

ONT.	GO ID	GO TERM	GENE RATIO	FDR	GENES
MF	GO:0004683	calcium/calmodulin-dependent protein kinase activity	1/1	0.006	MYLK2
MF	GO:0017022	myosin binding	1/1	0.008	MYLK2
BP	GO:0014816	skeletal muscle satellite cell differentiation	1/1	0.010	MYLK2
BP	GO:0030049	muscle filament sliding	1/1	0.010	MYLK2
BP	GO:0033275	actin-myosin filament sliding	1/1	0.010	MYLK2
BP	GO:0007274	neuromuscular synaptic transmission	1/1	0.010	MYLK2
BP	GO:0018107	peptidyl-threonine phosphorylation	1/1	0.010	MYLK2
BP	GO:0018210	peptidyl-threonine modification	1/1	0.010	MYLK2
BP	GO:1903115	regulation of actin filament-based movement	1/1	0.010	MYLK2
CC	GO:0030017	sarcomere	1/1	0.013	MYLK2
CC	GO:0030016	myofibril	1/1	0.013	MYLK2
CC	GO:0043292	contractile muscle fiber	1/1	0.013	MYLK2
BP	GO:0055008	cardiac muscle tissue morphogenesis	1/1	0.013	MYLK2
MF	GO:0005516	calmodulin binding	1/1	0.015	MYLK2
MF	GO:0004674	protein serine/threonine kinase activity	1/1	0.023	MYLK2

Showing the 15 most significant of 39 terms (max 5 per ontology; full breakdown: BP 32 · MF 4 · CC 3).
BP = biological process · MF = molecular function · CC = cellular component · FDR = p-value adjusted for multiple testing

Table 14 - GO enrichment for genes specific to PD (15 most significant of 39 terms).

3. RBD only. A single gene was specific to RBD (*CCDC62*), and no GO term was significant (Table 15).

GO enrichment – RBD only RBD

Genes in pattern: 1 · Significant GO terms (FDR < 0.05): 0 · Genes: *CCDC62*

ONT.	GO ID	GO TERM	GENE RATIO	FDR	GENES
No significant GO terms (FDR < 0.05)					

Table 15 - GO enrichment for genes specific to RBD.

All these GO enrichment analysis results are also summarized in *Supplementary materials* because of the length of some of these tables (Table S1 - S11 GO enrichment analysis).

CHAPTER 5 - Discussion

1. Summary of main findings

This study examined the spatial relationship between regional FDG-PET hypometabolism and the expression of GWAS risk genes across AD, PD, DLB and iRBD. Three principal findings were identified.

First, the extent of hypometabolism varied according to a clear severity gradient (DLB > AD > PD > RBD), while each condition retained a specific regional distribution.

Second, the genetic associations were predominantly shared across disorders. The 29 genes common to all four conditions converged on processes related to cytoskeletal anchoring and neurite development, including LRRK2, ANK3 and ADD1. A shared signature among AD, DLB and PD involved APP processing and synapse organisation, with APP, ADAM10 and APH1B contributing to this overlap.

Third, the four conditions displayed distinct patterns of genetic association. AD was the only disorder to exhibit a substantial disease-specific signature, comprising 45 genes enriched in endocytosis and lipid handling, including BIN1, CD2AP and ABCA7. PD showed shared enrichment in immune receptor signalling with RBD (CD33, PTPRC) and in clathrin-mediated endocytosis with DLB (APOE, PICALM). DLB, despite having no condition-specific genes, occupied an intermediate position between AD and PD. RBD shared MHC-binding pathways with PD and DLB, and chaperone and microglial pathways with AD, including CLU and SNCA.

2. FDG-PET patterns: comparison with existing literature

Overall, the FDG-PET findings observed in the present study are in agreement with previously described metabolic patterns from existing literature.

In **AD**, the temporoparietal distribution of hypometabolism is consistent with the classical pattern reported in the literature (Chételat et al., 2020). Posterior cingulate involvement was comparatively less pronounced than typically described, which may be related to the early disease stage represented in the cohort, since 81% of participants had a CDR of 0.5.

In **PD**, the posterior parietal and occipital reductions observed are comparable to the hypometabolic component of the PDRP (Meles et al., 2020). These abnormalities were detected despite preserved global cognitive performance, with a mean MMSE of 28.1.

In **DLB**, both occipital hypometabolism and the cingulate island sign were observed, consistent with the consensus criteria (McKeith et al., 2017). The involvement of occipital regions, which was almost absent in AD, distinguished the two dementias in accordance with previous observations (Caminiti et al., 2019).

Finally, although the metabolic reductions in **RBD** were mild, their distribution followed the same topographical pattern observed in PD and DLB. This finding is consistent with the existence of a metabolic continuum across α -synucleinopathies (Orso et al., 2026) and supports the potential utility of FDG-PET for risk stratification (Stefani et al., 2025).

3. Imaging-transcriptomic correlations: biological interpretation

The AHBA provides normative expression from six healthy brains, so a significant association means that regions where a gene is constitutively more, or less, expressed are the regions that are more hypometabolic in patients affected by neurodegenerative diseases. The approach therefore identifies molecular features of regional vulnerability rather than disease mechanisms in the strict sense (Martins et al., 2021). The Gene Ontology enrichment analysis results discussed below are presented in Figures 8–11.

3.1. Shared pathways between AD and synucleinopathies

1. AD+DLB+PD+RBD. Among the 29 genes shared across all four conditions were *LRRK2*, *RIT2* and *INPP5F*, all PD risk loci, together with *ADD1*, *ANK3* and *ADAM17* (Figure 8A).

RIT2 (Ras Like Without CAAX 2) and *INPP5F* (Inositol Polyphosphate-5-Phosphatase F), *ADAM17* (A Disintegrin and Metalloproteinase 17) are annotated to negative regulation of neuron projection development.

ANK3 (Ankyrin 3) and *ADD1* (Adducin 1) are key components of the spectrin–actin scaffold, where they contribute to the assembly and maintenance of the axon initial segment.

LRRK2 (Leucine-Rich Repeat Kinase 2) regulates cytoskeletal dynamics and vesicle trafficking.

Taken together, these genes converge on the neuronal cytoskeleton, linking membrane–cytoskeleton anchoring, axonal architecture and the control of neurite growth.

This shared core may therefore reflect a structural and axonal vulnerability that is already present during the prodromal stage, as indicated by the inclusion of RBD.

2. AD+DLB+PD. The strongest enrichment observed in the study involved APP catabolism (6/47 genes, FDR < 0.001) (Figure 8B).

This signal was driven by APP itself, the α -secretase ADAM10, the γ -secretase subunit APH1B, DYRK1A, EFNA1 and SLC2A13, together with ACE in amyloid- β metabolism.

The same gene set was also enriched for regulation of synapse and postsynapse organisation and dendritic spine organisation, involving AGRN, EFNA1, DOCK4, ABI3 and FCGR2B.

In DLB, this convergence is biologically plausible because amyloid co-pathology occurs in more than half of patients (McKeith et al., 2017). Since the PD cohort was cognitively unimpaired, the correspondence between amyloid-pathway genes and PD hypometabolism is unlikely to be explained by amyloid deposition. A more reasonable interpretation is that these genes identify association cortices that are rich in synapses and with high energetic demands, conferring metabolic vulnerability. Given that FDG uptake is largely determined by synaptic activity, and that APP processing is activity-dependent, the amyloid and synaptic enrichment terms may represent two aspects of the same regional characteristic.

A related observation was described by Habich et al. (2026), who found that regional expressions of APP, BIN1, GBA, MAPT, PINK1, SNCA and TMEM175 predicted grey matter atrophy in DLB. The present findings extend this observation from structural atrophy to metabolism and from DLB to PD.

Some of the enriched terms in this set, including regulation of blood circulation and heart contraction, are driven by genes with pleiotropic annotations, such as ACE, CAMK2D and PKP2. These terms should therefore be interpreted as annotation by-products rather than as evidence for cardiovascular involvement.

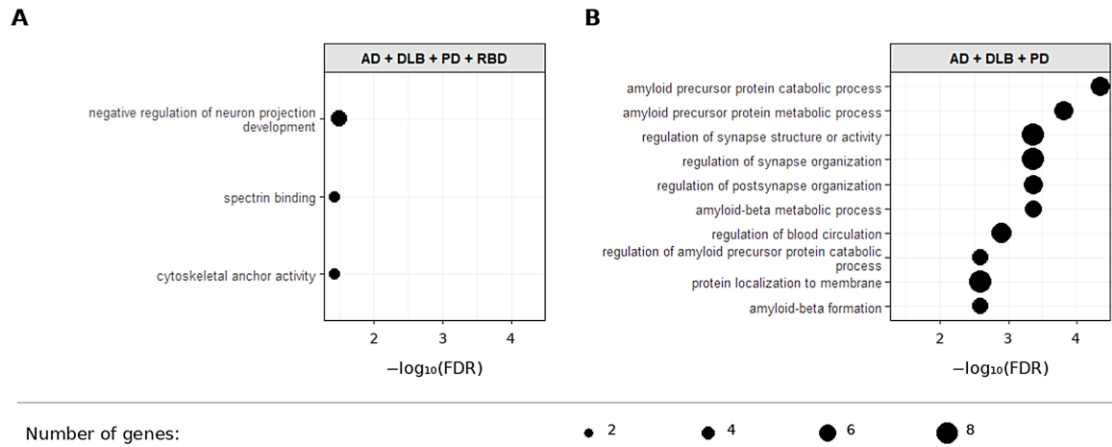


Figure 8 - GO enrichment of genes shared across multiple neurodegenerative conditions. (A) AD + DLB + PD + RBD; (B) AD + DLB + PD. Bubble size represents the number of genes; horizontal axis: $-\log_{10}(\text{FDR})$.

3. DLB-PD. No gene was exclusive to DLB, but all 123 genes associated with the condition were shared with either AD, PD or both. This distribution is compatible with the position of DLB between AD and PD from both clinical and genetic perspectives (Chia et al., 2021), and with the frequent coexistence of Lewy and AD pathology (Orso et al., 2026).

The genes shared exclusively with PD (APOE, PICALM, GAK) implicate clathrin-mediated endocytosis and lipoprotein receptor binding, thereby proving an additional connection between DLB and AD (Figure 9A).

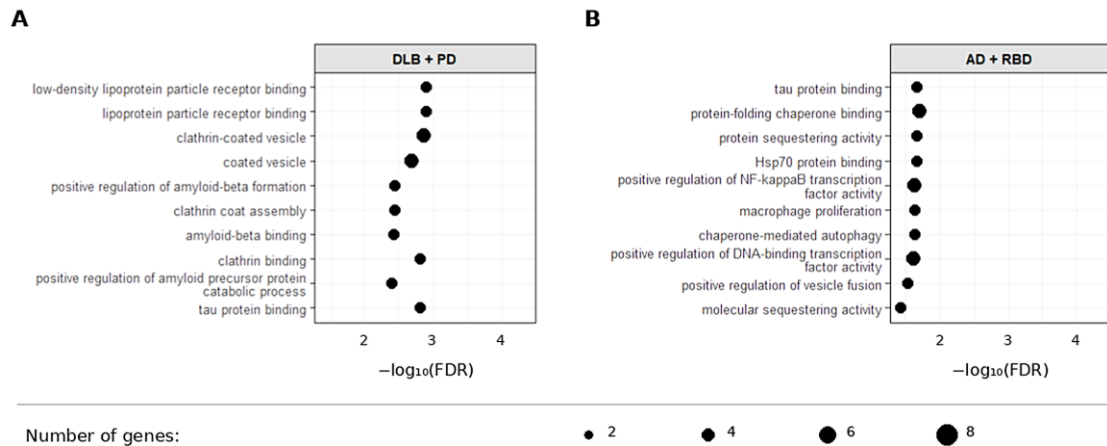


Figure 9 - GO enrichment of exact pairwise gene-sharing patterns. (A) DLB + PD; (B) AD + RBD. Panels represent two distinct pairwise overlaps; bubble size indicates the number of genes and horizontal axis indicates $-\log_{10}(\text{FDR})$.

4. DLB+PD+RBD. The genes shared between PD and RBD (CD33, FCGR2A, PTPRC, BLNK) were all annotated to immune receptor signalling, with additional enrichment for TNF production and Fc- γ receptor signalling. The genes showed enrichment for MHC protein complex binding, driven by HLA-DRB5 and LILRB2. HLA-DR variation is an established PD risk factor, while LILRB2 functions as a receptor for amyloid- β oligomers (Kim et al., 2013), providing a link between this immune-related axis and the amyloid theme (Figure 10A–B).

The inclusion of RBD in both immune-related patterns is particularly relevant from a clinical perspective. It suggests that the regions showing metabolic involvement in prodromal synucleinopathy are characterised by higher constitutive expression of immune genes. This interpretation is compatible with in vivo evidence of microglial activation in the substantia nigra of patients with isolated RBD.

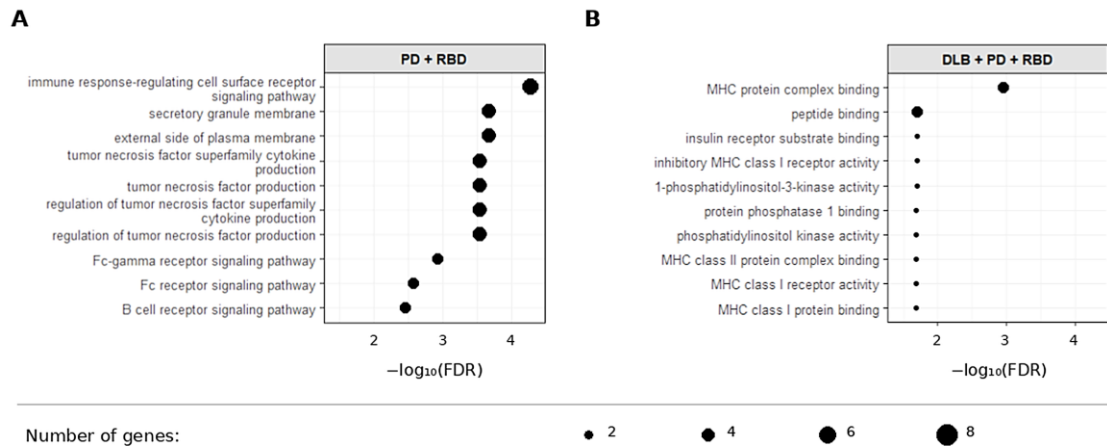


Figure 10 - GO enrichment of immune-related gene-sharing patterns in synucleinopathies. (A) PD + RBD; (B) DLB + PD + RBD. Bubble size represents the number of genes; horizontal axis: $-\log_{10}(\text{FDR})$.

5. AD+RBD. An unexpected finding was a group of 16 genes shared by AD and RBD, including SNCA, CLU, NOD2, GPNMB and IL34.

This set was enriched for chaperone binding, tau protein binding, chaperone-mediated autophagy and microglial activation. The observed overlap may be related to the subgroup of RBD patients who phenoconvert with dementia first (43.5% of converters; Postuma et al., 2019) (Figure 9B).

3.2. Disease-specific metabolic and genetic signatures

1. Alzheimer's disease. AD had a substantial exclusive signature, comprising 45 genes. These genes were enriched for actin filament and clathrin binding (BIN1, CD2AP, HIP1R, FERMT2, ARHGAP27), as well as lipid-protein complex assembly (ABCA7, APOC1, BIN1). Endocytosis and lipid metabolism represent two major functional axes emerging from AD GWAS (Bellenguez et al., 2022). Their spatial correspondence with AD hypometabolism suggests that the regions most affected during the early stages of AD are also those in which endocytic and lipid-handling machinery is most highly expressed. Part of this apparent

specificity may, however, be attributable to the greater spatial extent of the AD map, which provides more spatial variance with which gene expression patterns can align (Figure 11A).

2. Parkinson's disease. Within the PD pattern, only two genes, *IQCK* (IQ Motif Containing K) and *MYLK2* (Myosin Light Chain Kinase 2), were uniquely identified, whereas 97 of the 99 associated genes were also shared with at least one other condition. All 39 enriched terms were attributable exclusively to *MYLK2* and related to muscle contraction and calcium/calmodulin-dependent kinase activity (Figure 11B).

The other unique gene, *IQCK*, was not represented in any enriched term and has previously been identified as an AD risk locus (Kunkle et al., 2019).

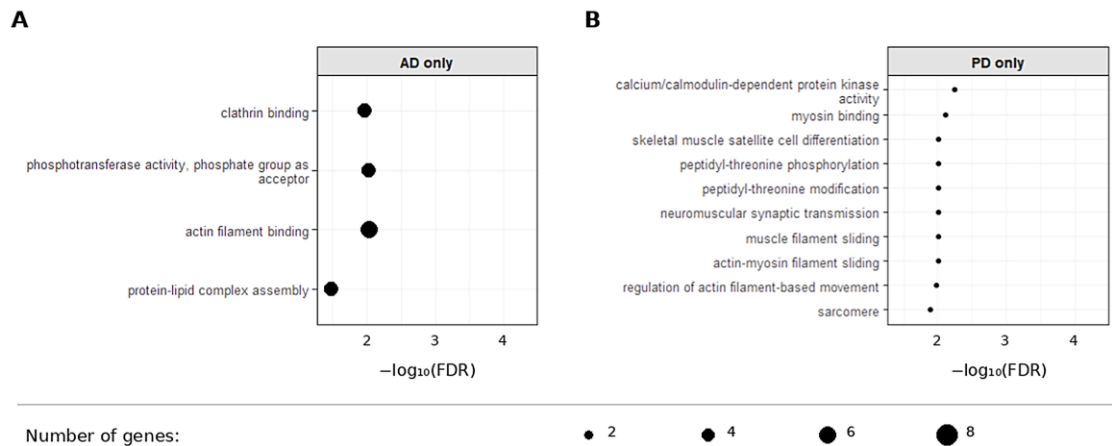


Figure 11 - GO enrichment of disease-specific genes. (A) AD only; (B) PD only. The PD-only enrichment is driven by *MYLK2* alone. Bubble size represents the number of genes; horizontal axis: $-\log_{10}(\text{FDR})$.

3. DLB and iRBD. No distinct molecular signature emerged for either condition. In DLB, none of the 123 genes identified in association with its pattern were exclusive to the disease, as the entire gene set was shared. This finding is in line with the intermediate clinical and genetic position of DLB relative to these two disorders (Chia et al., 2021).

For iRBD, only one gene, *CCDC62* (Coiled-Coil Domain Containing 62 protein), was uniquely identified; however, it was not associated with any enriched term, whereas the

remaining 55 genes were shared across the other conditions. This pattern is consistent with the characterization of iRBD as a prodromal state rather than an independent disease entity (Postuma et al., 2019).

4. Strengths and limitations of the study

Several strengths and limitations became apparent during study design and the subsequent analytical procedures, and these should be considered when interpreting the results.

Strengths

1. The four conditions, including a prodromal synucleinopathy iRBD, were examined at a single centre using the same scanner, acquisition protocol, and preprocessing pipeline, with all conditions evaluated against a common control group.
2. A total of 327 subjects were included, constituting a relatively large sample for a multi-disease FDG-PET study.
3. Gene selection was limited to risk genes identified through GWAS, thereby enabling the findings to be interpreted directly in relation to the genetic basis of the diseases.
4. Spatial permutation testing was used to account for spatial autocorrelation, which can lead to inflated estimates in naive correlations between brain maps (Alexander-Bloch et al., 2018).

Limitations

1. AHBA expression data are based on six post-mortem brains obtained from healthy donors, and right-hemisphere samples were available for only two individuals. The resulting atlas therefore reflects normative gene expression and does not capture

either disease-related or interindividual variability in gene expression (Arnatkeviciute et al., 2019).

2. As the four metabolic maps are not statistically independent, part of the observed overlap in gene associations may reflect similarities between the maps themselves rather than a shared genetic architecture.
3. The spin test was originally developed for cortical surface data; consequently, its use with a volumetric atlas that includes both subcortical and cerebellar regions may be suboptimal (Markello & Misic, 2021).

5. Clinical and translational implications

Although these findings do not have a direct diagnostic application, they carry three principal implications.

1. The substantial component shared among the conditions reinforces the view of neurodegenerative diseases as biologically overlapping entities, consistent with the frequent coexistence of mixed pathology. This supports the use of biomarker-based approaches to identify co-pathology, including amyloid and α -synuclein seed amplification.
2. The detection of an immune-related signal as early as RBD further identifies immune pathways as potential therapeutic targets during the prodromal window, when patients generally remain untreated (Stefani et al., 2025).

3. Finally, the convergence of amyloid- and synaptic-related signals across AD, DLB and PD suggests that amyloid-targeting strategies could potentially also be relevant for DLB patients with documented amyloid co-pathology.

6. Future directions

Future studies could build on this work in several ways.

1. Longitudinal follow-up of RBD patients should be undertaken to establish whether an AD-like or PD-like gene profile predicts subsequent phenoconversion to dementia or parkinsonism.
2. The use of group-level subtraction maps does not capture individual heterogeneity, including that associated with atypical AD variants and PD subtypes.
3. Replication should be performed in independent cohorts (e.g. ADNI, PPMI), using finer parcellations and surface-based or variogram-matched null models (Burt et al., 2020).

CHAPTER 6 – Conclusion

The present study identifies a precise and statistically significant topographic correspondence between the spatial distribution of in vivo metabolic impairment measured by FDG-PET and the constitutive baseline expression of a core set of risk genes, comprising APP, ADAM10, MAPT, CLU, BIN1 and LRRK2. Of the 192 genes reaching statistical significance, the majority were shared across at least two conditions. AD was the only condition to exhibit a substantial disease-specific molecular signature, while DLB showed no exclusive genes and iRBD was associated with only one.

These findings indicate that regional glucose metabolism is associated with potential molecular mechanisms underlying damage in both AD and α -synucleinopathies. They demonstrate, through imaging transcriptomics, that these same areas are associated with molecular processes involved in the production, macromolecular assembly and clearance of toxic proteins. Across AD, PD and DLB, these processes encompass APP processing and synaptic organisation, while endocytic trafficking and lipid handling were identified in AD, and chaperone activity in AD and iRBD. Within the α -synuclein spectrum, including prodromal iRBD stage, immune and antigen-presentation pathways provide an additional component of this molecular profile.

