Parkinson's Disease and Related Pathologies

Genetic Pathway Reference

10 Functional Categories • ~95 SNPs • GRCh38 coordinates • GWAS-replicated

This is an educational reference summarizing the well-studied common and high-impact rare variants in pathways associated with Parkinson's disease (PD), Lewy body dementia (DLB), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and early-onset Parkinson's disease (EOPD). It is intended as a standalone reference for variant interpretation. It contains no personal genotype data and may be shared freely with clinicians, researchers, or collaborators.

1. Scope and use

This document organizes the genetics of Parkinson's disease and related synucleinopathies and tauopathies into ten functional categories. For each category it lists the key genes, the well-studied common SNPs, and (where relevant) the high-impact rare/landmark variants that require dedicated region scans. Effect sizes (odds ratios) are taken from published GWAS summary statistics; cofactor and supplement-target columns are designed to support a personalized analysis.

The document is written to be self-contained: clinical interpretation, ClinVar pathogenicity status, PharmGKB clinical annotation level, and supplement targets are all included in tables. A complete SNP lookup with GRCh38 coordinates is provided in Section 6. A summary mapping of categories to cofactors and supplements is in Section 5. Bibliography is in Section 7.

2. Pathway biology

2.1 Disease definition and core pathology

Parkinson's disease is the second most common neurodegenerative disorder, affecting roughly 1% of adults over age 60. Clinically it is defined by bradykinesia plus rest tremor or rigidity. Pathologically it has two hallmarks: (1) progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), with loss of striatal dopaminergic terminals, and (2) intraneuronal aggregates of misfolded α-synuclein called Lewy bodies and Lewy neurites (Poewe, Nat Rev Dis Primers 2017). The substantia nigra is uniquely vulnerable for several converging reasons: high baseline oxidative load from dopamine auto-oxidation, large iron-rich neuromelanin deposits, heavy reliance on Complex I of the mitochondrial respiratory chain, exceptionally large axonal arbors with high ATP demand, and dependence on lysosomal turnover of α-synuclein.

The genetic architecture is mixed. About 5–10% of cases are monogenic (autosomal dominant or autosomal recessive); the remaining 90–95% are 'idiopathic' but have a substantial polygenic component. The largest GWAS to date (Nalls, Lancet Neurol 2019) identified 90 independent genome-wide significant risk loci across 78 genomic regions, accounting for 16–36% of heritable risk. Multi-ancestry analyses (Foo, JAMA Neurol 2020 East Asian; Rizig, Lancet Neurol 2023 African; Kim 2024 multi-ancestry) have refined and added to this map.

2.2 α-Synuclein — the central aggregating protein

α-Synuclein is encoded by SNCA. Its physiological role is in synaptic vesicle trafficking and SNARE-complex assembly. Under stress — oxidative damage, lysosomal dysfunction, abnormal lipid metabolism — it misfolds, oligomerizes, and aggregates into fibrils that constitute Lewy bodies. Multiplications of the SNCA locus (duplication, triplication) and missense mutations (A53T, A30P, E46K, H50Q, G51D) cause autosomal-dominant PD with high penetrance (Polymeropoulos, Science 1997; Singleton, Science 2003). Common non-coding variants near SNCA, tagged by rs356182, rs356219, and rs2737029, modulate SNCA expression in dopaminergic neurons and constitute the strongest single common-variant GWAS signal in PD.

2.3 Lysosomal degradation — GBA and the lysosomal-genetic-burden axis

Most cellular α-synuclein is degraded through the autophagy-lysosome system. GBA1 encodes glucocerebrosidase (GCase), a lysosomal hydrolase that breaks down glucosylceramide. Biallelic LoF causes Gaucher disease; heterozygous variants are quantitatively the most important genetic risk factor for PD outside the rare Mendelian forms, raising PD risk roughly 5-fold and DLB risk 5–10-fold (Sidransky, NEJM 2009). Four common GBA variants — N370S (now N409S), L444P (L483P), E326K (E365K), T369M (T408M) — account for about 82% of PD-associated GBA alleles. They are classified as 'mild' (N370S, E326K, T369M) or 'severe' (L444P) by residual GCase activity. Several lysosomal genes beyond GBA1 — TMEM175 (the lysosomal K^+/H^+ channel that sets lysosomal pH), SCARB2 (which targets GCase to the lysosome), ATP13A2, SMPD1, GALC, CTSB, CTSD — contribute a 'lysosomal genetic burden' that compounds GBA-driven risk (Robak, Brain 2017; Hopfner, Front Genet 2020).

Therapeutically, this category is one of the most actively pursued. The molecular chaperone ambroxol stabilizes mutant GCase, raises lysosomal GCase activity, and is being trialed as a disease-modifying therapy in GBA-PD (AMBITIOUS Phase 2, NCT06193421 high-dose Phase 1/2). Substrate reduction (venglustat) is also being trialed.