Accordingly, FDG-PET hypometabolism may represent an epiphenomenon of a local disruption of proteostasis.

Under this interpretation, regions with greater dependence on protein-handling processes and immune surveillance may be more susceptible to metabolic dysfunction.

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A Supplementary materials

1. Table S1 - MMSE slope

ROI	β std (IC 95%)	SE	t	p	p FDR
R Cerebellum 10	-0.29 (-0.53; -0.04)	0.123	-2.34	0.023	0.803
L Inferior parietal but supramarginal and angular gyri	0.34 (0.04; 0.63)	0.147	2.30	0.025	0.803
L Superior temporal gyrus	0.31 (0.03; 0.58)	0.137	2.24	0.028	0.803
L Postcentral gyrus	0.31 (0.02; 0.60)	0.147	2.12	0.038	0.803
L Cerebellum 10	-0.25 (-0.50; -0.00)	0.124	-2.01	0.049	0.803
Vermis 6	-0.25 (-0.51; 0.01)	0.131	-1.90	0.062	0.803
L Middle temporal gyrus	0.25 (-0.02; 0.51)	0.134	1.84	0.070	0.803
R Postcentral gyrus	0.24 (-0.02; 0.51)	0.132	1.83	0.072	0.803
R Cerebellum Crus2	-0.21 (-0.46; 0.05)	0.129	-1.60	0.115	0.803
R Inferior parietal but supramarginal and angular gyri	0.22 (-0.06; 0.49)	0.139	1.57	0.123	0.803
R Precuneus	-0.24 (-0.55; 0.07)	0.156	-1.53	0.132	0.803
R Cerebellum Crus1	-0.20 (-0.47; 0.06)	0.134	-1.52	0.132	0.803
Vermis 1 2	-0.19 (-0.44; 0.07)	0.125	-1.48	0.145	0.803
R Orbitofrontal cortex posterior	-0.21 (-0.50; 0.08)	0.144	-1.46	0.149	0.803
L Precuneus	-0.21 (-0.50; 0.09)	0.148	-1.39	0.168	0.803
R Supplementary motor area (Frontal lobe Medial Surface)	-0.18 (-0.44; 0.08)	0.129	-1.38	0.173	0.803
L Cerebellum 8	-0.18 (-0.44; 0.08)	0.131	-1.37	0.175	0.803
R Middle frontal gyrus	-0.17 (-0.42; 0.08)	0.126	-1.35	0.181	0.803
L Inferior frontal gyrus orbital part	0.18 (-0.09; 0.45)	0.135	1.34	0.184	0.803
L Superior frontal gyrus medial orbital	-0.18 (-0.45; 0.09)	0.135	-1.34	0.186	0.803
R Fusiform gyrus	0.17 (-0.09; 0.42)	0.127	1.32	0.191	0.803
R Middle temporal gyrus	0.17 (-0.09; 0.43)	0.131	1.32	0.192	0.803
R Superior frontal gyrus medial orbital	-0.19 (-0.48; 0.10)	0.145	-1.31	0.193	0.803
L Fusiform gyrus	0.18 (-0.10; 0.46)	0.139	1.31	0.196	0.803
R Lingual gyrus	0.17 (-0.09; 0.44)	0.135	1.29	0.200	0.803
R Cuneus	0.16 (-0.10; 0.42)	0.130	1.23	0.225	0.803
R Middle frontal gyrus orbital part	-0.16 (-0.43; 0.11)	0.134	-1.21	0.231	0.803
L Cerebellum Crus2	-0.15 (-0.41; 0.10)	0.129	-1.20	0.234	0.803
R Superior frontal gyrus orbital part	-0.16 (-0.44; 0.11)	0.137	-1.18	0.242	0.803
L Cerebellum 7b	-0.15 (-0.40; 0.11)	0.127	-1.16	0.250	0.803
L Temporal pole middle temporal gyrus	-0.14 (-0.39; 0.10)	0.125	-1.16	0.251	0.803

ROI	β std (IC 95%)	SE	t	p	p FDR
L Superior parietal gyrus	0.17 (-0.13; 0.47)	0.148	1.15	0.255	0.803
R Cerebelum 9	-0.15 (-0.42; 0.12)	0.135	-1.14	0.257	0.803
L Cerebelum Crus1	-0.15 (-0.41; 0.11)	0.131	-1.13	0.265	0.803
L Orbitofrontal cortex lateral	-0.15 (-0.43; 0.12)	0.140	-1.11	0.273	0.803
R Superior parietal gyrus	0.15 (-0.12; 0.42)	0.136	1.10	0.274	0.803
L Lenticular nucleus putamen	-0.14 (-0.40; 0.12)	0.130	-1.09	0.280	0.803
R Cerebelum 8	-0.14 (-0.40; 0.12)	0.130	-1.08	0.286	0.803
R Paracentral lobule	-0.14 (-0.39; 0.12)	0.128	-1.07	0.286	0.803
R Superior frontal gyrus medial	-0.14 (-0.41; 0.13)	0.133	-1.05	0.298	0.803
R Cerebelum 3	-0.13 (-0.38; 0.12)	0.127	-1.01	0.314	0.803
L Cuneus	0.14 (-0.13; 0.40)	0.134	1.01	0.315	0.803
L Paracentral lobule	-0.13 (-0.38; 0.13)	0.127	-1.00	0.320	0.803
R Posterior cingulate gyrus	-0.14 (-0.42; 0.14)	0.141	-1.00	0.323	0.803
L Middle frontal gyrus orbital part	-0.12 (-0.38; 0.13)	0.129	-0.96	0.342	0.803
L Insula	-0.13 (-0.42; 0.15)	0.145	-0.93	0.355	0.803
R Superior occipital gyrus	0.13 (-0.15; 0.41)	0.139	0.93	0.355	0.803
R Orbitofrontal cortex lateral	-0.14 (-0.43; 0.16)	0.147	-0.92	0.361	0.803
Vermis 4 5	-0.12 (-0.37; 0.14)	0.127	-0.92	0.363	0.803
L Lingual gyrus	0.13 (-0.16; 0.41)	0.142	0.90	0.369	0.803
L Inferior frontal gyrus triangular part	0.13 (-0.16; 0.42)	0.146	0.89	0.378	0.803
Vermis 4	-0.11 (-0.36; 0.14)	0.126	-0.87	0.389	0.803
L Cerebelum 3	-0.11 (-0.36; 0.14)	0.127	-0.85	0.396	0.803
R Temporal pole middle temporal gyrus	-0.11 (-0.36; 0.14)	0.126	-0.85	0.400	0.803
R Angular gyrus	-0.11 (-0.36; 0.15)	0.126	-0.84	0.404	0.803
R Superior temporal gyrus	0.11 (-0.16; 0.38)	0.134	0.84	0.404	0.803
L Cerebelum 6	-0.10 (-0.35; 0.15)	0.125	-0.83	0.407	0.803
R Insula	-0.12 (-0.42; 0.17)	0.148	-0.83	0.408	0.803
L Inferior temporal gyrus	-0.10 (-0.36; 0.15)	0.127	-0.82	0.416	0.803
R Heschl gyrus	-0.12 (-0.42; 0.18)	0.149	-0.81	0.420	0.803
R Lenticular nucleus putamen	-0.12 (-0.41; 0.17)	0.145	-0.81	0.422	0.803
L Rolandic operculum	0.10 (-0.16; 0.37)	0.133	0.78	0.437	0.807
L Cerebelum 9	-0.11 (-0.38; 0.17)	0.137	-0.78	0.439	0.807
R Cerebelum 6	-0.09 (-0.34; 0.15)	0.124	-0.76	0.450	0.815

ROI	β std (IC 95%)	SE	t	p	p FDR
L Angular gyrus	-0.09 (-0.35; 0.16)	0.128	-0.71	0.479	0.824
L Superior frontal gyrus orbital part	-0.09 (-0.35; 0.17)	0.130	-0.71	0.481	0.824
R Supramarginal gyrus	0.09 (-0.17; 0.35)	0.130	0.71	0.483	0.824
R Inferior temporal gyrus	-0.09 (-0.34; 0.16)	0.125	-0.71	0.483	0.824
L Supramarginal gyrus	0.09 (-0.18; 0.37)	0.137	0.67	0.505	0.850
R Cerebelum 7b	-0.08 (-0.34; 0.17)	0.128	-0.66	0.513	0.851
L Superior occipital gyrus	0.09 (-0.19; 0.38)	0.143	0.64	0.523	0.854
R Inferior frontal gyrus opercular part	-0.08 (-0.33; 0.18)	0.128	-0.60	0.549	0.869
R Olfactory cortex	-0.09 (-0.38; 0.20)	0.146	-0.60	0.550	0.869
L Temporal pole superior temporal gyrus	-0.08 (-0.35; 0.19)	0.136	-0.59	0.554	0.869
R Hippocampus	-0.08 (-0.34; 0.19)	0.134	-0.58	0.565	0.874
L Cerebelum 4 5	-0.07 (-0.32; 0.18)	0.125	-0.55	0.582	0.889
R Cerebelum 4 5	-0.06 (-0.31; 0.19)	0.125	-0.51	0.614	0.915
R Temporal pole superior temporal gyrus	-0.07 (-0.36; 0.22)	0.144	-0.51	0.615	0.915
L Superior frontal gyrus dorsolateral	0.07 (-0.22; 0.36)	0.145	0.49	0.627	0.921
R Gyrus rectus	-0.07 (-0.35; 0.22)	0.142	-0.47	0.639	0.922
L Caudate nucleus	-0.05 (-0.31; 0.20)	0.126	-0.43	0.666	0.922
L Supplementary motor area (Frontal lobe Medial Surface)	-0.06 (-0.32; 0.21)	0.133	-0.42	0.674	0.922
R Median cingulate and paracingulate gyri	-0.06 (-0.34; 0.22)	0.141	-0.42	0.677	0.922
L Precentral gyrus	0.05 (-0.22; 0.32)	0.135	0.40	0.692	0.922
R Calcarine fissure and surrounding cortex	-0.05 (-0.33; 0.22)	0.138	-0.39	0.696	0.922
L Hippocampus	-0.05 (-0.31; 0.21)	0.131	-0.39	0.699	0.922
R Caudate nucleus	-0.05 (-0.31; 0.21)	0.129	-0.39	0.699	0.922
L Thalamus	0.05 (-0.23; 0.34)	0.141	0.39	0.700	0.922
R Amygdala	0.05 (-0.22; 0.32)	0.133	0.38	0.707	0.922
L Posterior cingulate gyrus	-0.05 (-0.33; 0.23)	0.138	-0.36	0.721	0.929
L Orbitofrontal cortex posterior	-0.05 (-0.36; 0.25)	0.152	-0.34	0.734	0.934
L Middle frontal gyrus	-0.04 (-0.30; 0.22)	0.129	-0.32	0.752	0.934
L Superior frontal gyrus medial	-0.04 (-0.31; 0.23)	0.133	-0.30	0.762	0.934
L Heschl gyrus	-0.04 (-0.33; 0.25)	0.145	-0.30	0.763	0.934
R Inferior frontal gyrus triangular part	0.04 (-0.24; 0.33)	0.142	0.30	0.765	0.934
L Inferior frontal gyrus opercular part	0.04 (-0.23; 0.30)	0.132	0.27	0.791	0.948
R Rolandic operculum	-0.03 (-0.30; 0.24)	0.133	-0.23	0.820	0.948

ROI	β std (IC 95%)	SE	t	p	p FDR
R Inferior frontal gyrus orbital part	0.03 (-0.24; 0.30)	0.136	0.21	0.838	0.948
L Gyrus rectus	-0.03 (-0.31; 0.25)	0.139	-0.20	0.839	0.948
R Thalamus	0.03 (-0.25; 0.31)	0.139	0.20	0.841	0.948
L Olfactory cortex	-0.03 (-0.31; 0.26)	0.142	-0.20	0.842	0.948
L Calcarine fissure and surrounding cortex	-0.03 (-0.30; 0.25)	0.136	-0.19	0.850	0.948
R Parahippocampal gyrus	-0.03 (-0.30; 0.25)	0.136	-0.19	0.852	0.948
L Parahippocampal gyrus	-0.03 (-0.29; 0.24)	0.134	-0.19	0.852	0.948
L Lenticular nucleus pallidum	-0.03 (-0.31; 0.26)	0.144	-0.18	0.859	0.948
R Inferior occipital gyrus	0.02 (-0.24; 0.29)	0.133	0.17	0.866	0.948
R Anterior cingulate and paracingulate gyri	-0.02 (-0.28; 0.24)	0.128	-0.15	0.878	0.951
R Precentral gyrus	0.02 (-0.24; 0.28)	0.129	0.14	0.887	0.953
L Median cingulate and paracingulate gyri	0.02 (-0.26; 0.30)	0.141	0.12	0.902	0.960
L Inferior occipital gyrus	-0.01 (-0.28; 0.26)	0.135	-0.10	0.919	0.964
R Middle occipital gyrus	-0.01 (-0.29; 0.26)	0.137	-0.10	0.922	0.964
L Middle occipital gyrus	0.01 (-0.26; 0.27)	0.133	0.06	0.954	0.988
L Amygdala	0.01 (-0.26; 0.27)	0.134	0.04	0.970	0.994
R Superior frontal gyrus dorsolateral	0.00 (-0.26; 0.27)	0.134	0.02	0.982	0.994
L Anterior cingulate and paracingulate gyri	-0.00 (-0.28; 0.28)	0.139	-0.02	0.986	0.994
R Lenticular nucleus pallidum	0.00 (-0.30; 0.30)	0.150	0.01	0.994	0.994

Regressione lineare: MMSE slope standardizzato ~ FDG-ROI standardizzato + età + sesso + MMSE basale ($n = 69$). β std = coefficiente standardizzato; IC = intervallo di confidenza; p FDR = corretto con Benjamini-Hochberg sulle 116 ROI. $\beta > 0$: metabolismo più alto associato a declino cognitivo più lento. Nessuna ROI significativa dopo correzione FDR: risultati da considerarsi esplorativi.

2. Table S2 - A β 42/40 ratio

Tabella S2. Risultati completi A β 42/40 (1/4)					
ROI	β std (IC 95%)	SE	t	p	p FDR
L Inferior frontal gyrus orbital part	-0.44 (-0.71; -0.17)	0.132	-3.35	0.002	0.113
L Insula	-0.40 (-0.66; -0.13)	0.129	-3.07	0.004	0.113
L Superior parietal gyrus	-0.41 (-0.69; -0.13)	0.137	-2.97	0.005	0.113
L Lenticular nucleus putamen	-0.46 (-0.76; -0.17)	0.145	-3.19	0.003	0.113
R Lenticular nucleus putamen	-0.37 (-0.62; -0.11)	0.125	-2.94	0.006	0.113
L Superior temporal gyrus	-0.39 (-0.66; -0.13)	0.129	-3.05	0.004	0.113
L Superior frontal gyrus dorsolateral	-0.37 (-0.65; -0.10)	0.135	-2.77	0.009	0.119
L Inferior frontal gyrus triangular part	-0.38 (-0.66; -0.10)	0.138	-2.72	0.010	0.119
L Inferior parietal but supramarginal and angular gyri	-0.38 (-0.65; -0.10)	0.136	-2.77	0.009	0.119
L Thalamus	-0.39 (-0.67; -0.10)	0.140	-2.76	0.009	0.119
L Rolandic operculum	-0.39 (-0.69; -0.09)	0.148	-2.62	0.013	0.124
L Anterior cingulate and paracingulate gyri	-0.37 (-0.66; -0.08)	0.143	-2.59	0.014	0.124
L Middle temporal gyrus	-0.36 (-0.63; -0.08)	0.135	-2.65	0.012	0.124
R Inferior frontal gyrus orbital part	-0.36 (-0.65; -0.07)	0.144	-2.49	0.018	0.149
R Insula	-0.32 (-0.58; -0.05)	0.130	-2.44	0.020	0.155
R Superior frontal gyrus dorsolateral	-0.33 (-0.62; -0.04)	0.144	-2.29	0.028	0.196
R Rolandic operculum	-0.33 (-0.62; -0.04)	0.144	-2.28	0.029	0.196
L Precentral gyrus	-0.32 (-0.61; -0.02)	0.144	-2.20	0.034	0.202
L Olfactory cortex	-0.32 (-0.62; -0.02)	0.147	-2.20	0.035	0.202
L Superior frontal gyrus medial	-0.32 (-0.62; -0.03)	0.145	-2.23	0.033	0.202
L Supplementary motor area (Frontal lobe Medial Surface)	-0.32 (-0.63; -0.00)	0.154	-2.05	0.048	0.238
L Orbitofrontal cortex posterior	-0.29 (-0.58; -0.00)	0.141	-2.04	0.049	0.238
L Precuneus	-0.30 (-0.58; -0.01)	0.142	-2.08	0.045	0.238
L Caudate nucleus	-0.33 (-0.65; -0.01)	0.159	-2.07	0.046	0.238
R Olfactory cortex	-0.28 (-0.57; 0.02)	0.144	-1.91	0.065	0.268
L Gyrus rectus	-0.26 (-0.54; 0.02)	0.138	-1.91	0.064	0.268
L Postcentral gyrus	-0.26 (-0.55; 0.02)	0.139	-1.91	0.064	0.268
R Caudate nucleus	-0.30 (-0.62; 0.02)	0.155	-1.94	0.061	0.268
R Supplementary motor area (Frontal lobe Medial Surface)	-0.28 (-0.59; 0.03)	0.152	-1.86	0.072	0.283
L Parahippocampal gyrus	-0.26 (-0.55; 0.03)	0.141	-1.85	0.073	0.283
R Inferior frontal gyrus triangular part	-0.27 (-0.58; 0.03)	0.150	-1.82	0.078	0.283
L Heschl gyrus	-0.27 (-0.57; 0.03)	0.148	-1.83	0.076	0.283
L Inferior frontal gyrus opercular part	-0.27 (-0.60; 0.05)	0.161	-1.70	0.099	0.322
L Orbitofrontal cortex lateral	-0.25 (-0.55; 0.04)	0.146	-1.73	0.093	0.322
L Lenticular nucleus pallidum	-0.24 (-0.52; 0.05)	0.140	-1.70	0.099	0.322

Regressione lineare: FDG-ROI standardizzato ~ biomcatore standardizzato + età + sesso. β std = coefficiente standardizzato; IC = intervallo di confidenza; p FDR = p corretto con Benjamini-Hochberg sulle 116 ROI.

Tabella S2. Risultati completi A β 42/40 (2/4)

ROI	β std (IC 95%)	SE	t	p	p FDR
R Temporal pole middle temporal gyrus	-0.27 (-0.60; 0.06)	0.162	-1.69	0.100	0.322
R Precentral gyrus	-0.26 (-0.58; 0.06)	0.157	-1.65	0.108	0.339
R Lenticular nucleus pallidum	-0.23 (-0.51; 0.05)	0.139	-1.64	0.111	0.339
L Temporal pole middle temporal gyrus	-0.25 (-0.58; 0.08)	0.163	-1.53	0.136	0.406
L Calcarine fissure and surrounding cortex	-0.24 (-0.56; 0.08)	0.158	-1.51	0.140	0.407
L Middle frontal gyrus	-0.22 (-0.55; 0.12)	0.164	-1.33	0.192	0.457
L Middle frontal gyrus orbital part	-0.23 (-0.56; 0.10)	0.163	-1.42	0.164	0.457
R Orbitofrontal cortex lateral	-0.19 (-0.47; 0.10)	0.140	-1.35	0.185	0.457
L Amygdala	-0.22 (-0.55; 0.10)	0.160	-1.39	0.174	0.457
L Cuneus	-0.22 (-0.54; 0.11)	0.161	-1.34	0.191	0.457
L Lingual gyrus	-0.22 (-0.53; 0.10)	0.156	-1.40	0.171	0.457
R Paracentral lobule	-0.21 (-0.55; 0.12)	0.163	-1.32	0.196	0.457
L Temporal pole superior temporal gyrus	-0.21 (-0.53; 0.11)	0.158	-1.32	0.197	0.457
R Inferior temporal gyrus	-0.22 (-0.56; 0.12)	0.166	-1.33	0.192	0.457
L Cerebellum 9	-0.21 (-0.54; 0.12)	0.163	-1.30	0.201	0.457
Vermis 6	-0.21 (-0.53; 0.11)	0.159	-1.33	0.193	0.457
L Superior frontal gyrus orbital part	-0.20 (-0.53; 0.12)	0.160	-1.26	0.216	0.464
R Superior frontal gyrus orbital part	-0.19 (-0.50; 0.11)	0.151	-1.28	0.210	0.464
L Inferior temporal gyrus	-0.21 (-0.54; 0.13)	0.164	-1.26	0.215	0.464
R Superior frontal gyrus medial	-0.18 (-0.48; 0.12)	0.146	-1.23	0.226	0.477
R Orbitofrontal cortex posterior	-0.18 (-0.48; 0.12)	0.148	-1.22	0.233	0.482
L Inferior occipital gyrus	-0.18 (-0.49; 0.13)	0.154	-1.17	0.250	0.508
R Middle frontal gyrus orbital part	-0.18 (-0.49; 0.14)	0.155	-1.13	0.267	0.525
L Cerebellum 3	-0.19 (-0.53; 0.15)	0.167	-1.13	0.266	0.525
R Middle frontal gyrus	-0.18 (-0.51; 0.15)	0.163	-1.10	0.279	0.530
R Cerebellum 7b	-0.18 (-0.51; 0.15)	0.164	-1.11	0.275	0.530
L Hippocampus	-0.18 (-0.51; 0.16)	0.166	-1.06	0.296	0.536
R Precuneus	-0.15 (-0.43; 0.13)	0.138	-1.07	0.290	0.536
L Cerebellum 4 5	-0.18 (-0.52; 0.16)	0.168	-1.06	0.296	0.536
Vermis 4 5	-0.17 (-0.51; 0.16)	0.165	-1.04	0.303	0.541
L Cerebellum Crus2	-0.17 (-0.50; 0.16)	0.164	-1.03	0.309	0.542
L Paracentral lobule	-0.17 (-0.50; 0.17)	0.165	-1.01	0.318	0.551
L Superior frontal gyrus medial orbital	-0.15 (-0.47; 0.17)	0.157	-0.94	0.351	0.558
L Median cingulate and paracingulate gyri	-0.15 (-0.48; 0.17)	0.161	-0.95	0.350	0.558
L Middle occipital gyrus	-0.15 (-0.46; 0.17)	0.154	-0.96	0.344	0.558

Regressione lineare: FDG-ROI standardizzato ~ biomcatore standardizzato + età + sesso. β std = coefficiente standardizzato; IC = intervallo di confidenza; p FDR = p corretto con Benjamini-Hochberg sulle 116 ROI.

Tabella S2. Risultati completi A β 42/40 (3/4)

ROI	β std (IC 95%)	SE	t	p	p FDR
R Superior parietal gyrus	-0.16 (-0.49; 0.18)	0.166	-0.95	0.346	0.558
R Cerebelum 4 5	-0.16 (-0.50; 0.18)	0.169	-0.95	0.348	0.558
R Cerebelum 9	-0.16 (-0.50; 0.17)	0.165	-0.98	0.335	0.558
R Thalamus	-0.14 (-0.45; 0.17)	0.151	-0.92	0.364	0.562
R Cerebelum 3	-0.16 (-0.50; 0.18)	0.167	-0.93	0.360	0.562
R Gyrus rectus	-0.12 (-0.40; 0.16)	0.136	-0.88	0.384	0.582
R Parahippocampal gyrus	-0.12 (-0.41; 0.16)	0.142	-0.88	0.386	0.582
R Inferior frontal gyrus opercular part	-0.14 (-0.47; 0.20)	0.166	-0.82	0.420	0.622
R Hippocampus	-0.13 (-0.46; 0.20)	0.163	-0.80	0.429	0.622
L Supramarginal gyrus	-0.13 (-0.46; 0.20)	0.161	-0.81	0.426	0.622
L Fusiform gyrus	-0.12 (-0.46; 0.21)	0.165	-0.75	0.456	0.645
L Cerebelum Crus1	-0.12 (-0.46; 0.21)	0.165	-0.76	0.455	0.645
R Superior frontal gyrus medial orbital	-0.10 (-0.42; 0.22)	0.156	-0.64	0.524	0.724
R Anterior cingulate and paracingulate gyri	-0.10 (-0.44; 0.24)	0.166	-0.61	0.543	0.724
L Posterior cingulate gyrus	-0.09 (-0.42; 0.23)	0.160	-0.58	0.563	0.724
L Superior occipital gyrus	-0.09 (-0.41; 0.23)	0.159	-0.58	0.568	0.724
R Inferior occipital gyrus	-0.10 (-0.43; 0.22)	0.160	-0.63	0.534	0.724
R Inferior parietal but supramarginal and angular gyri	-0.10 (-0.44; 0.24)	0.168	-0.60	0.550	0.724
L Angular gyrus	-0.10 (-0.44; 0.23)	0.166	-0.63	0.534	0.724
L Cerebelum 6	-0.10 (-0.44; 0.25)	0.169	-0.58	0.567	0.724
Vermis 4	-0.10 (-0.44; 0.24)	0.167	-0.61	0.547	0.724
R Heschl gyrus	-0.08 (-0.39; 0.22)	0.150	-0.56	0.581	0.733
R Fusiform gyrus	0.08 (-0.27; 0.42)	0.171	0.45	0.658	0.821
R Middle occipital gyrus	-0.07 (-0.39; 0.25)	0.158	-0.44	0.665	0.821
R Lingual gyrus	-0.07 (-0.42; 0.27)	0.170	-0.42	0.678	0.824
R Cerebelum 6	-0.07 (-0.42; 0.28)	0.170	-0.41	0.682	0.824
R Cerebelum 10	0.06 (-0.27; 0.40)	0.166	0.39	0.699	0.836
R Cuneus	-0.06 (-0.41; 0.29)	0.171	-0.36	0.718	0.850
R Median cingulate and paracingulate gyri	-0.06 (-0.38; 0.27)	0.160	-0.35	0.728	0.853
R Amygdala	-0.04 (-0.38; 0.29)	0.164	-0.27	0.788	0.876
R Calcarine fissure and surrounding cortex	-0.05 (-0.38; 0.28)	0.161	-0.29	0.771	0.876
R Postcentral gyrus	-0.05 (-0.39; 0.29)	0.166	-0.30	0.768	0.876
R Angular gyrus	-0.04 (-0.38; 0.29)	0.165	-0.26	0.793	0.876
R Cerebelum Crus2	-0.05 (-0.40; 0.29)	0.169	-0.30	0.763	0.876
L Cerebelum 7b	-0.05 (-0.39; 0.30)	0.169	-0.27	0.786	0.876

Regressione lineare: FDG-ROI standardizzato ~ biomcatore standardizzato + età + sesso. β std = coefficiente standardizzato; IC = intervallo di confidenza; p FDR = p corretto con Benjamini-Hochberg sulle 116 ROI.

Tabella S2. Risultati completi A β 42/40 (4/4)

ROI	β std (IC 95%)	SE	t	p	p FDR
R Posterior cingulate gyrus	-0.03 (-0.34; 0.29)	0.156	-0.17	0.868	0.928
R Superior temporal gyrus	-0.03 (-0.37; 0.32)	0.168	-0.15	0.880	0.928
R Middle temporal gyrus	0.03 (-0.30; 0.35)	0.161	0.16	0.873	0.928
R Cerebellum Crus1	-0.03 (-0.37; 0.31)	0.167	-0.18	0.860	0.928
R Cerebellum 8	0.03 (-0.30; 0.35)	0.162	0.16	0.876	0.928
L Cerebellum 10	0.02 (-0.32; 0.37)	0.168	0.14	0.889	0.929
Vermis 1 2	-0.02 (-0.36; 0.32)	0.167	-0.12	0.904	0.936
R Suparmarginal gyrus	-0.00 (-0.34; 0.33)	0.167	-0.03	0.977	0.988
R Temporal pole superior temporal gyrus	-0.00 (-0.32; 0.31)	0.156	-0.03	0.979	0.988
L Cerebellum 8	0.01 (-0.33; 0.34)	0.165	0.04	0.971	0.988
R Superior occipital gyrus	-0.00 (-0.35; 0.35)	0.170	-0.00	0.999	0.999

Regressione lineare: FDG-ROI standardizzato ~ biomcatore standardizzato + età + sesso. β std = coefficiente standardizzato; IC = intervallo di confidenza; p FDR = p corretto con Benjamini-Hochberg sulle 116 ROI.

3. Table S3 - T-tau

Tabella S1. Risultati completi T-tau (1/4)					
ROI	β std (IC 95%)	SE	t	p	p FDR
L Olfactory cortex	0.37 (0.07; 0.68)	0.151	2.47	0.019	0.588
R Olfactory cortex	0.34 (0.04; 0.64)	0.148	2.29	0.028	0.588
L Orbitofrontal cortex lateral	0.33 (0.02; 0.63)	0.149	2.19	0.035	0.588
R Orbitofrontal cortex lateral	0.33 (0.05; 0.61)	0.139	2.38	0.023	0.588
L Precuneus	0.33 (0.03; 0.63)	0.147	2.26	0.030	0.588
R Precuneus	0.31 (0.03; 0.59)	0.136	2.28	0.029	0.588
L Lenticular nucleus pallidum	0.33 (0.04; 0.61)	0.142	2.30	0.028	0.588
L Orbitofrontal cortex posterior	0.29 (-0.01; 0.59)	0.149	1.96	0.058	0.616
R Lenticular nucleus pallidum	0.28 (-0.01; 0.57)	0.143	1.96	0.058	0.616
L Thalamus	0.31 (-0.00; 0.62)	0.153	2.01	0.052	0.616
L Heschl gyrus	0.30 (-0.01; 0.61)	0.153	1.96	0.058	0.616
L Parahippocampal gyrus	0.27 (-0.02; 0.57)	0.147	1.86	0.071	0.686
L Precentral gyrus	0.18 (-0.14; 0.50)	0.158	1.13	0.268	0.714
R Precentral gyrus	0.21 (-0.13; 0.55)	0.167	1.24	0.223	0.714
L Inferior frontal gyrus orbital part	0.27 (-0.04; 0.58)	0.152	1.78	0.084	0.714
R Inferior frontal gyrus orbital part	0.27 (-0.05; 0.59)	0.156	1.74	0.091	0.714
L Rolandic operculum	0.19 (-0.15; 0.53)	0.166	1.14	0.263	0.714
R Rolandic operculum	0.19 (-0.14; 0.51)	0.159	1.17	0.252	0.714
L Supplementary motor area (Frontal lobe Medial Surface)	0.23 (-0.10; 0.57)	0.166	1.41	0.168	0.714
R Superior frontal gyrus medial	0.19 (-0.12; 0.50)	0.153	1.25	0.219	0.714
L Superior frontal gyrus medial orbital	0.26 (-0.07; 0.59)	0.161	1.62	0.115	0.714
R Superior frontal gyrus medial orbital	0.21 (-0.12; 0.53)	0.160	1.30	0.202	0.714
R Gyrus rectus	0.20 (-0.09; 0.48)	0.140	1.42	0.165	0.714
R Orbitofrontal cortex posterior	0.19 (-0.13; 0.50)	0.155	1.20	0.237	0.714
L Insula	0.23 (-0.07; 0.53)	0.147	1.56	0.129	0.714
R Insula	0.20 (-0.09; 0.49)	0.143	1.38	0.176	0.714
L Posterior cingulate gyrus	0.22 (-0.11; 0.56)	0.164	1.35	0.185	0.714
R Posterior cingulate gyrus	0.21 (-0.11; 0.54)	0.160	1.34	0.189	0.714
R Hippocampus	0.23 (-0.11; 0.57)	0.168	1.36	0.183	0.714
R Parahippocampal gyrus	0.23 (-0.06; 0.52)	0.145	1.59	0.122	0.714
L Amygdala	0.22 (-0.12; 0.56)	0.168	1.33	0.194	0.714
L Calcarine fissure and surrounding cortex	0.21 (-0.13; 0.55)	0.167	1.24	0.224	0.714
R Calcarine fissure and surrounding cortex	0.26 (-0.07; 0.59)	0.163	1.61	0.117	0.714
R Middle occipital gyrus	0.19 (-0.14; 0.52)	0.163	1.18	0.246	0.714
L Inferior occipital gyrus	0.18 (-0.15; 0.51)	0.161	1.12	0.269	0.714

Regressione lineare: FDG-ROI standardizzato ~ biomcatore standardizzato + età + sesso. β std = coefficiente standardizzato; IC = intervallo di confidenza; p FDR = p corretto con Benjamini-Hochberg sulle 116 ROI.

Tabella S1. Risultati completi T-tau (2/4)

ROI	β std (IC 95%)	SE	t	p	p FDR
L Superior parietal gyrus	0.23 (-0.08; 0.55)	0.156	1.49	0.145	0.714
R Superior parietal gyrus	0.21 (-0.14; 0.56)	0.172	1.20	0.239	0.714
L Lenticular nucleus putamen	0.28 (-0.06; 0.62)	0.166	1.69	0.101	0.714
R Lenticular nucleus putamen	0.21 (-0.08; 0.50)	0.142	1.49	0.145	0.714
L Temporal pole superior temporal gyrus	0.22 (-0.11; 0.56)	0.165	1.36	0.184	0.714
R Cerebelum Crus1	0.19 (-0.16; 0.54)	0.171	1.11	0.277	0.714
L Cerebelum 8	0.19 (-0.15; 0.54)	0.169	1.14	0.264	0.714
R Cerebelum 8	0.24 (-0.10; 0.57)	0.164	1.45	0.155	0.714
R Cerebelum 9	0.22 (-0.13; 0.57)	0.171	1.28	0.210	0.714
L Cerebelum 10	0.19 (-0.16; 0.54)	0.173	1.11	0.275	0.714
R Median cingulate and paracingulate gyri	0.17 (-0.17; 0.50)	0.165	1.02	0.315	0.764
R Superior occipital gyrus	0.18 (-0.18; 0.53)	0.175	1.02	0.316	0.764
L Cerebelum 9	0.18 (-0.17; 0.53)	0.172	1.03	0.311	0.764
L Superior frontal gyrus medial	0.16 (-0.17; 0.48)	0.160	0.97	0.338	0.784
R Heschl gyrus	0.15 (-0.16; 0.47)	0.155	0.98	0.335	0.784
L Gyrus rectus	0.14 (-0.16; 0.44)	0.150	0.93	0.357	0.812
R Supplementary motor area (Frontal lobe Medial Surface)	0.13 (-0.20; 0.47)	0.166	0.80	0.432	0.814
R Superior frontal gyrus orbital part	0.13 (-0.19; 0.46)	0.160	0.83	0.411	0.814
L Middle frontal gyrus orbital part	0.14 (-0.22; 0.49)	0.174	0.78	0.442	0.814
L Hippocampus	0.14 (-0.22; 0.49)	0.174	0.78	0.442	0.814
L Cuneus	0.14 (-0.20; 0.49)	0.171	0.85	0.404	0.814
R Lingual gyrus	0.15 (-0.21; 0.50)	0.176	0.83	0.414	0.814
R Thalamus	0.13 (-0.20; 0.45)	0.159	0.80	0.429	0.814
L Middle temporal gyrus	0.13 (-0.19; 0.44)	0.153	0.82	0.415	0.814
L Cerebelum Crus1	0.15 (-0.20; 0.49)	0.172	0.84	0.404	0.814
L Cerebelum Crus2	0.15 (-0.20; 0.50)	0.172	0.87	0.391	0.814
R Cerebelum Crus2	0.16 (-0.20; 0.51)	0.175	0.90	0.373	0.814
Vermis 6	0.14 (-0.20; 0.48)	0.169	0.84	0.407	0.814
R Amygdala	0.13 (-0.22; 0.47)	0.170	0.75	0.460	0.833
R Inferior occipital gyrus	0.12 (-0.22; 0.46)	0.167	0.73	0.470	0.839
L Median cingulate and paracingulate gyri	0.11 (-0.23; 0.46)	0.169	0.68	0.503	0.859
L Lingual gyrus	0.12 (-0.22; 0.45)	0.166	0.70	0.492	0.859
L Middle occipital gyrus	0.11 (-0.22; 0.44)	0.163	0.68	0.501	0.859
L Inferior frontal gyrus opercular part	0.11 (-0.25; 0.46)	0.174	0.61	0.545	0.867
R Middle frontal gyrus orbital part	0.10 (-0.23; 0.44)	0.165	0.62	0.538	0.867

Regressione lineare: FDG-ROI standardizzato ~ biomarcatore standardizzato + età + sesso. β std = coefficiente standardizzato; IC = intervallo di confidenza; p FDR = p corretto con Benjamini-Hochberg sulle 116 ROI.

Tabella S1. Risultati completi T-tau (3/4)

ROI	β std (IC 95%)	SE	t	p	p FDR
L Postcentral gyrus	0.09 (-0.21; 0.40)	0.152	0.62	0.539	0.867
L Angular gyrus	0.11 (-0.24; 0.46)	0.174	0.64	0.529	0.867
L Paracentral lobule	0.11 (-0.24; 0.47)	0.174	0.65	0.520	0.867
L Middle frontal gyrus	0.10 (-0.26; 0.45)	0.175	0.54	0.591	0.870
R Middle frontal gyrus	0.09 (-0.26; 0.44)	0.172	0.51	0.613	0.870
L Inferior frontal gyrus triangular part	0.08 (-0.25; 0.40)	0.159	0.49	0.627	0.870
R Inferior frontal gyrus triangular part	0.08 (-0.25; 0.42)	0.164	0.50	0.619	0.870
L Superior frontal gyrus orbital part	0.09 (-0.25; 0.44)	0.170	0.54	0.593	0.870
R Anterior cingulate and paracingulate gyri	-0.08 (-0.44; 0.27)	0.174	-0.48	0.638	0.870
R Supramarginal gyrus	-0.09 (-0.44; 0.27)	0.174	-0.51	0.616	0.870
R Paracentral lobule	0.10 (-0.26; 0.45)	0.174	0.56	0.582	0.870
R Caudate nucleus	0.08 (-0.26; 0.43)	0.171	0.48	0.633	0.870
L Superior temporal gyrus	0.09 (-0.22; 0.40)	0.152	0.58	0.562	0.870
L Temporal pole middle temporal gyrus	0.08 (-0.27; 0.44)	0.175	0.48	0.635	0.870
Vermis 1 2	0.08 (-0.27; 0.44)	0.174	0.49	0.630	0.870
L Superior occipital gyrus	0.08 (-0.26; 0.41)	0.166	0.45	0.653	0.881
L Cerebellum 7b	0.07 (-0.28; 0.43)	0.176	0.42	0.679	0.906
R Superior frontal gyrus dorsolateral	0.05 (-0.28; 0.38)	0.162	0.32	0.749	0.928
R Cuneus	0.06 (-0.31; 0.42)	0.179	0.32	0.751	0.928
L Fusiform gyrus	0.06 (-0.29; 0.41)	0.173	0.35	0.725	0.928
R Fusiform gyrus	-0.06 (-0.42; 0.31)	0.179	-0.32	0.752	0.928
R Angular gyrus	0.06 (-0.29; 0.41)	0.172	0.37	0.716	0.928
L Caudate nucleus	0.06 (-0.30; 0.42)	0.176	0.34	0.738	0.928
L Inferior temporal gyrus	0.06 (-0.29; 0.42)	0.176	0.35	0.725	0.928
L Inferior parietal but supramarginal and angular gyri	0.04 (-0.28; 0.36)	0.157	0.28	0.780	0.945
L Cerebellum 6	0.05 (-0.31; 0.41)	0.177	0.28	0.782	0.945
R Middle temporal gyrus	-0.04 (-0.38; 0.30)	0.168	-0.26	0.797	0.947
L Cerebellum 3	0.05 (-0.32; 0.41)	0.177	0.26	0.800	0.947
L Superior frontal gyrus dorsolateral	0.04 (-0.28; 0.35)	0.156	0.24	0.813	0.952
R Cerebellum 7b	0.04 (-0.32; 0.39)	0.174	0.22	0.826	0.958
R Inferior frontal gyrus opercular part	0.01 (-0.35; 0.37)	0.175	0.05	0.959	0.959
L Anterior cingulate and paracingulate gyri	0.02 (-0.32; 0.35)	0.164	0.10	0.920	0.959
R Postcentral gyrus	0.03 (-0.33; 0.38)	0.174	0.15	0.879	0.959
R Inferior parietal but supramarginal and angular gyri	-0.02 (-0.38; 0.34)	0.176	-0.10	0.922	0.959
L Supramarginal gyrus	-0.01 (-0.36; 0.34)	0.170	-0.06	0.953	0.959

Regressione lineare: FDG-ROI standardizzato ~ biomcatore standardizzato + età + sesso. β std = coefficiente standardizzato; IC = intervallo di confidenza; p FDR = p corretto con Benjamini-Hochberg sulle 116 ROI.

Tabella S1. Risultati completi T-tau (4/4)

ROI	β std (IC 95%)	SE	t	p	p FDR
R Superior temporal gyrus	-0.01 (-0.37; 0.35)	0.175	-0.06	0.954	0.959
R Temporal pole superior temporal gyrus	0.01 (-0.32; 0.34)	0.164	0.08	0.938	0.959
R Temporal pole middle temporal gyrus	0.02 (-0.34; 0.37)	0.176	0.09	0.932	0.959
R Inferior temporal gyrus	-0.01 (-0.37; 0.35)	0.178	-0.06	0.949	0.959
R Cerebellum 3	0.02 (-0.34; 0.38)	0.177	0.11	0.910	0.959
L Cerebellum 4 5	0.03 (-0.33; 0.39)	0.178	0.17	0.865	0.959
R Cerebellum 4 5	-0.02 (-0.39; 0.34)	0.179	-0.12	0.902	0.959
R Cerebellum 6	0.01 (-0.35; 0.37)	0.179	0.06	0.956	0.959
R Cerebellum 10	0.03 (-0.32; 0.39)	0.174	0.19	0.847	0.959
Vermis 4	0.03 (-0.33; 0.39)	0.176	0.17	0.864	0.959
Vermis 4 5	0.03 (-0.32; 0.39)	0.175	0.18	0.858	0.959

Regressione lineare: FDG-ROI standardizzato ~ biomarcatore standardizzato + età + sesso. β std = coefficiente standardizzato; IC = intervallo di confidenza; p FDR = p corretto con Benjamini-Hochberg sulle 116 ROI.

4. Table S1 - S11 GO enrichment analysis

Table S1 – GO enrichment analysis: AD + DLB + PD + RBD

29 genes in pattern · 3 significant GO terms (FDR < 0.05)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
1	BP	GO:0010977	negative regulation of neuron projection development	4/27	132/18860	3.55×10 ⁻⁵	3.17×10 ⁻²	ADAM17, INPP5F, LRRK2, RIT2
2	MF	GO:0008093	cytoskeletal anchor activity	2/26	26/18662	5.94×10 ⁻⁴	3.82×10 ⁻²	ADD1, ANK3
3	MF	GO:0030507	spectrin binding	2/26	27/18662	6.41×10 ⁻⁴	3.82×10 ⁻²	ADD1, ANK3

BP = biological process · MF = molecular function · CC = cellular component

GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S2 – GO enrichment analysis: AD + DLB + PD

51 genes in pattern · 53 significant GO terms (FDR < 0.05)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
1	BP	GO:0042987	amyloid precursor protein catabolic process	6/47	74/18860	2.81×10 ⁻⁴	4.54×10 ⁻⁵	ADAM10, APH1B, APP, DYRK1A, EFNA1, SLC2A13
2	BP	GO:0042982	amyloid precursor protein metabolic process	6/47	102/18860	1.94×10 ⁻⁷	1.57×10 ⁻⁴	ADAM10, APH1B, APP, DYRK1A, EFNA1, SLC2A13
3	BP	GO:0050435	amyloid-beta metabolic process	5/47	74/18860	1.09×10 ⁻⁶	4.33×10 ⁻⁴	ACE, APH1B, DYRK1A, EFNA1, SLC2A13
4	BP	GO:0050807	regulation of synapse organization	8/47	322/18860	1.17×10 ⁻⁶	4.33×10 ⁻⁴	AB13, ADAM10, AGRN, APP, DMPK, DOCK4, EFNA1, FCGR2B
5	BP	GO:0050803	regulation of synapse structure or activity	8/47	329/18860	1.37×10 ⁻⁶	4.33×10 ⁻⁴	AB13, ADAM10, AGRN, APP, DMPK, DOCK4, EFNA1, FCGR2B
6	BP	GO:0099175	regulation of postsynapse organization	6/47	146/18860	1.60×10 ⁻⁶	4.33×10 ⁻⁴	AB13, ADAM10, APP, DOCK4, EFNA1, FCGR2B
7	BP	GO:1903522	regulation of blood circulation	7/47	279/18860	5.45×10 ⁻⁶	1.26×10 ⁻³	ACE, APP, CAMK2D, DMPK, DOCK4, HBEGF, PKP2
8	BP	GO:0034205	amyloid-beta formation	4/47	60/18860	1.49×10 ⁻⁵	2.52×10 ⁻³	APH1B, DYRK1A, EFNA1, SLC2A13
9	BP	GO:1902991	regulation of amyloid precursor protein catabolic process	4/47	60/18860	1.49×10 ⁻⁵	2.52×10 ⁻³	APP, DYRK1A, EFNA1, SLC2A13
10	BP	GO:0072657	protein localization to membrane	8/47	458/18860	1.56×10 ⁻⁵	2.52×10 ⁻³	AB13, ADAM10, AGRN, CAMK2D, KCNIP3, NSF, PKP2, SCARB2
11	BP	GO:1990778	protein localization to cell periphery	7/47	365/18860	3.10×10 ⁻⁵	4.20×10 ⁻³	AB13, ADAM10, CAMK2D, KCNIP3, NSF, PKP2, SCARB2
12	BP	GO:0099173	postsynapse organization	6/47	245/18860	3.11×10 ⁻⁵	4.20×10 ⁻³	AB13, ADAM10, APP, DOCK4, EFNA1, FCGR2B
13	BP	GO:1902993	positive regulation of amyloid precursor protein catabolic process	3/47	27/18860	4.07×10 ⁻⁵	5.07×10 ⁻³	APP, EFNA1, SLC2A13
14	BP	GO:0097061	dendritic spine organization	4/47	83/18860	5.38×10 ⁻⁵	6.23×10 ⁻³	AB13, APP, EFNA1, FCGR2B
15	BP	GO:1901888	regulation of cell junction assembly	6/47	285/18860	7.21×10 ⁻⁵	7.49×10 ⁻³	AB13, ACE, AGRN, APP, DOCK4, MAP4K4
16	BP	GO:0034248	regulation of amide metabolic process	4/47	90/18860	7.39×10 ⁻⁵	7.49×10 ⁻³	DYRK1A, EFNA1, SCARB2, SLC2A13
17	BP	GO:0106027	neuron projection organization	4/47	93/18860	8.40×10 ⁻⁵	7.85×10 ⁻³	AB13, APP, EFNA1, FCGR2B
18	BP	GO:0072659	protein localization to plasma membrane	6/47	295/18860	8.72×10 ⁻⁵	7.85×10 ⁻³	AB13, CAMK2D, KCNIP3, NSF, PKP2, SCARB2
19	BP	GO:0086091	regulation of heart rate by cardiac conduction	3/47	43/18860	1.67×10 ⁻⁴	1.42×10 ⁻²	ACE, CAMK2D, PKP2
20	MF	GO:0030165	PDZ domain binding	4/49	84/18662	6.93×10 ⁻⁵	1.79×10 ⁻²	CLCN3, DOCK4, NSF, PLEKHA1
21	BP	GO:0008016	regulation of heart contraction	5/47	225/18860	2.36×10 ⁻⁴	1.91×10 ⁻²	ACE, CAMK2D, DMPK, HBEGF, PKP2
22	BP	GO:0010634	positive regulation of epithelial cell migration	3/47	50/18860	2.62×10 ⁻⁴	2.02×10 ⁻²	HBEGF, IRS2, MAP4K4
23	BP	GO:1902003	regulation of amyloid-beta formation	3/47	52/18860	2.94×10 ⁻⁴	2.17×10 ⁻²	DYRK1A, EFNA1, SLC2A13
24	MF	GO:0004222	metalloendopeptidase activity	4/49	109/18662	1.91×10 ⁻⁴	2.46×10 ⁻²	ACE, ADAM10, ADAM15, ADAMTS4
25	BP	GO:0051549	positive regulation of keratinocyte migration	2/47	12/18860	3.95×10 ⁻⁴	2.78×10 ⁻²	HBEGF, MAP4K4
26	CC	GO:0043198	dendritic shaft	3/50	42/19944	1.59×10 ⁻⁴	2.86×10 ⁻²	AB13, APP, NSF
27	BP	GO:0060047	heart contraction	5/47	265/18860	5.00×10 ⁻⁴	3.14×10 ⁻²	ACE, CAMK2D, DMPK, HBEGF, PKP2
28	BP	GO:0090257	regulation of muscle system process	5/47	266/18860	5.08×10 ⁻⁴	3.14×10 ⁻²	CAMK2D, DMPK, DOCK4, LMNA, PKP2
29	BP	GO:0046328	regulation of JNK cascade	4/47	150/18860	5.26×10 ⁻⁴	3.14×10 ⁻²	APP, AXIN1, FCGR2B, MAP4K4
30	BP	GO:0051547	regulation of keratinocyte migration	2/47	14/18860	5.43×10 ⁻⁴	3.14×10 ⁻²	HBEGF, MAP4K4
31	BP	GO:0033619	membrane protein proteolysis	3/47	64/18860	5.43×10 ⁻⁴	3.14×10 ⁻²	ADAM10, APH1B, APP
32	BP	GO:0003015	heart process	5/47	275/18860	5.91×10 ⁻⁴	3.30×10 ⁻²	ACE, CAMK2D, DMPK, HBEGF, PKP2
33	BP	GO:1902950	regulation of dendritic spine maintenance	2/47	15/18860	6.25×10 ⁻⁴	3.38×10 ⁻²	APP, FCGR2B
34	BP	GO:0030888	regulation of B cell proliferation	3/47	68/18860	6.49×10 ⁻⁴	3.39×10 ⁻²	BST1, FCGR2B, IRS2
35	BP	GO:0010632	regulation of epithelial cell migration	3/47	72/18860	7.67×10 ⁻⁴	3.76×10 ⁻²	HBEGF, IRS2, MAP4K4
36	BP	GO:0022617	extracellular matrix disassembly	3/47	72/18860	7.67×10 ⁻⁴	3.76×10 ⁻²	ADAM10, ADAM15, ADAMTS4
37	BP	GO:0030167	proteoglycan catabolic process	2/47	17/18860	8.07×10 ⁻⁴	3.85×10 ⁻²	ADAMTS4, IDUA
38	BP	GO:0002028	regulation of sodium ion transport	3/47	76/18860	8.98×10 ⁻⁴	4.15×10 ⁻²	CAMK2D, DMPK, PKP2
39	BP	GO:0040029	epigenetic regulation of gene expression	5/47	305/18860	9.42×10 ⁻⁴	4.24×10 ⁻²	APP, AXIN1, DYRK1A, LMNA, MTF2
40	BP	GO:0006937	regulation of muscle contraction	4/47	181/18860	1.06×10 ⁻³	4.52×10 ⁻²	CAMK2D, DMPK, DOCK4, PKP2
41	BP	GO:0051963	regulation of synapse assembly	4/47	181/18860	1.06×10 ⁻³	4.52×10 ⁻²	AB13, AGRN, APP, DOCK4
42	MF	GO:0016805	dipeptidase activity	2/49	18/18662	1.01×10 ⁻³	4.63×10 ⁻²	ACE, ADAM10
43	MF	GO:0043395	heparan sulfate proteoglycan binding	2/49	19/18662	1.12×10 ⁻³	4.63×10 ⁻²	AGRN, APP
44	MF	GO:0019207	kinase regulator activity	5/49	308/18662	1.25×10 ⁻³	4.63×10 ⁻²	AXIN1, CAB39L, HBEGF, IRS2, RHOH
45	MF	GO:0008237	metallopeptidase activity	4/49	185/18662	1.40×10 ⁻³	4.63×10 ⁻²	ACE, ADAM10, ADAM15, ADAMTS4
46	MF	GO:0031406	carboxylic acid binding	4/49	186/18662	1.43×10 ⁻³	4.63×10 ⁻²	AGRN, APP, MCCCI, PAM
47	MF	GO:0043177	organic acid binding	4/49	188/18662	1.48×10 ⁻³	4.63×10 ⁻²	AGRN, APP, MCCCI, PAM
48	MF	GO:0005158	insulin receptor binding	2/49	23/18662	1.65×10 ⁻³	4.63×10 ⁻²	APP, IRS2
49	MF	GO:0120283	protein serine/threonine kinase binding	2/49	24/18662	1.80×10 ⁻³	4.63×10 ⁻²	APP, AXIN1
50	BP	GO:0051546	keratinocyte migration	2/47	20/18860	1.12×10 ⁻³	4.66×10 ⁻²	HBEGF, MAP4K4
51	BP	GO:0022411	cellular component disassembly	6/47	483/18860	1.21×10 ⁻³	4.78×10 ⁻²	ADAM10, ADAM15, ADAMTS4, MAP4K4, NSF, SHARPIN
52	BP	GO:0007254	JNK cascade	4/47	188/18860	1.22×10 ⁻³	4.78×10 ⁻²	APP, AXIN1, FCGR2B, MAP4K4
53	BP	GO:1902004	positive regulation of amyloid-beta formation	2/47	21/18860	1.24×10 ⁻³	4.78×10 ⁻²	EFNA1, SLC2A13

BP = biological process · MF = molecular function · CC = cellular component

GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S3 – GO enrichment analysis: AD + PD + RBD

1 genes in pattern · 0 significant GO terms (FDR < 0.05)

No significant GO terms (FDR < 0.05).

Table S4 – GO enrichment analysis: DLB + PD + RBD

5 genes in pattern · 80 significant GO terms (FDR < 0.05) · page 1 of 2 (rows 1–60)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
1	MF	GO:0023023	MHC protein complex binding	2/5	37/18662	3.81×10 ⁻³	1.11×10 ⁻³	HLA-DRB5, LILRB2
2	MF	GO:0042277	peptide binding	2/5	234/18662	1.53×10 ⁻³	2.02×10 ⁻²	HLA-DRB5, LILRB2
3	MF	GO:0016303	1-phosphatidylinositol-3-kinase activity	1/5	10/18662	2.68×10 ⁻³	2.02×10 ⁻²	PIK3CA
4	MF	GO:0032396	inhibitory MHC class I receptor activity	1/5	13/18662	3.48×10 ⁻³	2.02×10 ⁻²	LILRB2
5	MF	GO:0043560	insulin receptor substrate binding	1/5	13/18662	3.48×10 ⁻³	2.02×10 ⁻²	PIK3CA
6	MF	GO:0032393	MHC class I receptor activity	1/5	18/18662	4.81×10 ⁻³	2.09×10 ⁻²	LILRB2
7	MF	GO:0042288	MHC class I protein binding	1/5	20/18662	5.35×10 ⁻³	2.09×10 ⁻²	LILRB2
8	MF	GO:0008157	protein phosphatase 1 binding	1/5	26/18662	6.95×10 ⁻³	2.09×10 ⁻²	LILRB2
9	MF	GO:0052742	phosphatidylinositol kinase activity	1/5	26/18662	6.95×10 ⁻³	2.09×10 ⁻²	PIK3CA
10	MF	GO:0023026	MHC class II protein complex binding	1/5	27/18662	7.21×10 ⁻³	2.09×10 ⁻²	HLA-DRB5
11	MF	GO:0001727	lipid kinase activity	1/5	41/18662	1.09×10 ⁻²	2.64×10 ⁻²	PIK3CA
12	MF	GO:0042287	MHC protein binding	1/5	41/18662	1.09×10 ⁻²	2.64×10 ⁻²	LILRB2
13	MF	GO:0042605	peptide antigen binding	1/5	45/18662	1.20×10 ⁻²	2.68×10 ⁻²	HLA-DRB5
14	MF	GO:0098632	cell-cell adhesion mediator activity	1/5	61/18662	1.62×10 ⁻²	3.36×10 ⁻²	CNTN1
15	MF	GO:0140299	molecular sensor activity	1/5	75/18662	1.99×10 ⁻²	3.85×10 ⁻²	ICA1
16	MF	GO:0001540	amyloid-beta binding	1/5	84/18662	2.23×10 ⁻²	3.85×10 ⁻²	LILRB2
17	MF	GO:0098631	cell adhesion mediator activity	1/5	85/18662	2.26×10 ⁻²	3.85×10 ⁻²	CNTN1
18	CC	GO:0030658	transport vesicle membrane	2/5	259/19944	1.64×10 ⁻³	4.10×10 ⁻²	HLA-DRB5, ICA1
19	CC	GO:0030667	secretory granule membrane	2/5	325/19944	2.56×10 ⁻³	4.10×10 ⁻²	ICA1, LILRB2
20	CC	GO:0005942	phosphatidylinositol 3-kinase complex	1/5	16/19944	4.01×10 ⁻³	4.10×10 ⁻²	PIK3CA
21	CC	GO:0042613	MHC class II protein complex	1/5	17/19944	4.26×10 ⁻³	4.10×10 ⁻²	HLA-DRB5
22	CC	GO:0030133	transport vesicle	2/5	451/19944	4.88×10 ⁻³	4.10×10 ⁻²	HLA-DRB5, ICA1
23	CC	GO:0042611	MHC protein complex	1/5	25/19944	6.25×10 ⁻³	4.38×10 ⁻²	HLA-DRB5
24	BP	GO:0019882	antigen processing and presentation	2/5	120/18860	3.96×10 ⁻³	4.38×10 ⁻²	HLA-DRB5, LILRB2
25	BP	GO:0050870	positive regulation of T cell activation	2/5	267/18860	1.94×10 ⁻³	4.38×10 ⁻²	HLA-DRB5, LILRB2
26	BP	GO:1903039	positive regulation of leukocyte cell-cell adhesion	2/5	289/18860	2.27×10 ⁻³	4.38×10 ⁻²	HLA-DRB5, LILRB2
27	BP	GO:0002666	positive regulation of T cell tolerance induction	1/5	10/18860	2.65×10 ⁻³	4.38×10 ⁻²	LILRB2
28	BP	GO:0002765	immune response-inhibiting signal transduction	1/5	11/18860	2.91×10 ⁻³	4.38×10 ⁻²	LILRB2
29	BP	GO:0014854	response to inactivity	1/5	11/18860	2.91×10 ⁻³	4.38×10 ⁻²	PIK3CA
30	BP	GO:0002645	positive regulation of tolerance induction	1/5	12/18860	3.18×10 ⁻³	4.38×10 ⁻²	LILRB2
31	BP	GO:0009415	response to water	1/5	12/18860	3.18×10 ⁻³	4.38×10 ⁻²	PIK3CA
32	BP	GO:0140105	interleukin-10-mediated signaling pathway	1/5	12/18860	3.18×10 ⁻³	4.38×10 ⁻²	LILRB2
33	BP	GO:0022409	positive regulation of cell-cell adhesion	2/5	343/18860	3.18×10 ⁻³	4.38×10 ⁻²	HLA-DRB5, LILRB2
34	BP	GO:0051251	positive regulation of lymphocyte activation	2/5	346/18860	3.24×10 ⁻³	4.38×10 ⁻²	HLA-DRB5, LILRB2
35	BP	GO:0010639	negative regulation of organelle organization	2/5	367/18860	3.63×10 ⁻³	4.38×10 ⁻²	LILRB2, PIK3CA
36	BP	GO:0031346	positive regulation of cell projection organization	2/5	367/18860	3.63×10 ⁻³	4.38×10 ⁻²	CNTN1, PIK3CA
37	BP	GO:0002664	regulation of T cell tolerance induction	1/5	14/18860	3.71×10 ⁻³	4.38×10 ⁻²	LILRB2
38	BP	GO:2001198	regulation of dendritic cell differentiation	1/5	14/18860	3.71×10 ⁻³	4.38×10 ⁻²	LILRB2
39	BP	GO:0010959	regulation of metal ion transport	2/5	377/18860	3.83×10 ⁻³	4.38×10 ⁻²	CNTN1, LILRB2
40	BP	GO:0002696	positive regulation of leukocyte activation	2/5	381/18860	3.91×10 ⁻³	4.38×10 ⁻²	HLA-DRB5, LILRB2
41	BP	GO:0043201	response to L-leucine	1/5	15/18860	3.97×10 ⁻³	4.38×10 ⁻²	PIK3CA
42	BP	GO:1900452	regulation of long-term synaptic depression	1/5	15/18860	3.97×10 ⁻³	4.38×10 ⁻²	LILRB2
43	BP	GO:0002768	immune response-regulating cell surface receptor signaling pathway	2/5	385/18860	3.99×10 ⁻³	4.38×10 ⁻²	LILRB2, PIK3CA
44	BP	GO:0002399	MHC class II protein complex assembly	1/5	16/18860	4.24×10 ⁻³	4.38×10 ⁻²	HLA-DRB5
45	BP	GO:0002503	peptide antigen assembly with MHC class II protein complex	1/5	16/18860	4.24×10 ⁻³	4.38×10 ⁻²	HLA-DRB5
46	BP	GO:0002517	T cell tolerance induction	1/5	16/18860	4.24×10 ⁻³	4.38×10 ⁻²	LILRB2
47	BP	GO:0050867	positive regulation of cell activation	2/5	401/18860	4.32×10 ⁻³	4.38×10 ⁻²	HLA-DRB5, LILRB2
48	BP	GO:1903037	regulation of leukocyte cell-cell adhesion	2/5	401/18860	4.32×10 ⁻³	4.38×10 ⁻²	HLA-DRB5, LILRB2
49	BP	GO:0050863	regulation of T cell activation	2/5	404/18860	4.39×10 ⁻³	4.38×10 ⁻²	HLA-DRB5, LILRB2
50	BP	GO:0055119	relaxation of cardiac muscle	1/5	17/18860	4.50×10 ⁻³	4.38×10 ⁻²	PIK3CA
51	BP	GO:2000811	negative regulation of anoikis	1/5	19/18860	5.03×10 ⁻³	4.38×10 ⁻²	PIK3CA
52	BP	GO:0007159	leukocyte cell-cell adhesion	2/5	439/18860	5.16×10 ⁻³	4.38×10 ⁻²	HLA-DRB5, LILRB2
53	BP	GO:0002643	regulation of tolerance induction	1/5	20/18860	5.29×10 ⁻³	4.38×10 ⁻²	LILRB2
54	BP	GO:0043269	regulation of monoatomic ion transport	2/5	449/18860	5.39×10 ⁻³	4.38×10 ⁻²	CNTN1, LILRB2
55	BP	GO:0071514	genomic imprinting	1/5	21/18860	5.56×10 ⁻³	4.38×10 ⁻²	PIK3CA
56	BP	GO:1905874	regulation of postsynaptic density organization	1/5	21/18860	5.56×10 ⁻³	4.38×10 ⁻²	LILRB2
57	BP	GO:2000269	regulation of fibroblast apoptotic process	1/5	21/18860	5.56×10 ⁻³	4.38×10 ⁻²	PIK3CA
58	BP	GO:0032288	myelin assembly	1/5	22/18860	5.82×10 ⁻³	4.38×10 ⁻²	CNTN1
59	BP	GO:0002577	regulation of antigen processing and presentation	1/5	23/18860	6.08×10 ⁻³	4.38×10 ⁻²	LILRB2
60	BP	GO:0036092	phosphatidylinositol-3-phosphate biosynthetic process	1/5	23/18860	6.08×10 ⁻³	4.38×10 ⁻²	PIK3CA

BP = biological process · MF = molecular function · CC = cellular component
 GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S4 – GO enrichment analysis: DLB + PD + RBD

5 genes in pattern · 80 significant GO terms (FDR < 0.05) · page 2 of 2 (rows 61–80)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
61	BP	GO:0002396	MHC protein complex assembly	1/5	24/18860	6.35×10 ⁻³	4.38×10 ⁻²	HLA-DRB5
62	BP	GO:0002501	peptide antigen assembly with MHC protein complex	1/5	24/18860	6.35×10 ⁻³	4.38×10 ⁻²	HLA-DRB5
63	BP	GO:0045591	positive regulation of regulatory T cell differentiation	1/5	24/18860	6.35×10 ⁻³	4.38×10 ⁻²	LILRB2
64	BP	GO:0048015	phosphatidylinositol-mediated signaling	1/5	24/18860	6.35×10 ⁻³	4.38×10 ⁻²	PIK3CA
65	BP	GO:0022010	central nervous system myelination	1/5	25/18860	6.61×10 ⁻³	4.38×10 ⁻²	CNTN1
66	BP	GO:0032291	axon ensheathment in central nervous system	1/5	25/18860	6.61×10 ⁻³	4.38×10 ⁻²	CNTN1
67	BP	GO:0035994	response to muscle stretch	1/5	26/18860	6.87×10 ⁻³	4.38×10 ⁻²	PIK3CA
68	BP	GO:2000209	regulation of anoikis	1/5	26/18860	6.87×10 ⁻³	4.38×10 ⁻²	PIK3CA
69	BP	GO:0044346	fibroblast apoptotic process	1/5	27/18860	7.14×10 ⁻³	4.45×10 ⁻²	PIK3CA
70	BP	GO:0010592	positive regulation of lamellipodium assembly	1/5	28/18860	7.40×10 ⁻³	4.52×10 ⁻²	PIK3CA
71	BP	GO:0002507	tolerance induction	1/5	31/18860	8.19×10 ⁻³	4.80×10 ⁻²	LILRB2
72	BP	GO:0019886	antigen processing and presentation of exogenous peptide antigen via MHC class II	1/5	31/18860	8.19×10 ⁻³	4.80×10 ⁻²	HLA-DRB5
73	BP	GO:0060292	long-term synaptic depression	1/5	33/18860	8.72×10 ⁻³	4.87×10 ⁻²	LILRB2
74	BP	GO:0002495	antigen processing and presentation of peptide antigen via MHC class II	1/5	35/18860	9.25×10 ⁻³	4.87×10 ⁻²	HLA-DRB5
75	BP	GO:0010765	positive regulation of sodium ion transport	1/5	35/18860	9.25×10 ⁻³	4.87×10 ⁻²	CNTN1
76	BP	GO:0043045	epigenetic programming of gene expression	1/5	36/18860	9.51×10 ⁻³	4.87×10 ⁻²	PIK3CA
77	BP	GO:0043276	anoikis	1/5	36/18860	9.51×10 ⁻³	4.87×10 ⁻²	PIK3CA
78	BP	GO:0090075	relaxation of muscle	1/5	36/18860	9.51×10 ⁻³	4.87×10 ⁻²	PIK3CA
79	BP	GO:1902745	positive regulation of lamellipodium organization	1/5	36/18860	9.51×10 ⁻³	4.87×10 ⁻²	PIK3CA
80	BP	GO:0002504	antigen processing and presentation of peptide or polysaccharide antigen via MHC class II	1/5	37/18860	9.77×10 ⁻³	4.92×10 ⁻²	HLA-DRB5

BP = biological process · MF = molecular function · CC = cellular component
GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S5 – GO enrichment analysis: AD + DLB

31 genes in pattern · 1 significant GO terms (FDR < 0.05)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
1	MF	GO:0180030	inositol phosphate kinase activity	2/28	11/18662	1.18×10 ⁻⁴	2.29×10 ⁻²	IP6K2, IPMK

BP = biological process · MF = molecular function · CC = cellular component
GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S6 – GO enrichment analysis: AD + RBD

16 genes in pattern · 24 significant GO terms (FDR < 0.05)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
1	MF	GO:0051087	protein-folding chaperone binding	3/16	135/18662	1.94×10 ⁻⁴	1.95×10 ⁻²	CLU, NOD2, SNCA
2	MF	GO:0048156	tau protein binding	2/16	44/18662	6.38×10 ⁻⁴	2.16×10 ⁻²	CLU, SNCA
3	MF	GO:0140311	protein sequestering activity	2/16	47/18662	7.28×10 ⁻⁴	2.16×10 ⁻²	CLU, SNCA
4	MF	GO:0030544	Hsp70 protein binding	2/16	51/18662	8.57×10 ⁻⁴	2.16×10 ⁻²	NOD2, SNCA
5	BP	GO:0051092	positive regulation of NF-kappaB transcription factor activity	3/16	80/18860	3.95×10 ⁻⁵	2.29×10 ⁻²	CLU, DDRGK1, NOD2
6	BP	GO:0061517	macrophage proliferation	2/16	13/18860	5.23×10 ⁻⁵	2.29×10 ⁻²	CLU, IL34
7	BP	GO:0061684	chaperone-mediated autophagy	2/16	16/18860	8.04×10 ⁻⁵	2.35×10 ⁻²	CLU, SNCA
8	BP	GO:0051091	positive regulation of DNA-binding transcription factor activity	3/16	113/18860	1.11×10 ⁻⁴	2.43×10 ⁻²	CLU, DDRGK1, NOD2
9	BP	GO:0031340	positive regulation of vesicle fusion	2/16	23/18860	1.69×10 ⁻⁴	2.96×10 ⁻²	DOC2A, SNCA
10	MF	GO:0140313	molecular sequestering activity	2/16	75/18662	1.84×10 ⁻³	3.72×10 ⁻²	CLU, SNCA
11	BP	GO:0031338	regulation of vesicle fusion	2/16	36/18860	4.18×10 ⁻⁴	4.40×10 ⁻²	DOC2A, SNCA
12	BP	GO:0051090	regulation of DNA-binding transcription factor activity	3/16	189/18860	5.04×10 ⁻⁴	4.40×10 ⁻²	CLU, DDRGK1, NOD2
13	BP	GO:0032640	tumor necrosis factor production	3/16	196/18860	5.60×10 ⁻⁴	4.40×10 ⁻²	CLU, GPNMB, NOD2
14	BP	GO:0032680	regulation of tumor necrosis factor production	3/16	196/18860	5.60×10 ⁻⁴	4.40×10 ⁻²	CLU, GPNMB, NOD2
15	BP	GO:0043410	positive regulation of MAPK cascade	4/16	474/18860	5.64×10 ⁻⁴	4.40×10 ⁻²	GPNMB, IL34, LAMTOR2, NOD2
16	BP	GO:0071706	tumor necrosis factor superfamily cytokine production	3/16	201/18860	6.03×10 ⁻⁴	4.40×10 ⁻²	CLU, GPNMB, NOD2
17	BP	GO:1903555	regulation of tumor necrosis factor superfamily cytokine production	3/16	201/18860	6.03×10 ⁻⁴	4.40×10 ⁻²	CLU, GPNMB, NOD2
18	BP	GO:1990000	amyloid fibril formation	2/16	45/18860	6.54×10 ⁻⁴	4.41×10 ⁻²	CLU, SNCA
19	BP	GO:0001774	microglial cell activation	2/16	48/18860	7.44×10 ⁻⁴	4.41×10 ⁻²	CLU, SNCA
20	BP	GO:0002269	leukocyte activation involved in inflammatory response	2/16	51/18860	8.40×10 ⁻⁴	4.41×10 ⁻²	CLU, SNCA
21	BP	GO:1903573	negative regulation of response to endoplasmic reticulum stress	2/16	51/18860	8.40×10 ⁻⁴	4.41×10 ⁻²	CLU, DDRGK1
22	BP	GO:0035384	thioester biosynthetic process	2/16	53/18860	9.07×10 ⁻⁴	4.41×10 ⁻²	ELOVL7, SNCA
23	BP	GO:0071616	acyl-CoA biosynthetic process	2/16	53/18860	9.07×10 ⁻⁴	4.41×10 ⁻²	ELOVL7, SNCA
24	BP	GO:0061900	glial cell activation	2/16	56/18860	1.01×10 ⁻³	4.66×10 ⁻²	CLU, SNCA

BP = biological process · MF = molecular function · CC = cellular component
GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S7 – GO enrichment analysis: DLB + PD

7 genes in pattern · 236 significant GO terms (FDR < 0.05) · page 1 of 4 (rows 1–60)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
1	MF	GO:0050750	low-density lipoprotein particle receptor binding	2/7	26/18662	3.90×10 ⁻⁵	1.28×10 ⁻³	APOE, PICALM
2	MF	GO:0070325	lipoprotein particle receptor binding	2/7	31/18662	5.58×10 ⁻⁵	1.28×10 ⁻³	APOE, PICALM
3	CC	GO:0030136	clathrin-coated vesicle	3/6	223/19944	2.69×10 ⁻⁵	1.35×10 ⁻³	APOE, GAK, PICALM
4	MF	GO:0048156	tau protein binding	2/7	44/18662	1.13×10 ⁻⁴	1.55×10 ⁻³	APOE, PICALM
5	MF	GO:0030276	clathrin binding	2/7	48/18662	1.35×10 ⁻⁴	1.55×10 ⁻³	GAK, PICALM
6	CC	GO:0030135	coated vesicle	3/6	323/19944	8.12×10 ⁻⁵	2.03×10 ⁻³	APOE, GAK, PICALM
7	BP	GO:0048268	clathrin coat assembly	2/6	21/18860	1.77×10 ⁻⁵	3.69×10 ⁻³	GAK, PICALM
8	BP	GO:1902004	positive regulation of amyloid-beta formation	2/6	21/18860	1.77×10 ⁻⁵	3.69×10 ⁻³	APOE, PICALM
9	MF	GO:0001540	amyloid-beta binding	2/7	84/18662	4.14×10 ⁻⁴	3.81×10 ⁻³	APOE, PICALM
10	BP	GO:1902993	positive regulation of amyloid precursor protein catabolic process	2/6	27/18860	2.95×10 ⁻⁵	4.08×10 ⁻³	APOE, PICALM
11	BP	GO:0034250	positive regulation of amide metabolic process	2/6	31/18860	3.91×10 ⁻⁵	4.08×10 ⁻³	APOE, PICALM
12	BP	GO:0006898	receptor-mediated endocytosis	3/6	279/18860	6.20×10 ⁻⁵	5.03×10 ⁻³	APOE, GAK, PICALM
13	BP	GO:0097242	amyloid-beta clearance	2/6	42/18860	7.22×10 ⁻⁵	5.03×10 ⁻³	APOE, PICALM
14	CC	GO:0045334	clathrin-coated endocytic vesicle	2/6	94/19944	3.26×10 ⁻⁴	5.43×10 ⁻³	APOE, PICALM
15	BP	GO:0072583	clathrin-dependent endocytosis	2/6	49/18860	9.85×10 ⁻⁵	5.80×10 ⁻³	GAK, PICALM
16	BP	GO:1902003	regulation of amyloid-beta formation	2/6	52/18860	1.11×10 ⁻⁴	5.80×10 ⁻³	APOE, PICALM
17	BP	GO:0034205	amyloid-beta formation	2/6	60/18860	1.48×10 ⁻⁴	6.19×10 ⁻³	APOE, PICALM
18	BP	GO:1902991	regulation of amyloid precursor protein catabolic process	2/6	60/18860	1.48×10 ⁻⁴	6.19×10 ⁻³	APOE, PICALM
19	BP	GO:0042987	amyloid precursor protein metabolic process	2/6	74/18860	2.26×10 ⁻⁴	7.86×10 ⁻³	APOE, PICALM
20	BP	GO:0050435	amyloid-beta metabolic process	2/6	74/18860	2.26×10 ⁻⁴	7.86×10 ⁻³	APOE, PICALM
21	BP	GO:0072657	protein localization to membrane	3/6	458/18860	2.69×10 ⁻⁴	8.66×10 ⁻³	APOE, GAK, PICALM
22	BP	GO:0034248	regulation of amide metabolic process	2/6	90/18860	3.34×10 ⁻⁴	9.96×10 ⁻³	APOE, PICALM
23	BP	GO:0042982	amyloid precursor protein metabolic process	2/6	102/18860	4.28×10 ⁻⁴	1.19×10 ⁻²	APOE, PICALM
24	BP	GO:0010977	negative regulation of neuron projection development	2/6	132/18860	7.16×10 ⁻⁴	1.87×10 ⁻²	APOE, GAK
25	MF	GO:0042277	peptide binding	2/7	234/18662	3.15×10 ⁻³	2.19×10 ⁻²	APOE, PICALM
26	MF	GO:0033218	amide binding	2/7	245/18662	3.45×10 ⁻³	2.19×10 ⁻²	APOE, PICALM
27	MF	GO:0032050	clathrin heavy chain binding	1/7	11/18662	4.12×10 ⁻³	2.19×10 ⁻²	PICALM
28	MF	GO:0046974	histone H3K9 methyltransferase activity	1/7	13/18662	4.87×10 ⁻³	2.19×10 ⁻²	ASH1L
29	MF	GO:0046975	histone H3K36 methyltransferase activity	1/7	13/18662	4.87×10 ⁻³	2.19×10 ⁻²	ASH1L
30	MF	GO:0005545	1-phosphatidylinositol binding	1/7	14/18662	5.24×10 ⁻³	2.19×10 ⁻²	PICALM
31	MF	GO:0042800	histone H3K4 methyltransferase activity	1/7	19/18662	7.11×10 ⁻³	2.51×10 ⁻²	ASH1L
32	MF	GO:0043395	heparan sulfate proteoglycan binding	1/7	19/18662	7.11×10 ⁻³	2.51×10 ⁻²	APOE
33	CC	GO:0042627	chylomicron	1/6	13/19944	3.91×10 ⁻³	2.60×10 ⁻²	APOE
34	CC	GO:0008250	oligosaccharyltransferase complex	1/6	14/19944	4.20×10 ⁻³	2.60×10 ⁻²	KRTCAP2
35	CC	GO:0034362	low-density lipoprotein particle	1/6	15/19944	4.50×10 ⁻³	2.60×10 ⁻²	APOE
36	CC	GO:0030139	endocytic vesicle	2/6	361/19944	4.67×10 ⁻³	2.60×10 ⁻²	APOE, PICALM
37	CC	GO:0030132	clathrin coat of coated pit	1/6	18/19944	5.40×10 ⁻³	2.60×10 ⁻²	PICALM
38	CC	GO:0099243	extrinsic component of synaptic membrane	1/6	20/19944	6.00×10 ⁻³	2.60×10 ⁻²	PICALM
39	CC	GO:0034361	very-low-density lipoprotein particle	1/6	21/19944	6.30×10 ⁻³	2.60×10 ⁻²	APOE
40	CC	GO:0034385	triglyceride-rich plasma lipoprotein particle	1/6	21/19944	6.30×10 ⁻³	2.60×10 ⁻²	APOE
41	CC	GO:0071682	endocytic vesicle lumen	1/6	23/19944	6.90×10 ⁻³	2.60×10 ⁻²	APOE
42	CC	GO:0005769	early endosome	2/6	448/19944	7.11×10 ⁻³	2.60×10 ⁻²	APOE, PICALM
43	CC	GO:0043083	synaptic cleft	1/6	25/19944	7.50×10 ⁻³	2.60×10 ⁻²	APOE
44	CC	GO:0034364	high-density lipoprotein particle	1/6	27/19944	8.10×10 ⁻³	2.60×10 ⁻²	APOE
45	CC	GO:0043025	neuronal cell body	2/6	486/19944	8.33×10 ⁻³	2.60×10 ⁻²	APOE, PICALM
46	MF	GO:0120020	cholesterol transfer activity	1/7	25/18662	9.34×10 ⁻³	3.07×10 ⁻²	APOE
47	CC	GO:0034358	plasma lipoprotein particle	1/6	37/19944	1.11×10 ⁻²	3.08×10 ⁻²	APOE
48	CC	GO:1990777	lipoprotein particle	1/6	37/19944	1.11×10 ⁻²	3.08×10 ⁻²	APOE
49	CC	GO:0032994	protein-lipid complex	1/6	40/19944	1.20×10 ⁻²	3.15×10 ⁻²	APOE
50	MF	GO:0071813	lipoprotein particle binding	1/7	32/18662	1.19×10 ⁻²	3.23×10 ⁻²	APOE
51	MF	GO:0071814	protein-lipid complex binding	1/7	32/18662	1.19×10 ⁻²	3.23×10 ⁻²	APOE
52	MF	GO:0120015	sterol transfer activity	1/7	32/18662	1.19×10 ⁻²	3.23×10 ⁻²	APOE
53	MF	GO:0030332	cyclin binding	1/7	34/18662	1.27×10 ⁻²	3.24×10 ⁻²	GAK
54	BP	GO:0043409	negative regulation of MAPK cascade	2/6	183/18860	1.37×10 ⁻³	3.32×10 ⁻²	APOE, ASH1L
55	BP	GO:0031345	negative regulation of cell projection organization	2/6	192/18860	1.51×10 ⁻³	3.32×10 ⁻²	APOE, GAK
56	BP	GO:0050728	negative regulation of inflammatory response	2/6	210/18860	1.80×10 ⁻³	3.32×10 ⁻²	APOE, ASH1L
57	BP	GO:1903828	negative regulation of protein localization	2/6	222/18860	2.01×10 ⁻³	3.32×10 ⁻²	APOE, PICALM
58	BP	GO:0016358	dendrite development	2/6	241/18860	2.36×10 ⁻³	3.32×10 ⁻²	APOE, PICALM
59	BP	GO:0061000	negative regulation of dendritic spine development	1/6	10/18860	3.18×10 ⁻³	3.32×10 ⁻²	APOE
60	BP	GO:0097113	AMPA glutamate receptor clustering	1/6	10/18860	3.18×10 ⁻³	3.32×10 ⁻²	APOE

BP = biological process · MF = molecular function · CC = cellular component

GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S7 – GO enrichment analysis: DLB + PD

7 genes in pattern · 236 significant GO terms (FDR < 0.05) · page 2 of 4 (rows 61–120)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
61	BP	GO:0097688	glutamate receptor clustering	1/6	10/18860	3.18×10 ⁻³	3.32×10 ⁻²	APOE
62	BP	GO:0007611	learning or memory	2/6	284/18860	3.26×10 ⁻³	3.32×10 ⁻²	APOE, PICALM
63	BP	GO:0038060	nitric oxide-cGMP-mediated signaling	1/6	11/18860	3.49×10 ⁻³	3.32×10 ⁻²	APOE
64	BP	GO:0048733	sebaceous gland development	1/6	11/18860	3.49×10 ⁻³	3.32×10 ⁻²	ASH1L
65	BP	GO:0061771	response to caloric restriction	1/6	11/18860	3.49×10 ⁻³	3.32×10 ⁻²	APOE
66	BP	GO:0090160	Golgi to lysosome transport	1/6	11/18860	3.49×10 ⁻³	3.32×10 ⁻²	GAK
67	BP	GO:0097090	presynaptic membrane organization	1/6	11/18860	3.49×10 ⁻³	3.32×10 ⁻²	APOE
68	BP	GO:2000822	regulation of behavioral fear response	1/6	11/18860	3.49×10 ⁻³	3.32×10 ⁻²	APOE
69	BP	GO:0072659	protein localization to plasma membrane	2/6	295/18860	3.51×10 ⁻³	3.32×10 ⁻²	GAK, PICALM
70	BP	GO:0017038	protein import	1/6	12/18860	3.81×10 ⁻³	3.32×10 ⁻²	APOE
71	BP	GO:0032489	regulation of Cdc42 protein signal transduction	1/6	12/18860	3.81×10 ⁻³	3.32×10 ⁻²	APOE
72	BP	GO:0045541	negative regulation of cholesterol biosynthetic process	1/6	12/18860	3.81×10 ⁻³	3.32×10 ⁻²	APOE
73	BP	GO:0106119	negative regulation of sterol biosynthetic process	1/6	12/18860	3.81×10 ⁻³	3.32×10 ⁻²	APOE
74	BP	GO:1903365	regulation of fear response	1/6	12/18860	3.81×10 ⁻³	3.32×10 ⁻²	APOE
75	BP	GO:2000009	negative regulation of protein localization to cell surface	1/6	12/18860	3.81×10 ⁻³	3.32×10 ⁻²	PICALM
76	BP	GO:0031348	negative regulation of defense response	2/6	313/18860	3.94×10 ⁻³	3.32×10 ⁻²	APOE, ASH1L
77	BP	GO:0051056	regulation of small GTPase mediated signal transduction	2/6	314/18860	3.97×10 ⁻³	3.32×10 ⁻²	APOE, PICALM
78	BP	GO:0030100	regulation of endocytosis	2/6	318/18860	4.06×10 ⁻³	3.32×10 ⁻²	APOE, PICALM
79	BP	GO:0002674	negative regulation of acute inflammatory response	1/6	13/18860	4.13×10 ⁻³	3.32×10 ⁻²	ASH1L
80	BP	GO:0034380	high-density lipoprotein particle assembly	1/6	13/18860	4.13×10 ⁻³	3.32×10 ⁻²	APOE
81	BP	GO:1900272	negative regulation of long-term synaptic potentiation	1/6	13/18860	4.13×10 ⁻³	3.32×10 ⁻²	APOE
82	BP	GO:2000644	regulation of receptor catabolic process	1/6	13/18860	4.13×10 ⁻³	3.32×10 ⁻²	APOE
83	BP	GO:0010642	negative regulation of platelet-derived growth factor receptor signaling pathway	1/6	14/18860	4.45×10 ⁻³	3.32×10 ⁻²	APOE
84	BP	GO:0033700	phospholipid efflux	1/6	14/18860	4.45×10 ⁻³	3.32×10 ⁻²	APOE
85	BP	GO:0042159	lipoprotein catabolic process	1/6	14/18860	4.45×10 ⁻³	3.32×10 ⁻²	APOE
86	BP	GO:1905907	negative regulation of amyloid fibril formation	1/6	14/18860	4.45×10 ⁻³	3.32×10 ⁻²	APOE
87	BP	GO:0050890	cognition	2/6	333/18860	4.45×10 ⁻³	3.32×10 ⁻²	APOE, PICALM
88	BP	GO:0032488	Cdc42 protein signal transduction	1/6	15/18860	4.76×10 ⁻³	3.32×10 ⁻²	APOE
89	BP	GO:0034372	very-low-density lipoprotein particle remodeling	1/6	15/18860	4.76×10 ⁻³	3.32×10 ⁻²	APOE
90	BP	GO:0090206	negative regulation of cholesterol metabolic process	1/6	15/18860	4.76×10 ⁻³	3.32×10 ⁻²	APOE
91	BP	GO:1902950	regulation of dendritic spine maintenance	1/6	15/18860	4.76×10 ⁻³	3.32×10 ⁻²	APOE
92	BP	GO:1905809	negative regulation of synapse organization	1/6	15/18860	4.76×10 ⁻³	3.32×10 ⁻²	APOE
93	BP	GO:2001138	regulation of phospholipid transport	1/6	15/18860	4.76×10 ⁻³	3.32×10 ⁻²	APOE
94	BP	GO:2001140	positive regulation of phospholipid transport	1/6	15/18860	4.76×10 ⁻³	3.32×10 ⁻²	APOE
95	BP	GO:0034370	triglyceride-rich lipoprotein particle remodeling	1/6	16/18860	5.08×10 ⁻³	3.32×10 ⁻²	APOE
96	BP	GO:0034374	low-density lipoprotein particle remodeling	1/6	16/18860	5.08×10 ⁻³	3.32×10 ⁻²	APOE
97	BP	GO:0035641	locomotory exploration behavior	1/6	16/18860	5.08×10 ⁻³	3.32×10 ⁻²	APOE
98	BP	GO:0032535	regulation of cellular component size	2/6	361/18860	5.21×10 ⁻³	3.32×10 ⁻²	APOE, PICALM
99	BP	GO:1990778	protein localization to cell periphery	2/6	365/18860	5.32×10 ⁻³	3.32×10 ⁻²	GAK, PICALM
100	BP	GO:0043117	positive regulation of vascular permeability	1/6	17/18860	5.40×10 ⁻³	3.32×10 ⁻²	APOE
101	BP	GO:0051044	positive regulation of membrane protein ectodomain proteolysis	1/6	17/18860	5.40×10 ⁻³	3.32×10 ⁻²	APOE
102	BP	GO:0090209	negative regulation of triglyceride metabolic process	1/6	17/18860	5.40×10 ⁻³	3.32×10 ⁻²	APOE
103	BP	GO:0010544	negative regulation of platelet activation	1/6	18/18860	5.71×10 ⁻³	3.32×10 ⁻²	APOE
104	BP	GO:0034384	high-density lipoprotein particle clearance	1/6	18/18860	5.71×10 ⁻³	3.32×10 ⁻²	APOE
105	BP	GO:0046579	positive regulation of Ras protein signal transduction	1/6	18/18860	5.71×10 ⁻³	3.32×10 ⁻²	PICALM
106	BP	GO:0055089	fatty acid homeostasis	1/6	18/18860	5.71×10 ⁻³	3.32×10 ⁻²	APOE
107	BP	GO:0097494	regulation of vesicle size	1/6	18/18860	5.71×10 ⁻³	3.32×10 ⁻²	PICALM
108	BP	GO:1902931	negative regulation of alcohol biosynthetic process	1/6	18/18860	5.71×10 ⁻³	3.32×10 ⁻²	APOE
109	BP	GO:1905906	regulation of amyloid fibril formation	1/6	18/18860	5.71×10 ⁻³	3.32×10 ⁻²	APOE
110	MF	GO:0043394	proteoglycan binding	1/7	37/18662	1.38×10 ⁻²	3.34×10 ⁻²	APOE
111	BP	GO:0006896	Golgi to vacuole transport	1/6	19/18860	6.03×10 ⁻³	3.41×10 ⁻²	GAK
112	BP	GO:0072578	neurotransmitter-gated ion channel clustering	1/6	19/18860	6.03×10 ⁻³	3.41×10 ⁻²	APOE
113	BP	GO:0043116	negative regulation of vascular permeability	1/6	20/18860	6.35×10 ⁻³	3.48×10 ⁻²	APOE
114	BP	GO:0016050	vesicle organization	2/6	401/18860	6.39×10 ⁻³	3.48×10 ⁻²	APOE, PICALM
115	BP	GO:0034375	high-density lipoprotein particle remodeling	1/6	21/18860	6.66×10 ⁻³	3.48×10 ⁻²	APOE
116	BP	GO:0043691	reverse cholesterol transport	1/6	21/18860	6.66×10 ⁻³	3.48×10 ⁻²	APOE
117	BP	GO:0045056	transcytosis	1/6	21/18860	6.66×10 ⁻³	3.48×10 ⁻²	PICALM
118	BP	GO:1900221	regulation of amyloid-beta clearance	1/6	21/18860	6.66×10 ⁻³	3.48×10 ⁻²	APOE
119	BP	GO:0090083	regulation of inclusion body assembly	1/6	23/18860	7.30×10 ⁻³	3.67×10 ⁻²	APOE
120	BP	GO:0043254	regulation of protein-containing complex assembly	2/6	438/18860	7.59×10 ⁻³	3.67×10 ⁻²	APOE, GAK

BP = biological process · MF = molecular function · CC = cellular component

GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini–Hochberg adjusted p-value

Table S7 – GO enrichment analysis: DLB + PD

7 genes in pattern · 236 significant GO terms (FDR < 0.05) · page 3 of 4 (rows 121-180)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
121	BP	GO:0097062	dendritic spine maintenance	1/6	24/18860	7.61×10 ⁻³	3.67×10 ⁻²	APOE
122	BP	GO:0010975	regulation of neuron projection development	2/6	448/18860	7.93×10 ⁻³	3.67×10 ⁻²	APOE, GAK
123	BP	GO:0046697	decidualization	1/6	25/18860	7.93×10 ⁻³	3.67×10 ⁻²	ASH1L
124	BP	GO:0032102	negative regulation of response to external stimulus	2/6	452/18860	8.06×10 ⁻³	3.67×10 ⁻²	APOE, ASH1L
125	BP	GO:0006706	steroid catabolic process	1/6	26/18860	8.24×10 ⁻³	3.67×10 ⁻²	APOE
126	BP	GO:0007263	nitric oxide mediated signal transduction	1/6	26/18860	8.24×10 ⁻³	3.67×10 ⁻²	APOE
127	BP	GO:0042953	lipoprotein transport	1/6	26/18860	8.24×10 ⁻³	3.67×10 ⁻²	APOE
128	BP	GO:0090370	negative regulation of cholesterol efflux	1/6	26/18860	8.24×10 ⁻³	3.67×10 ⁻²	APOE
129	BP	GO:0050727	regulation of inflammatory response	2/6	460/18860	8.34×10 ⁻³	3.67×10 ⁻²	APOE, ASH1L
130	BP	GO:0010875	positive regulation of cholesterol efflux	1/6	27/18860	8.56×10 ⁻³	3.67×10 ⁻²	APOE
131	BP	GO:0016188	synaptic vesicle maturation	1/6	27/18860	8.56×10 ⁻³	3.67×10 ⁻²	PICALM
132	BP	GO:0034377	plasma lipoprotein particle assembly	1/6	27/18860	8.56×10 ⁻³	3.67×10 ⁻²	APOE
133	BP	GO:0044872	lipoprotein localization	1/6	27/18860	8.56×10 ⁻³	3.67×10 ⁻²	APOE
134	BP	GO:0051051	negative regulation of transport	2/6	468/18860	8.63×10 ⁻³	3.67×10 ⁻²	APOE, PICALM
135	BP	GO:0007409	axonogenesis	2/6	472/18860	8.77×10 ⁻³	3.67×10 ⁻²	APOE, PICALM
136	BP	GO:0010640	regulation of platelet-derived growth factor receptor signaling pathway	1/6	28/18860	8.88×10 ⁻³	3.67×10 ⁻²	APOE
137	BP	GO:0051043	regulation of membrane protein ectodomain proteolysis	1/6	28/18860	8.88×10 ⁻³	3.67×10 ⁻²	APOE
138	BP	GO:0060065	uterus development	1/6	28/18860	8.88×10 ⁻³	3.67×10 ⁻²	ASH1L
139	BP	GO:0060586	multicellular organismal-level iron ion homeostasis	1/6	28/18860	8.88×10 ⁻³	3.67×10 ⁻²	PICALM
140	MF	GO:0140938	histone H3 methyltransferase activity	1/7	43/18662	1.60×10 ⁻²	3.68×10 ⁻²	ASH1L
141	CC	GO:0030118	clathrin coat	1/6	51/19944	1.52×10 ⁻²	3.81×10 ⁻²	PICALM
142	BP	GO:0065005	protein-lipid complex assembly	1/6	30/18860	9.51×10 ⁻³	3.86×10 ⁻²	APOE
143	BP	GO:1903077	negative regulation of protein localization to plasma membrane	1/6	30/18860	9.51×10 ⁻³	3.86×10 ⁻²	PICALM
144	BP	GO:0010894	negative regulation of steroid biosynthetic process	1/6	31/18860	9.82×10 ⁻³	3.87×10 ⁻²	APOE
145	BP	GO:0032801	receptor catabolic process	1/6	31/18860	9.82×10 ⁻³	3.87×10 ⁻²	APOE
146	BP	GO:0090205	positive regulation of cholesterol metabolic process	1/6	31/18860	9.82×10 ⁻³	3.87×10 ⁻²	APOE
147	BP	GO:1902430	negative regulation of amyloid-beta formation	1/6	32/18860	1.01×10 ⁻²	3.88×10 ⁻²	APOE
148	BP	GO:1904376	negative regulation of protein localization to cell periphery	1/6	32/18860	1.01×10 ⁻²	3.88×10 ⁻²	PICALM
149	BP	GO:0007271	synaptic transmission, cholinergic	1/6	33/18860	1.05×10 ⁻²	3.88×10 ⁻²	APOE
150	BP	GO:0034067	protein localization to Golgi apparatus	1/6	33/18860	1.05×10 ⁻²	3.88×10 ⁻²	GAK
151	BP	GO:0070841	inclusion body assembly	1/6	33/18860	1.05×10 ⁻²	3.88×10 ⁻²	APOE
152	BP	GO:1905476	negative regulation of protein localization to membrane	1/6	33/18860	1.05×10 ⁻²	3.88×10 ⁻²	PICALM
153	BP	GO:0032372	negative regulation of sterol transport	1/6	34/18860	1.08×10 ⁻²	3.88×10 ⁻²	APOE
154	BP	GO:0032375	negative regulation of cholesterol transport	1/6	34/18860	1.08×10 ⁻²	3.88×10 ⁻²	APOE
155	BP	GO:0048261	negative regulation of receptor-mediated endocytosis	1/6	34/18860	1.08×10 ⁻²	3.88×10 ⁻²	PICALM
156	BP	GO:1902992	negative regulation of amyloid precursor protein catabolic process	1/6	34/18860	1.08×10 ⁻²	3.88×10 ⁻²	APOE
157	BP	GO:0001893	maternal placenta development	1/6	36/18860	1.14×10 ⁻²	3.89×10 ⁻²	ASH1L
158	BP	GO:0002021	response to dietary excess	1/6	36/18860	1.14×10 ⁻²	3.89×10 ⁻²	APOE
159	BP	GO:0019068	virion assembly	1/6	36/18860	1.14×10 ⁻²	3.89×10 ⁻²	APOE
160	BP	GO:0032373	positive regulation of sterol transport	1/6	36/18860	1.14×10 ⁻²	3.89×10 ⁻²	APOE
161	BP	GO:0032376	positive regulation of cholesterol transport	1/6	36/18860	1.14×10 ⁻²	3.89×10 ⁻²	APOE
162	BP	GO:0007616	long-term memory	1/6	37/18860	1.17×10 ⁻²	3.89×10 ⁻²	APOE
163	BP	GO:0035459	vesicle cargo loading	1/6	37/18860	1.17×10 ⁻²	3.89×10 ⁻²	PICALM
164	BP	GO:0045540	regulation of cholesterol biosynthetic process	1/6	37/18860	1.17×10 ⁻²	3.89×10 ⁻²	APOE
165	BP	GO:0045939	negative regulation of steroid metabolic process	1/6	37/18860	1.17×10 ⁻²	3.89×10 ⁻²	APOE
166	BP	GO:0106118	regulation of sterol biosynthetic process	1/6	37/18860	1.17×10 ⁻²	3.89×10 ⁻²	APOE
167	BP	GO:0019934	cGMP-mediated signaling	1/6	38/18860	1.20×10 ⁻²	3.90×10 ⁻²	APOE
168	BP	GO:0044794	host-mediated activation of viral process	1/6	38/18860	1.20×10 ⁻²	3.90×10 ⁻²	APOE
169	BP	GO:0046164	alcohol catabolic process	1/6	38/18860	1.20×10 ⁻²	3.90×10 ⁻²	APOE
170	BP	GO:0032438	melanosome organization	1/6	39/18860	1.23×10 ⁻²	3.94×10 ⁻²	APOE
171	BP	GO:0034249	negative regulation of amide metabolic process	1/6	39/18860	1.23×10 ⁻²	3.94×10 ⁻²	APOE
172	BP	GO:0035640	exploration behavior	1/6	40/18860	1.27×10 ⁻²	3.95×10 ⁻²	APOE
173	BP	GO:0048753	pigment granule organization	1/6	40/18860	1.27×10 ⁻²	3.95×10 ⁻²	APOE
174	BP	GO:0055094	response to lipoprotein particle	1/6	40/18860	1.27×10 ⁻²	3.95×10 ⁻²	APOE
175	BP	GO:0034368	protein-lipid complex remodeling	1/6	41/18860	1.30×10 ⁻²	3.99×10 ⁻²	APOE
176	BP	GO:0034369	plasma lipoprotein particle remodeling	1/6	41/18860	1.30×10 ⁻²	3.99×10 ⁻²	APOE
177	BP	GO:0045429	positive regulation of nitric oxide biosynthetic process	1/6	42/18860	1.33×10 ⁻²	4.03×10 ⁻²	APOE
178	BP	GO:0060999	positive regulation of dendritic spine development	1/6	42/18860	1.33×10 ⁻²	4.03×10 ⁻²	APOE
179	BP	GO:0034367	protein-containing complex remodeling	1/6	43/18860	1.36×10 ⁻²	4.06×10 ⁻²	APOE
180	BP	GO:2000008	regulation of protein localization to cell surface	1/6	43/18860	1.36×10 ⁻²	4.06×10 ⁻²	PICALM

BP = biological process · MF = molecular function · CC = cellular component

GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S7 – GO enrichment analysis: DLB + PD

7 genes in pattern · 236 significant GO terms (FDR < 0.05) · page 4 of 4 (rows 181–236)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
181	BP	GO:0001941	postsynaptic membrane organization	1/6	44/18860	1.39×10 ⁻²	4.07×10 ⁻²	APOE
182	BP	GO:0018279	protein N-linked glycosylation via asparagine	1/6	44/18860	1.39×10 ⁻²	4.07×10 ⁻²	KRTCAP2
183	BP	GO:0045940	positive regulation of steroid metabolic process	1/6	44/18860	1.39×10 ⁻²	4.07×10 ⁻²	APOE
184	BP	GO:1900271	regulation of long-term synaptic potentiation	1/6	45/18860	1.42×10 ⁻²	4.07×10 ⁻²	APOE
185	BP	GO:1904407	positive regulation of nitric oxide metabolic process	1/6	45/18860	1.42×10 ⁻²	4.07×10 ⁻²	APOE
186	BP	GO:1990000	amyloid fibril formation	1/6	45/18860	1.42×10 ⁻²	4.07×10 ⁻²	APOE
187	BP	GO:0042158	lipoprotein biosynthetic process	1/6	46/18860	1.45×10 ⁻²	4.14×10 ⁻²	APOE
188	BP	GO:0070328	triglyceride homeostasis	1/6	47/18860	1.49×10 ⁻²	4.14×10 ⁻²	APOE
189	BP	GO:0071402	cellular response to lipoprotein particle stimulus	1/6	47/18860	1.49×10 ⁻²	4.14×10 ⁻²	APOE
190	BP	GO:0090207	regulation of triglyceride metabolic process	1/6	47/18860	1.49×10 ⁻²	4.14×10 ⁻²	APOE
191	BP	GO:0001662	behavioral fear response	1/6	48/18860	1.52×10 ⁻²	4.15×10 ⁻²	APOE
192	BP	GO:0055090	acylglycerol homeostasis	1/6	48/18860	1.52×10 ⁻²	4.15×10 ⁻²	APOE
193	BP	GO:0002209	behavioral defense response	1/6	49/18860	1.55×10 ⁻²	4.15×10 ⁻²	APOE
194	BP	GO:0002673	regulation of acute inflammatory response	1/6	49/18860	1.55×10 ⁻²	4.15×10 ⁻²	ASH1L
195	BP	GO:0006509	membrane protein ectodomain proteolysis	1/6	49/18860	1.55×10 ⁻²	4.15×10 ⁻²	APOE
196	BP	GO:0046578	regulation of Ras protein signal transduction	1/6	49/18860	1.55×10 ⁻²	4.15×10 ⁻²	PICALM
197	BP	GO:1904646	cellular response to amyloid-beta	1/6	50/18860	1.58×10 ⁻²	4.21×10 ⁻²	APOE
198	BP	GO:0030195	negative regulation of blood coagulation	1/6	52/18860	1.64×10 ⁻²	4.29×10 ⁻²	APOE
199	BP	GO:0032369	negative regulation of lipid transport	1/6	52/18860	1.64×10 ⁻²	4.29×10 ⁻²	APOE
200	BP	GO:0043114	regulation of vascular permeability	1/6	52/18860	1.64×10 ⁻²	4.29×10 ⁻²	APOE
201	BP	GO:1900047	negative regulation of hemostasis	1/6	53/18860	1.67×10 ⁻²	4.35×10 ⁻²	APOE
202	BP	GO:0042596	fear response	1/6	54/18860	1.71×10 ⁻²	4.40×10 ⁻²	APOE
203	BP	GO:0010543	regulation of platelet activation	1/6	55/18860	1.74×10 ⁻²	4.46×10 ⁻²	APOE
204	BP	GO:0050819	negative regulation of coagulation	1/6	56/18860	1.77×10 ⁻²	4.51×10 ⁻²	APOE
205	BP	GO:0010874	regulation of cholesterol efflux	1/6	57/18860	1.80×10 ⁻²	4.53×10 ⁻²	APOE
206	BP	GO:0060998	regulation of dendritic spine development	1/6	57/18860	1.80×10 ⁻²	4.53×10 ⁻²	APOE
207	BP	GO:0071827	plasma lipoprotein particle organization	1/6	58/18860	1.83×10 ⁻²	4.58×10 ⁻²	APOE
208	BP	GO:0090181	regulation of cholesterol metabolic process	1/6	59/18860	1.86×10 ⁻²	4.63×10 ⁻²	APOE
209	BP	GO:0042311	vasodilation	1/6	60/18860	1.89×10 ⁻²	4.63×10 ⁻²	APOE
210	BP	GO:0060135	maternal process involved in female pregnancy	1/6	60/18860	1.89×10 ⁻²	4.63×10 ⁻²	ASH1L
211	BP	GO:1902930	regulation of alcohol biosynthetic process	1/6	60/18860	1.89×10 ⁻²	4.63×10 ⁻²	APOE
212	BP	GO:0048168	regulation of neuronal synaptic plasticity	1/6	61/18860	1.93×10 ⁻²	4.63×10 ⁻²	APOE
213	BP	GO:0071825	protein-lipid complex organization	1/6	61/18860	1.93×10 ⁻²	4.63×10 ⁻²	APOE
214	BP	GO:1904645	response to amyloid-beta	1/6	61/18860	1.93×10 ⁻²	4.63×10 ⁻²	APOE
215	MF	GO:0042054	histone methyltransferase activity	1/7	58/18662	2.16×10 ⁻²	4.72×10 ⁻²	ASH1L
216	BP	GO:0048008	platelet-derived growth factor receptor signaling pathway	1/6	63/18860	1.99×10 ⁻²	4.75×10 ⁻²	APOE
217	MF	GO:0016279	protein-lysine N-methyltransferase activity	1/7	63/18662	2.34×10 ⁻²	4.75×10 ⁻²	ASH1L
218	MF	GO:0016278	lysine N-methyltransferase activity	1/7	64/18662	2.38×10 ⁻²	4.75×10 ⁻²	ASH1L
219	BP	GO:0033619	membrane protein proteolysis	1/6	64/18860	2.02×10 ⁻²	4.76×10 ⁻²	APOE
220	BP	GO:0034381	plasma lipoprotein particle clearance	1/6	64/18860	2.02×10 ⁻²	4.76×10 ⁻²	APOE
221	BP	GO:0015909	long-chain fatty acid transport	1/6	65/18860	2.05×10 ⁻²	4.76×10 ⁻²	APOE
222	BP	GO:0033059	cellular pigmentation	1/6	65/18860	2.05×10 ⁻²	4.76×10 ⁻²	APOE
223	BP	GO:0045428	regulation of nitric oxide biosynthetic process	1/6	65/18860	2.05×10 ⁻²	4.76×10 ⁻²	APOE
224	MF	GO:0120013	lipid transfer activity	1/7	67/18662	2.49×10 ⁻²	4.77×10 ⁻²	APOE
225	BP	GO:0043113	receptor clustering	1/6	66/18860	2.08×10 ⁻²	4.81×10 ⁻²	APOE
226	CC	GO:0005771	multivesicular body	1/6	68/19944	2.03×10 ⁻²	4.83×10 ⁻²	APOE
227	CC	GO:0016234	inclusion body	1/6	75/19944	2.24×10 ⁻²	4.84×10 ⁻²	PICALM
228	CC	GO:0030669	clathrin-coated endocytic vesicle membrane	1/6	76/19944	2.27×10 ⁻²	4.84×10 ⁻²	APOE
229	CC	GO:0005905	clathrin-coated pit	1/6	78/19944	2.32×10 ⁻²	4.84×10 ⁻²	PICALM
230	BP	GO:0034394	protein localization to cell surface	1/6	68/18860	2.14×10 ⁻²	4.92×10 ⁻²	PICALM
231	BP	GO:0080164	regulation of nitric oxide metabolic process	1/6	69/18860	2.18×10 ⁻²	4.97×10 ⁻²	APOE
232	BP	GO:0030193	regulation of blood coagulation	1/6	70/18860	2.21×10 ⁻²	4.98×10 ⁻²	APOE
233	BP	GO:1905953	negative regulation of lipid localization	1/6	70/18860	2.21×10 ⁻²	4.98×10 ⁻²	APOE
234	BP	GO:0006695	cholesterol biosynthetic process	1/6	71/18860	2.24×10 ⁻²	4.98×10 ⁻²	APOE
235	BP	GO:0048662	negative regulation of smooth muscle cell proliferation	1/6	71/18860	2.24×10 ⁻²	4.98×10 ⁻²	APOE
236	BP	GO:1902653	secondary alcohol biosynthetic process	1/6	71/18860	2.24×10 ⁻²	4.98×10 ⁻²	APOE

BP = biological process · MF = molecular function · CC = cellular component

GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S8 – GO enrichment analysis: PD + RBD

4 genes in pattern · 226 significant GO terms (FDR < 0.05) · page 1 of 4 (rows 1–60)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
1	BP	GO:0002768	immune response-regulating cell surface receptor signaling pathway	4/4	385/18860	1.71×10 ⁻⁷	5.15×10 ⁻⁵	BLNK, CD33, FCGR2A, PTPRC
2	CC	GO:0030667	secretory granule membrane	3/4	325/19944	1.69×10 ⁻⁵	2.10×10 ⁻⁴	CD33, FCGR2A, PTPRC
3	CC	GO:0009897	external side of plasma membrane	3/4	393/19944	2.99×10 ⁻⁵	2.10×10 ⁻⁴	CD33, FCGR2A, PTPRC
4	BP	GO:0032640	tumor necrosis factor production	3/4	196/18860	4.39×10 ⁻⁶	2.85×10 ⁻⁴	CD33, FCGR2A, PTPRC
5	BP	GO:0032680	regulation of tumor necrosis factor production	3/4	196/18860	4.39×10 ⁻⁶	2.85×10 ⁻⁴	CD33, FCGR2A, PTPRC
6	BP	GO:0071706	tumor necrosis factor superfamily cytokine production	3/4	201/18860	4.73×10 ⁻⁶	2.85×10 ⁻⁴	CD33, FCGR2A, PTPRC
7	BP	GO:1903555	regulation of tumor necrosis factor superfamily cytokine production	3/4	201/18860	4.73×10 ⁻⁶	2.85×10 ⁻⁴	CD33, FCGR2A, PTPRC
8	BP	GO:0038094	Fc-gamma receptor signaling pathway	2/4	38/18860	2.37×10 ⁻⁵	1.19×10 ⁻³	CD33, FCGR2A
9	BP	GO:0038093	Fc receptor signaling pathway	2/4	61/18860	6.15×10 ⁻⁵	2.64×10 ⁻³	CD33, FCGR2A
10	BP	GO:0050853	B cell receptor signaling pathway	2/4	78/18860	1.01×10 ⁻⁴	3.46×10 ⁻³	BLNK, PTPRC
11	BP	GO:0050766	positive regulation of phagocytosis	2/4	79/18860	1.03×10 ⁻⁴	3.46×10 ⁻³	FCGR2A, PTPRC
12	BP	GO:0032637	interleukin-8 production	2/4	105/18860	1.83×10 ⁻⁴	4.85×10 ⁻³	CD33, PTPRC
13	BP	GO:0032677	regulation of interleukin-8 production	2/4	105/18860	1.83×10 ⁻⁴	4.85×10 ⁻³	CD33, PTPRC
14	BP	GO:0050764	regulation of phagocytosis	2/4	108/18860	1.93×10 ⁻⁴	4.85×10 ⁻³	FCGR2A, PTPRC
15	BP	GO:0032760	positive regulation of tumor necrosis factor production	2/4	113/18860	2.12×10 ⁻⁴	4.88×10 ⁻³	FCGR2A, PTPRC
16	BP	GO:1903557	positive regulation of tumor necrosis factor superfamily cytokine production	2/4	117/18860	2.27×10 ⁻⁴	4.88×10 ⁻³	FCGR2A, PTPRC
17	BP	GO:0030183	B cell differentiation	2/4	147/18860	3.58×10 ⁻⁴	7.19×10 ⁻³	BLNK, PTPRC
18	BP	GO:0001909	leukocyte mediated cytotoxicity	2/4	157/18860	4.09×10 ⁻⁴	7.69×10 ⁻³	FCGR2A, PTPRC
19	BP	GO:0045807	positive regulation of endocytosis	2/4	165/18860	4.51×10 ⁻⁴	7.99×10 ⁻³	FCGR2A, PTPRC
20	BP	GO:0016064	immunoglobulin mediated immune response	2/4	203/18860	6.82×10 ⁻⁴	1.10×10 ⁻²	FCGR2A, PTPRC
21	BP	GO:0019724	B cell mediated immunity	2/4	206/18860	7.02×10 ⁻⁴	1.10×10 ⁻²	FCGR2A, PTPRC
22	BP	GO:0020695	negative regulation of leukocyte activation	2/4	212/18860	7.43×10 ⁻⁴	1.10×10 ⁻²	CD33, PTPRC
23	BP	GO:0050851	antigen receptor-mediated signaling pathway	2/4	215/18860	7.65×10 ⁻⁴	1.10×10 ⁻²	BLNK, PTPRC
24	BP	GO:0050866	negative regulation of cell activation	2/4	235/18860	9.12×10 ⁻⁴	1.25×10 ⁻²	CD33, PTPRC
25	BP	GO:0006909	phagocytosis	2/4	251/18860	1.04×10 ⁻³	1.35×10 ⁻²	FCGR2A, PTPRC
26	BP	GO:0002274	myeloid leukocyte activation	2/4	255/18860	1.07×10 ⁻³	1.35×10 ⁻²	CD33, PTPRC
27	BP	GO:0001906	cell killing	2/4	281/18860	1.30×10 ⁻³	1.57×10 ⁻²	FCGR2A, PTPRC
28	BP	GO:0042113	B cell activation	2/4	291/18860	1.39×10 ⁻³	1.61×10 ⁻²	BLNK, PTPRC
29	BP	GO:0006959	humoral immune response	2/4	307/18860	1.55×10 ⁻³	1.73×10 ⁻²	BLNK, PTPRC
30	BP	GO:0030100	regulation of endocytosis	2/4	318/18860	1.66×10 ⁻³	1.76×10 ⁻²	FCGR2A, PTPRC
31	BP	GO:0002429	immune response-activating cell surface receptor signaling pathway	2/4	353/18860	2.04×10 ⁻³	1.76×10 ⁻²	BLNK, PTPRC
32	BP	GO:0001788	antibody-dependent cellular cytotoxicity	1/4	10/18860	2.12×10 ⁻³	1.76×10 ⁻²	FCGR2A
33	BP	GO:0001915	negative regulation of T cell mediated cytotoxicity	1/4	10/18860	2.12×10 ⁻³	1.76×10 ⁻²	PTPRC
34	BP	GO:0035701	hematopoietic stem cell migration	1/4	10/18860	2.12×10 ⁻³	1.76×10 ⁻²	PTPRC
35	BP	GO:0002765	immune response-inhibiting signal transduction	1/4	11/18860	2.33×10 ⁻³	1.76×10 ⁻²	CD33
36	BP	GO:0045586	regulation of gamma-delta T cell differentiation	1/4	11/18860	2.33×10 ⁻³	1.76×10 ⁻²	PTPRC
37	BP	GO:0046645	positive regulation of gamma-delta T cell activation	1/4	11/18860	2.33×10 ⁻³	1.76×10 ⁻²	PTPRC
38	BP	GO:0048304	positive regulation of isotype switching to IgG isotypes	1/4	11/18860	2.33×10 ⁻³	1.76×10 ⁻²	PTPRC
39	BP	GO:0060368	regulation of Fc receptor mediated stimulatory signaling pathway	1/4	11/18860	2.33×10 ⁻³	1.76×10 ⁻²	PTPRC
40	BP	GO:0002449	lymphocyte mediated immunity	2/4	388/18860	2.46×10 ⁻³	1.76×10 ⁻²	FCGR2A, PTPRC
41	BP	GO:0001794	type Ila hypersensitivity	1/4	12/18860	2.54×10 ⁻³	1.76×10 ⁻²	FCGR2A
42	BP	GO:0002445	type II hypersensitivity	1/4	12/18860	2.54×10 ⁻³	1.76×10 ⁻²	FCGR2A
43	BP	GO:0035771	interleukin-4-mediated signaling pathway	1/4	12/18860	2.54×10 ⁻³	1.76×10 ⁻²	PTPRC
44	BP	GO:0045060	negative thymic T cell selection	1/4	12/18860	2.54×10 ⁻³	1.76×10 ⁻²	PTPRC
45	BP	GO:0002460	adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	2/4	402/18860	2.64×10 ⁻³	1.76×10 ⁻²	FCGR2A, PTPRC
46	BP	GO:0001818	negative regulation of cytokine production	2/4	405/18860	2.68×10 ⁻³	1.76×10 ⁻²	CD33, PTPRC
47	BP	GO:0042117	monocyte activation	1/4	13/18860	2.75×10 ⁻³	1.76×10 ⁻²	CD33
48	BP	GO:0043383	negative T cell selection	1/4	13/18860	2.75×10 ⁻³	1.76×10 ⁻²	PTPRC
49	BP	GO:0046643	regulation of gamma-delta T cell activation	1/4	13/18860	2.75×10 ⁻³	1.76×10 ⁻²	PTPRC
50	BP	GO:0030098	lymphocyte differentiation	2/4	441/18860	3.17×10 ⁻³	1.88×10 ⁻²	BLNK, PTPRC
51	BP	GO:0042492	gamma-delta T cell differentiation	1/4	15/18860	3.18×10 ⁻³	1.88×10 ⁻²	PTPRC
52	BP	GO:0045059	positive thymic T cell selection	1/4	15/18860	3.18×10 ⁻³	1.88×10 ⁻²	PTPRC
53	BP	GO:0048302	regulation of isotype switching to IgG isotypes	1/4	15/18860	3.18×10 ⁻³	1.88×10 ⁻²	PTPRC
54	MF	GO:0030292	protein tyrosine kinase inhibitor activity	1/4	10/18662	2.14×10 ⁻³	1.88×10 ⁻²	PTPRC
55	MF	GO:0019763	immunoglobulin receptor activity	1/4	14/18662	3.00×10 ⁻³	1.88×10 ⁻²	FCGR2A
56	MF	GO:0019864	IgG binding	1/4	14/18662	3.00×10 ⁻³	1.88×10 ⁻²	FCGR2A
57	MF	GO:0005001	transmembrane receptor protein tyrosine phosphatase activity	1/4	17/18662	3.64×10 ⁻³	1.88×10 ⁻²	PTPRC
58	MF	GO:0005068	transmembrane receptor protein tyrosine kinase adaptor activity	1/4	17/18662	3.64×10 ⁻³	1.88×10 ⁻²	BLNK
59	MF	GO:0019198	transmembrane receptor protein phosphatase activity	1/4	17/18662	3.64×10 ⁻³	1.88×10 ⁻²	PTPRC
60	MF	GO:0030506	ankyrin binding	1/4	19/18662	4.07×10 ⁻³	1.88×10 ⁻²	PTPRC

BP = biological process · MF = molecular function · CC = cellular component
GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S8 – GO enrichment analysis: PD + RBD

4 genes in pattern · 226 significant GO terms (FDR < 0.05) · page 2 of 4 (rows 61–120)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
61	MF	GO:0043395	heparan sulfate proteoglycan binding	1/4	19/18662	4.07×10 ⁻³	1.88×10 ⁻²	PTPRC
62	MF	GO:0033691	sialic acid binding	1/4	22/18662	4.71×10 ⁻³	1.88×10 ⁻²	CD33
63	MF	GO:0043274	phospholipase binding	1/4	23/18662	4.92×10 ⁻³	1.88×10 ⁻²	BLNK
64	MF	GO:0072542	protein phosphatase activator activity	1/4	24/18662	5.13×10 ⁻³	1.88×10 ⁻²	CD33
65	MF	GO:0030507	spectrin binding	1/4	27/18662	5.78×10 ⁻³	1.88×10 ⁻²	PTPRC
66	MF	GO:0019211	phosphatase activator activity	1/4	29/18662	6.20×10 ⁻³	1.88×10 ⁻²	CD33
67	MF	GO:0019865	immunoglobulin binding	1/4	30/18662	6.42×10 ⁻³	1.88×10 ⁻²	FCGR2A
68	BP	GO:0002923	regulation of humoral immune response mediated by circulating immunoglobulin	1/4	16/18860	3.39×10 ⁻³	1.92×10 ⁻²	PTPRC
69	BP	GO:0048291	isotype switching to IgG isotypes	1/4	16/18860	3.39×10 ⁻³	1.92×10 ⁻²	PTPRC
70	BP	GO:1904044	response to aldosterone	1/4	17/18860	3.60×10 ⁻³	2.01×10 ⁻²	PTPRC
71	BP	GO:0002443	leukocyte mediated immunity	2/4	488/18860	3.87×10 ⁻³	2.09×10 ⁻²	FCGR2A, PTPRC
72	BP	GO:0043031	negative regulation of macrophage activation	1/4	19/18860	4.02×10 ⁻³	2.09×10 ⁻²	PTPRC
73	BP	GO:0150079	negative regulation of neuroinflammatory response	1/4	19/18860	4.02×10 ⁻³	2.09×10 ⁻²	PTPRC
74	BP	GO:1903978	regulation of microglial cell activation	1/4	19/18860	4.02×10 ⁻³	2.09×10 ⁻²	PTPRC
75	MF	GO:0043394	proteoglycan binding	1/4	37/18662	7.91×10 ⁻³	2.16×10 ⁻²	PTPRC
76	MF	GO:0042169	SH2 domain binding	1/4	41/18662	8.76×10 ⁻³	2.24×10 ⁻²	BLNK
77	BP	GO:0002524	hypersensitivity	1/4	21/18860	4.45×10 ⁻³	2.27×10 ⁻²	FCGR2A
78	BP	GO:0046426	negative regulation of receptor signaling pathway via JAK-STAT	1/4	23/18860	4.87×10 ⁻³	2.44×10 ⁻²	PTPRC
79	BP	GO:0045061	thymic T cell selection	1/4	24/18860	5.08×10 ⁻³	2.47×10 ⁻²	PTPRC
80	BP	GO:0046641	positive regulation of alpha-beta T cell proliferation	1/4	24/18860	5.08×10 ⁻³	2.47×10 ⁻²	PTPRC
81	MF	GO:0140693	molecular condensate scaffold activity	1/4	49/18662	1.05×10 ⁻²	2.48×10 ⁻²	BLNK
82	MF	GO:0030159	signaling receptor complex adaptor activity	1/4	51/18662	1.09×10 ⁻²	2.48×10 ⁻²	BLNK
83	BP	GO:0002922	positive regulation of humoral immune response	1/4	25/18860	5.29×10 ⁻³	2.53×10 ⁻²	PTPRC
84	BP	GO:0001779	natural killer cell differentiation	1/4	27/18860	5.71×10 ⁻³	2.69×10 ⁻²	PTPRC
85	BP	GO:0032703	negative regulation of interleukin-2 production	1/4	28/18860	5.93×10 ⁻³	2.70×10 ⁻²	PTPRC
86	BP	GO:0046629	gamma-delta T cell activation	1/4	28/18860	5.93×10 ⁻³	2.70×10 ⁻²	PTPRC
87	BP	GO:0006929	substrate-dependent cell migration	1/4	29/18860	6.14×10 ⁻³	2.72×10 ⁻²	PTPRC
88	BP	GO:0045830	positive regulation of isotype switching	1/4	29/18860	6.14×10 ⁻³	2.72×10 ⁻²	PTPRC
89	BP	GO:0031579	membrane raft organization	1/4	30/18860	6.35×10 ⁻³	2.73×10 ⁻²	PTPRC
90	BP	GO:0050857	positive regulation of antigen receptor-mediated signaling pathway	1/4	30/18860	6.35×10 ⁻³	2.73×10 ⁻²	PTPRC
91	BP	GO:0001911	negative regulation of leukocyte mediated cytotoxicity	1/4	31/18860	6.56×10 ⁻³	2.78×10 ⁻²	PTPRC
92	BP	GO:0002438	acute inflammatory response to antigenic stimulus	1/4	32/18860	6.77×10 ⁻³	2.83×10 ⁻²	FCGR2A
93	BP	GO:0002431	Fc receptor mediated stimulatory signaling pathway	1/4	35/18860	7.40×10 ⁻³	2.94×10 ⁻²	PTPRC
94	BP	GO:0031342	negative regulation of cell killing	1/4	36/18860	7.61×10 ⁻³	2.94×10 ⁻²	PTPRC
95	BP	GO:0071353	cellular response to interleukin-4	1/4	36/18860	7.61×10 ⁻³	2.94×10 ⁻²	PTPRC
96	BP	GO:1904893	negative regulation of receptor signaling pathway via STAT	1/4	36/18860	7.61×10 ⁻³	2.94×10 ⁻²	PTPRC
97	BP	GO:0002710	negative regulation of T cell mediated immunity	1/4	37/18860	7.82×10 ⁻³	2.94×10 ⁻²	PTPRC
98	BP	GO:0032717	negative regulation of interleukin-8 production	1/4	37/18860	7.82×10 ⁻³	2.94×10 ⁻²	CD33
99	BP	GO:0032743	positive regulation of interleukin-2 production	1/4	37/18860	7.82×10 ⁻³	2.94×10 ⁻²	PTPRC
100	BP	GO:0051385	response to mineralocorticoid	1/4	37/18860	7.82×10 ⁻³	2.94×10 ⁻²	PTPRC
101	BP	GO:0001916	positive regulation of T cell mediated cytotoxicity	1/4	38/18860	8.04×10 ⁻³	2.95×10 ⁻²	PTPRC
102	BP	GO:0045191	regulation of isotype switching	1/4	38/18860	8.04×10 ⁻³	2.95×10 ⁻²	PTPRC
103	BP	GO:0070670	response to interleukin-4	1/4	39/18860	8.25×10 ⁻³	2.99×10 ⁻²	PTPRC
104	BP	GO:0002714	positive regulation of B cell mediated immunity	1/4	43/18860	9.09×10 ⁻³	3.18×10 ⁻²	PTPRC
105	BP	GO:0002891	positive regulation of immunoglobulin mediated immune response	1/4	43/18860	9.09×10 ⁻³	3.18×10 ⁻²	PTPRC
106	BP	GO:0046640	regulation of alpha-beta T cell proliferation	1/4	43/18860	9.09×10 ⁻³	3.18×10 ⁻²	PTPRC
107	BP	GO:0032691	negative regulation of interleukin-1 beta production	1/4	45/18860	9.51×10 ⁻³	3.29×10 ⁻²	CD33
108	BP	GO:0150077	regulation of neuroinflammatory response	1/4	46/18860	9.72×10 ⁻³	3.32×10 ⁻²	PTPRC
109	BP	GO:0030890	positive regulation of B cell proliferation	1/4	47/18860	9.93×10 ⁻³	3.32×10 ⁻²	PTPRC
110	BP	GO:0046633	alpha-beta T cell proliferation	1/4	47/18860	9.93×10 ⁻³	3.32×10 ⁻²	PTPRC
111	BP	GO:0001774	microglial cell activation	1/4	48/18860	1.01×10 ⁻²	3.32×10 ⁻²	PTPRC
112	BP	GO:0001914	regulation of T cell mediated cytotoxicity	1/4	48/18860	1.01×10 ⁻²	3.32×10 ⁻²	PTPRC
113	BP	GO:0002920	regulation of humoral immune response	1/4	50/18860	1.06×10 ⁻²	3.39×10 ⁻²	PTPRC
114	BP	GO:0002269	leukocyte activation involved in inflammatory response	1/4	51/18860	1.08×10 ⁻²	3.39×10 ⁻²	PTPRC
115	BP	GO:0043368	positive T cell selection	1/4	51/18860	1.08×10 ⁻²	3.39×10 ⁻²	PTPRC
116	BP	GO:0002455	humoral immune response mediated by circulating immunoglobulin	1/4	52/18860	1.10×10 ⁻²	3.39×10 ⁻²	PTPRC
117	BP	GO:0010332	response to gamma radiation	1/4	53/18860	1.12×10 ⁻²	3.39×10 ⁻²	PTPRC
118	BP	GO:0050856	regulation of T cell receptor signaling pathway	1/4	53/18860	1.12×10 ⁻²	3.39×10 ⁻²	PTPRC
119	BP	GO:0032692	negative regulation of interleukin-1 production	1/4	54/18860	1.14×10 ⁻²	3.39×10 ⁻²	CD33
120	BP	GO:0002204	somatic recombination of immunoglobulin genes involved in immune response	1/4	55/18860	1.16×10 ⁻²	3.39×10 ⁻²	PTPRC

BP = biological process · MF = molecular function · CC = cellular component

GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S8 – GO enrichment analysis: PD + RBD

4 genes in pattern · 226 significant GO terms (FDR < 0.05) · page 3 of 4 (rows 121–180)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
121	BP	GO:0002208	somatic diversification of immunoglobulins involved in immune response	1/4	55/18860	1.16×10 ⁻²	3.39×10 ⁻²	PTPRC
122	BP	GO:0045190	isotype switching	1/4	55/18860	1.16×10 ⁻²	3.39×10 ⁻²	PTPRC
123	BP	GO:2000648	positive regulation of stem cell proliferation	1/4	55/18860	1.16×10 ⁻²	3.39×10 ⁻²	PTPRC
124	BP	GO:0061900	glial cell activation	1/4	56/18860	1.18×10 ⁻²	3.42×10 ⁻²	PTPRC
125	BP	GO:0002381	immunoglobulin production involved in immunoglobulin-mediated immune response	1/4	59/18860	1.25×10 ⁻²	3.47×10 ⁻²	PTPRC
126	BP	GO:0002639	positive regulation of immunoglobulin production	1/4	59/18860	1.25×10 ⁻²	3.47×10 ⁻²	PTPRC
127	BP	GO:0050850	positive regulation of calcium-mediated signaling	1/4	59/18860	1.25×10 ⁻²	3.47×10 ⁻²	PTPRC
128	BP	GO:2001238	positive regulation of extrinsic apoptotic signaling pathway	1/4	59/18860	1.25×10 ⁻²	3.47×10 ⁻²	PTPRC
129	BP	GO:0001913	T cell mediated cytotoxicity	1/4	61/18860	1.29×10 ⁻²	3.49×10 ⁻²	PTPRC
130	BP	GO:0034113	heterotypic cell-cell adhesion	1/4	61/18860	1.29×10 ⁻²	3.49×10 ⁻²	PTPRC
131	BP	GO:0043030	regulation of macrophage activation	1/4	61/18860	1.29×10 ⁻²	3.49×10 ⁻²	PTPRC
132	BP	GO:0002712	regulation of B cell mediated immunity	1/4	62/18860	1.31×10 ⁻²	3.49×10 ⁻²	PTPRC
133	BP	GO:0002889	regulation of immunoglobulin mediated immune response	1/4	62/18860	1.31×10 ⁻²	3.49×10 ⁻²	PTPRC
134	BP	GO:0016447	somatic recombination of immunoglobulin gene segments	1/4	63/18860	1.33×10 ⁻²	3.51×10 ⁻²	PTPRC
135	BP	GO:0045058	T cell selection	1/4	64/18860	1.35×10 ⁻²	3.54×10 ⁻²	PTPRC
136	BP	GO:0032623	interleukin-2 production	1/4	66/18860	1.39×10 ⁻²	3.58×10 ⁻²	PTPRC
137	BP	GO:0032663	regulation of interleukin-2 production	1/4	66/18860	1.39×10 ⁻²	3.58×10 ⁻²	PTPRC
138	BP	GO:0030888	regulation of B cell proliferation	1/4	68/18860	1.43×10 ⁻²	3.64×10 ⁻²	PTPRC
139	BP	GO:0002707	negative regulation of lymphocyte mediated immunity	1/4	69/18860	1.46×10 ⁻²	3.64×10 ⁻²	PTPRC
140	BP	GO:0016445	somatic diversification of immunoglobulins	1/4	69/18860	1.46×10 ⁻²	3.64×10 ⁻²	PTPRC
141	BP	GO:0001912	positive regulation of leukocyte mediated cytotoxicity	1/4	70/18860	1.48×10 ⁻²	3.64×10 ⁻²	PTPRC
142	BP	GO:0002823	negative regulation of adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	1/4	70/18860	1.48×10 ⁻²	3.64×10 ⁻²	PTPRC
143	BP	GO:0002562	somatic diversification of immune receptors via germline recombination within a single locus	1/4	72/18860	1.52×10 ⁻²	3.67×10 ⁻²	PTPRC
144	BP	GO:0016444	somatic cell DNA recombination	1/4	72/18860	1.52×10 ⁻²	3.67×10 ⁻²	PTPRC
145	BP	GO:0031343	positive regulation of cell killing	1/4	73/18860	1.54×10 ⁻²	3.67×10 ⁻²	PTPRC
146	BP	GO:0002711	positive regulation of T cell mediated immunity	1/4	74/18860	1.56×10 ⁻²	3.67×10 ⁻²	PTPRC
147	BP	GO:0002820	negative regulation of adaptive immune response	1/4	74/18860	1.56×10 ⁻²	3.67×10 ⁻²	PTPRC
148	BP	GO:0050854	regulation of antigen receptor-mediated signaling pathway	1/4	74/18860	1.56×10 ⁻²	3.67×10 ⁻²	PTPRC
149	BP	GO:0006469	negative regulation of protein kinase activity	1/4	76/18860	1.60×10 ⁻²	3.71×10 ⁻²	PTPRC
150	BP	GO:0046635	positive regulation of alpha-beta T cell activation	1/4	76/18860	1.60×10 ⁻²	3.71×10 ⁻²	PTPRC
151	MF	GO:0030971	receptor tyrosine kinase binding	1/4	81/18662	1.73×10 ⁻²	3.72×10 ⁻²	BLNK
152	BP	GO:0002200	somatic diversification of immune receptors	1/4	79/18860	1.67×10 ⁻²	3.73×10 ⁻²	PTPRC
153	BP	GO:0002437	inflammatory response to antigenic stimulus	1/4	79/18860	1.67×10 ⁻²	3.73×10 ⁻²	FCGR2A
154	BP	GO:0045911	positive regulation of DNA recombination	1/4	79/18860	1.67×10 ⁻²	3.73×10 ⁻²	PTPRC
155	BP	GO:0046425	regulation of receptor signaling pathway via JAK-STAT	1/4	79/18860	1.67×10 ⁻²	3.73×10 ⁻²	PTPRC
156	BP	GO:0002637	regulation of immunoglobulin production	1/4	80/18860	1.69×10 ⁻²	3.73×10 ⁻²	PTPRC
157	BP	GO:0002704	negative regulation of leukocyte mediated immunity	1/4	80/18860	1.69×10 ⁻²	3.73×10 ⁻²	PTPRC
158	BP	GO:0032720	negative regulation of tumor necrosis factor production	1/4	81/18860	1.71×10 ⁻²	3.75×10 ⁻²	CD33
159	BP	GO:0033673	negative regulation of kinase activity	1/4	83/18860	1.75×10 ⁻²	3.79×10 ⁻²	PTPRC
160	BP	GO:1903556	negative regulation of tumor necrosis factor superfamily cytokine production	1/4	83/18860	1.75×10 ⁻²	3.79×10 ⁻²	CD33
161	BP	GO:0070373	negative regulation of ERK1 and ERK2 cascade	1/4	84/18860	1.77×10 ⁻²	3.81×10 ⁻²	PTPRC
162	MF	GO:0004860	protein kinase inhibitor activity	1/4	91/18662	1.94×10 ⁻²	3.88×10 ⁻²	PTPRC
163	MF	GO:0019210	kinase inhibitor activity	1/4	96/18662	2.04×10 ⁻²	3.88×10 ⁻²	PTPRC
164	MF	GO:0004725	protein tyrosine phosphatase activity	1/4	98/18662	2.08×10 ⁻²	3.88×10 ⁻²	PTPRC
165	BP	GO:0006470	protein dephosphorylation	1/4	87/18860	1.83×10 ⁻²	3.88×10 ⁻²	PTPRC
166	BP	GO:0050871	positive regulation of B cell activation	1/4	87/18860	1.83×10 ⁻²	3.88×10 ⁻²	PTPRC
167	BP	GO:0048864	stem cell development	1/4	88/18860	1.85×10 ⁻²	3.90×10 ⁻²	PTPRC
168	BP	GO:0033077	T cell differentiation in thymus	1/4	89/18860	1.87×10 ⁻²	3.92×10 ⁻²	PTPRC
169	BP	GO:0150076	neuroinflammatory response	1/4	91/18860	1.92×10 ⁻²	3.98×10 ⁻²	PTPRC
170	BP	GO:0042100	B cell proliferation	1/4	94/18860	1.98×10 ⁻²	4.08×10 ⁻²	PTPRC
171	BP	GO:0072091	regulation of stem cell proliferation	1/4	95/18860	2.00×10 ⁻²	4.09×10 ⁻²	PTPRC
172	MF	GO:0019888	protein phosphatase regulator activity	1/4	110/18662	2.34×10 ⁻²	4.17×10 ⁻²	CD33
173	BP	GO:0050848	regulation of calcium-mediated signaling	1/4	99/18860	2.08×10 ⁻²	4.18×10 ⁻²	PTPRC
174	BP	GO:0051348	negative regulation of transferase activity	1/4	99/18860	2.08×10 ⁻²	4.18×10 ⁻²	PTPRC
175	BP	GO:1904892	regulation of receptor signaling pathway via STAT	1/4	99/18860	2.08×10 ⁻²	4.18×10 ⁻²	PTPRC
176	BP	GO:0001910	regulation of leukocyte mediated cytotoxicity	1/4	101/18860	2.13×10 ⁻²	4.24×10 ⁻²	PTPRC
177	MF	GO:1990782	protein tyrosine kinase binding	1/4	118/18662	2.51×10 ⁻²	4.28×10 ⁻²	BLNK
178	MF	GO:0019208	phosphatase regulator activity	1/4	123/18662	2.61×10 ⁻²	4.28×10 ⁻²	CD33
179	MF	GO:0035591	signaling adaptor activity	1/4	130/18662	2.76×10 ⁻²	4.35×10 ⁻²	BLNK
180	BP	GO:0048534	hematopoietic or lymphoid organ development	1/4	106/18860	2.23×10 ⁻²	4.35×10 ⁻²	PTPRC

BP = biological process · MF = molecular function · CC = cellular component

GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S8 – GO enrichment analysis: PD + RBD

4 genes in pattern · 226 significant GO terms (FDR < 0.05) · page 4 of 4 (rows 181–226)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
181	BP	GO:0002312	B cell activation involved in immune response	1/4	107/18860	2.25×10 ⁻²	4.35×10 ⁻²	PTPRC
182	BP	GO:0030101	natural killer cell activation	1/4	107/18860	2.25×10 ⁻²	4.35×10 ⁻²	PTPRC
183	BP	GO:0001960	negative regulation of cytokine-mediated signaling pathway	1/4	108/18860	2.27×10 ⁻²	4.35×10 ⁻²	PTPRC
184	BP	GO:0002709	regulation of T cell mediated immunity	1/4	108/18860	2.27×10 ⁻²	4.35×10 ⁻²	PTPRC
185	BP	GO:0042102	positive regulation of T cell proliferation	1/4	108/18860	2.27×10 ⁻²	4.35×10 ⁻²	PTPRC
186	BP	GO:0002377	immunoglobulin production	1/4	111/18860	2.33×10 ⁻²	4.43×10 ⁻²	PTPRC
187	BP	GO:0002526	acute inflammatory response	1/4	112/18860	2.35×10 ⁻²	4.43×10 ⁻²	FCGR2A
188	BP	GO:0031341	regulation of cell killing	1/4	112/18860	2.35×10 ⁻²	4.43×10 ⁻²	PTPRC
189	BP	GO:0060761	negative regulation of response to cytokine stimulus	1/4	113/18860	2.38×10 ⁻²	4.44×10 ⁻²	PTPRC
190	BP	GO:0001933	negative regulation of protein phosphorylation	1/4	114/18860	2.40×10 ⁻²	4.45×10 ⁻²	PTPRC
191	BP	GO:0042116	macrophage activation	1/4	115/18860	2.42×10 ⁻²	4.45×10 ⁻²	PTPRC
192	BP	GO:0032611	interleukin-1 beta production	1/4	116/18860	2.44×10 ⁻²	4.45×10 ⁻²	CD33
193	BP	GO:0032651	regulation of interleukin-1 beta production	1/4	116/18860	2.44×10 ⁻²	4.45×10 ⁻²	CD33
194	BP	GO:0002444	myeloid leukocyte mediated immunity	1/4	118/18860	2.48×10 ⁻²	4.50×10 ⁻²	FCGR2A
195	BP	GO:0046634	regulation of alpha-beta T cell activation	1/4	124/18860	2.60×10 ⁻²	4.69×10 ⁻²	PTPRC
196	BP	GO:0045582	positive regulation of T cell differentiation	1/4	125/18860	2.63×10 ⁻²	4.70×10 ⁻²	PTPRC
197	BP	GO:0042326	negative regulation of phosphorylation	1/4	126/18860	2.65×10 ⁻²	4.71×10 ⁻²	PTPRC
198	BP	GO:0045860	positive regulation of protein kinase activity	1/4	128/18860	2.69×10 ⁻²	4.75×10 ⁻²	PTPRC
199	BP	GO:0072089	stem cell proliferation	1/4	131/18860	2.75×10 ⁻²	4.75×10 ⁻²	PTPRC
200	BP	GO:0002824	positive regulation of adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	1/4	132/18860	2.77×10 ⁻²	4.75×10 ⁻²	PTPRC
201	BP	GO:0051209	release of sequestered calcium ion into cytosol	1/4	133/18860	2.79×10 ⁻²	4.75×10 ⁻²	PTPRC
202	BP	GO:0050864	regulation of B cell activation	1/4	134/18860	2.81×10 ⁻²	4.75×10 ⁻²	PTPRC
203	BP	GO:0051283	negative regulation of sequestering of calcium ion	1/4	134/18860	2.81×10 ⁻²	4.75×10 ⁻²	PTPRC
204	BP	GO:0007259	cell surface receptor signaling pathway via JAK-STAT	1/4	135/18860	2.83×10 ⁻²	4.75×10 ⁻²	PTPRC
205	BP	GO:0002244	hematopoietic progenitor cell differentiation	1/4	136/18860	2.85×10 ⁻²	4.75×10 ⁻²	PTPRC
206	BP	GO:0032612	interleukin-1 production	1/4	136/18860	2.85×10 ⁻²	4.75×10 ⁻²	CD33
207	BP	GO:0032652	regulation of interleukin-1 production	1/4	136/18860	2.85×10 ⁻²	4.75×10 ⁻²	CD33
208	BP	GO:0051282	regulation of sequestering of calcium ion	1/4	136/18860	2.85×10 ⁻²	4.75×10 ⁻²	PTPRC
209	BP	GO:0002708	positive regulation of lymphocyte mediated immunity	1/4	137/18860	2.87×10 ⁻²	4.75×10 ⁻²	PTPRC
210	BP	GO:0033674	positive regulation of kinase activity	1/4	137/18860	2.87×10 ⁻²	4.75×10 ⁻²	PTPRC
211	BP	GO:0002821	positive regulation of adaptive immune response	1/4	138/18860	2.90×10 ⁻²	4.76×10 ⁻²	PTPRC
212	BP	GO:0002698	negative regulation of immune effector process	1/4	140/18860	2.94×10 ⁻²	4.76×10 ⁻²	PTPRC
213	BP	GO:0051208	sequestering of calcium ion	1/4	140/18860	2.94×10 ⁻²	4.76×10 ⁻²	PTPRC
214	BP	GO:0002456	T cell mediated immunity	1/4	141/18860	2.96×10 ⁻²	4.76×10 ⁻²	PTPRC
215	BP	GO:0045621	positive regulation of lymphocyte differentiation	1/4	141/18860	2.96×10 ⁻²	4.76×10 ⁻²	PTPRC
216	MF	GO:0019903	protein phosphatase binding	1/4	150/18662	3.18×10 ⁻²	4.82×10 ⁻²	CD33
217	BP	GO:0000018	regulation of DNA recombination	1/4	145/18860	3.04×10 ⁻²	4.84×10 ⁻²	PTPRC
218	BP	GO:0010212	response to ionizing radiation	1/4	145/18860	3.04×10 ⁻²	4.84×10 ⁻²	PTPRC
219	BP	GO:0002702	positive regulation of production of molecular mediator of immune response	1/4	146/18860	3.06×10 ⁻²	4.85×10 ⁻²	PTPRC
220	MF	GO:0140375	immune receptor activity	1/4	157/18662	3.32×10 ⁻²	4.87×10 ⁻²	FCGR2A
221	BP	GO:0016311	dephosphorylation	1/4	151/18860	3.16×10 ⁻²	4.98×10 ⁻²	PTPRC
222	BP	GO:0050671	positive regulation of lymphocyte proliferation	1/4	153/18860	3.21×10 ⁻²	4.98×10 ⁻²	PTPRC
223	BP	GO:0050852	T cell receptor signaling pathway	1/4	153/18860	3.21×10 ⁻²	4.98×10 ⁻²	PTPRC
224	BP	GO:0031960	response to corticosteroid	1/4	154/18860	3.23×10 ⁻²	4.98×10 ⁻²	PTPRC
225	BP	GO:2001235	positive regulation of apoptotic signaling pathway	1/4	154/18860	3.23×10 ⁻²	4.98×10 ⁻²	PTPRC
226	BP	GO:0032946	positive regulation of mononuclear cell proliferation	1/4	155/18860	3.25×10 ⁻²	4.99×10 ⁻²	PTPRC

BP = biological process · MF = molecular function · CC = cellular component

GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini–Hochberg adjusted p-value

Table S9 – GO enrichment analysis: AD only

45 genes in pattern · 4 significant GO terms (FDR < 0.05)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
1	MF	GO:0016776	phosphotransferase activity, phosphate group as acceptor	3/42	38/18662	8.46×10 ⁻³	9.17×10 ⁻³	DLG2, ITPKB, PMVK
2	MF	GO:0051015	actin filament binding	5/42	208/18662	9.97×10 ⁻³	9.17×10 ⁻³	ARHGAP27, BIN1, CD2AP, FERMT2, HIP1R
3	MF	GO:0030276	clathrin binding	3/42	48/18662	1.71×10 ⁻⁴	1.05×10 ⁻²	BIN1, CD2AP, HIP1R
4	BP	GO:0065005	protein-lipid complex assembly	3/39	30/18860	3.19×10 ⁻³	3.27×10 ⁻²	ABCA7, APOC1, BIN1

BP = biological process · MF = molecular function · CC = cellular component

GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini–Hochberg adjusted p-value

Table S10 – GO enrichment analysis: PD only

2 genes in pattern · 39 significant GO terms (FDR < 0.05)

#	Ont.	GO ID	GO term	GeneRatio	BgRatio	p-value	FDR (adj. p)	Genes
1	MF	GO:0004683	calcium/calmodulin-dependent protein kinase activity	1/1	27/18662	1.45×10 ⁻³	5.79×10 ⁻³	MYLK2
2	MF	GO:0017022	myosin binding	1/1	73/18662	3.91×10 ⁻³	7.82×10 ⁻³	MYLK2
3	BP	GO:0014816	skeletal muscle satellite cell differentiation	1/1	13/18860	6.89×10 ⁻⁴	9.90×10 ⁻³	MYLK2
4	BP	GO:0030049	muscle filament sliding	1/1	17/18860	9.01×10 ⁻⁴	9.90×10 ⁻³	MYLK2
5	BP	GO:0033275	actin-myosin filament sliding	1/1	19/18860	1.01×10 ⁻³	9.90×10 ⁻³	MYLK2
6	BP	GO:0007274	neuromuscular synaptic transmission	1/1	33/18860	1.75×10 ⁻³	9.90×10 ⁻³	MYLK2
7	BP	GO:0018107	peptidyl-threonine phosphorylation	1/1	35/18860	1.86×10 ⁻³	9.90×10 ⁻³	MYLK2
8	BP	GO:0018210	peptidyl-threonine modification	1/1	35/18860	1.86×10 ⁻³	9.90×10 ⁻³	MYLK2
9	BP	GO:1903115	regulation of actin filament-based movement	1/1	43/18860	2.28×10 ⁻³	1.04×10 ⁻²	MYLK2
10	CC	GO:0030017	sarcomere	1/1	222/19944	1.11×10 ⁻²	1.27×10 ⁻²	MYLK2
11	CC	GO:0030016	myofibril	1/1	243/19944	1.22×10 ⁻²	1.27×10 ⁻²	MYLK2
12	CC	GO:0043292	contractile muscle fiber	1/1	253/19944	1.27×10 ⁻²	1.27×10 ⁻²	MYLK2
13	BP	GO:0055008	cardiac muscle tissue morphogenesis	1/1	62/18860	3.29×10 ⁻³	1.31×10 ⁻²	MYLK2
14	BP	GO:0060415	muscle tissue morphogenesis	1/1	77/18860	4.08×10 ⁻³	1.31×10 ⁻²	MYLK2
15	BP	GO:0035914	skeletal muscle cell differentiation	1/1	83/18860	4.40×10 ⁻³	1.31×10 ⁻²	MYLK2
16	BP	GO:0048644	muscle organ morphogenesis	1/1	85/18860	4.51×10 ⁻³	1.31×10 ⁻²	MYLK2
17	MF	GO:0005516	calmodulin binding	1/1	206/18662	1.10×10 ⁻²	1.47×10 ⁻²	MYLK2
18	BP	GO:0070252	actin-mediated cell contraction	1/1	124/18860	6.57×10 ⁻³	1.75×10 ⁻²	MYLK2
19	BP	GO:0046777	protein autophosphorylation	1/1	134/18860	7.10×10 ⁻³	1.75×10 ⁻²	MYLK2
20	BP	GO:0030048	actin filament-based movement	1/1	147/18860	7.79×10 ⁻³	1.75×10 ⁻²	MYLK2
21	BP	GO:0060048	cardiac muscle contraction	1/1	155/18860	8.22×10 ⁻³	1.75×10 ⁻²	MYLK2
22	BP	GO:0006937	regulation of muscle contraction	1/1	181/18860	9.60×10 ⁻³	1.83×10 ⁻²	MYLK2
23	BP	GO:0007519	skeletal muscle tissue development	1/1	183/18860	9.70×10 ⁻³	1.83×10 ⁻²	MYLK2
24	BP	GO:0060538	skeletal muscle organ development	1/1	197/18860	1.04×10 ⁻²	1.86×10 ⁻²	MYLK2
25	BP	GO:0006941	striated muscle contraction	1/1	208/18860	1.10×10 ⁻²	1.86×10 ⁻²	MYLK2
26	BP	GO:0048738	cardiac muscle tissue development	1/1	255/18860	1.35×10 ⁻²	1.89×10 ⁻²	MYLK2
27	BP	GO:0060047	heart contraction	1/1	265/18860	1.41×10 ⁻²	1.89×10 ⁻²	MYLK2
28	BP	GO:0090257	regulation of muscle system process	1/1	266/18860	1.41×10 ⁻²	1.89×10 ⁻²	MYLK2
29	BP	GO:0003015	heart process	1/1	275/18860	1.46×10 ⁻²	1.89×10 ⁻²	MYLK2
30	BP	GO:0003007	heart morphogenesis	1/1	278/18860	1.47×10 ⁻²	1.89×10 ⁻²	MYLK2
31	BP	GO:0032386	regulation of intracellular transport	1/1	279/18860	1.48×10 ⁻²	1.89×10 ⁻²	MYLK2
32	MF	GO:0004674	protein serine/threonine kinase activity	1/1	433/18662	2.32×10 ⁻²	2.32×10 ⁻²	MYLK2
33	BP	GO:0006936	muscle contraction	1/1	372/18860	1.97×10 ⁻²	2.34×10 ⁻²	MYLK2
34	BP	GO:0007517	muscle organ development	1/1	373/18860	1.98×10 ⁻²	2.34×10 ⁻²	MYLK2
35	BP	GO:0032970	regulation of actin filament-based process	1/1	402/18860	2.13×10 ⁻²	2.36×10 ⁻²	MYLK2
36	BP	GO:0018193	peptidyl-amino acid modification	1/1	404/18860	2.14×10 ⁻²	2.36×10 ⁻²	MYLK2
37	BP	GO:0014706	striated muscle tissue development	1/1	430/18860	2.28×10 ⁻²	2.43×10 ⁻²	MYLK2
38	BP	GO:0060537	muscle tissue development	1/1	453/18860	2.40×10 ⁻²	2.48×10 ⁻²	MYLK2
39	BP	GO:0003012	muscle system process	1/1	485/18860	2.57×10 ⁻²	2.57×10 ⁻²	MYLK2

BP = biological process · MF = molecular function · CC = cellular component

GeneRatio = pattern genes annotated to the term / pattern genes annotated in the ontology · BgRatio = background genes annotated to the term / background · FDR = Benjamini-Hochberg adjusted p-value

Table S11 – GO enrichment analysis: RBD only

1 genes in pattern · 0 significant GO terms (FDR < 0.05)

No significant GO terms (FDR < 0.05).

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