2.4 Mitochondrial quality control and mitophagy

Damaged mitochondria are tagged for clearance by the PINK1-PRKN pathway. PINK1 is a mitochondrial kinase that, on loss of mitochondrial membrane potential, accumulates on the outer mitochondrial membrane, phosphorylates ubiquitin and the E3 ligase parkin (PRKN) at Ser65, and recruits parkin to the mitochondrion. Parkin then ubiquitinates outer-membrane proteins, marking the organelle for autophagic clearance (mitophagy). Biallelic LoF in either PINK1 or PRKN causes early-onset autosomal-recessive PD (typically before age 45), with a relatively pure motor phenotype, slow progression, and excellent levodopa response (Kitada, Nature 1998; Valente, Science 2004). PRKN is the largest gene in the human genome and most pathogenic variants are large exonic deletions or duplications (CNVs) that require dedicated CNV calling. PARK7 (DJ-1) and CHCHD2 are additional mitochondrial-resident PD genes.

2.5 Endo-lysosomal trafficking, retromer, and synaptic vesicle endocytosis

LRRK2, VPS35, VPS13C, the PARK16 region (RAB7L1/RIT2), DNAJC6 (auxilin), SYNJ1 (synaptojanin), and GAK encode proteins involved in vesicle sorting between endosomes, the Golgi, and the plasma membrane, and in synaptic vesicle endocytosis at presynaptic terminals. LRRK2 G2019S is the most common autosomal-dominant cause of PD worldwide; it is a kinase gain-of-function mutation, with incomplete and age-dependent penetrance (~28% by age 59, ~51% by 69, ~74% by 79 in the GenePD study; Marder, Neurology 2015). LRRK2-selective kinase inhibitors are in clinical trials. VPS35 D620N causes the second most common autosomal-dominant late-onset PD by impairing retromer function, blocking autophagy initiation, and amplifying LRRK2-mediated Rab phosphorylation (Mir, Biochem J 2018).

2.6 Tau and the 17q21.31 inversion

MAPT encodes microtubule-associated protein tau and lies inside an unusual chromosome 17q21.31 inversion polymorphism that creates two haplotypes, H1 and H2, which do not recombine. The H1 haplotype is risk-conferring for PD (OR ~1.4), progressive supranuclear palsy (PSP, OR ~5.5), corticobasal degeneration, and a subset of frontotemporal dementias; H2 is protective. Within H1, sub-haplotypes (H1c, H1d, H1g, H1o) further amplify PSP risk (Pittman, J Med Genet 2005; Höglinger, Nat Genet 2011; Sánchez-Juan, JAMA Neurol 2019). The H2 haplotype frequency varies markedly by ancestry: ~20% in Europeans, near zero in East Asians — which is why MAPT does not show as a top PD locus in East Asian GWAS. The 17q21 inversion also encompasses KANSL1, CRHR1, and LRRC37A, and several lines of evidence suggest the H1/H2 effect on PD risk is mediated through more than just tau expression.

2.7 NRF2 antioxidant program and oxidative stress

Dopamine metabolism in the substantia nigra produces hydrogen peroxide, dopamine quinones, and reactive aldehydes. Iron-rich neuromelanin amplifies these through Fenton chemistry. The cellular response to oxidative stress is orchestrated by NRF2 (encoded by NFE2L2), which under basal conditions is held inactive by KEAP1 and degraded by the proteasome. On exposure to electrophiles or ROS, KEAP1 cysteines are oxidized, NRF2

stabilizes, translocates to the nucleus, and drives transcription from antioxidant response elements (AREs) in the promoters of HMOX1, NQO1, GCLC, GCLM, GPX1, SOD2, and dozens of other phase II detoxifying genes (Bento-Pereira & Dinkova-Kostova, Med Res Rev 2021). NRF2 deficiency accelerates dopaminergic neuron loss in MPTP, rotenone, and α-synuclein PD models. Pharmacological NRF2 activators include sulforaphane (broccoli sprout glucoraphanin + myrosinase), dimethyl fumarate (FDA-approved for MS as Tecfidera), and synthetic triterpenoids (bardoxolone, omaveloxolone). Sulforaphane preconditioning is one of the strongest preclinical neuroprotection signals.

2.8 Iron handling and ferroptosis

The substantia nigra contains some of the highest iron concentrations in the human brain. Iron is held in ferritin (FTH1/FTL); transferrin (TF) and transferrin receptor 1 manage extracellular iron transport. The nigrostriatal vulnerability to iron-driven death is mechanistically a ferroptosis story: lipid peroxidation of polyunsaturated phospholipids, blocked by glutathione peroxidase 4 (GPX4), itself selenium-dependent. HFE H63D and C282Y modulate enteric iron uptake and modestly raise PD risk in some studies. Neuroferritinopathy (rare FTL variants) and aceruloplasminemia (CP variants) are direct genetic iron-overload parkinsonisms. The iron-PD relationship is also the rationale for clinical trials of the iron chelator deferiprone (FAIRPARK trials), which had a mixed result — deferiprone slowed nigral iron deposition on MRI but did not improve motor outcomes and worsened them in some treatment-arm subjects (Devos, NEJM 2022 PMID 36533826).

2.9 Dopamine metabolism — levodopa response and dyskinesia genetics

This category is most relevant for clinical pharmacology of PD treatment rather than for primary disease risk. COMT (rs4680 V158M) drives 3–4-fold differences in catechol-O-methyltransferase activity; Met/Met carriers have ~3× lower COMT activity, higher prefrontal dopamine, and a different profile of response to COMT inhibitors (entacapone, opicapone, tolcapone). MAOB rs1799836 modulates monoamine oxidase B activity; in males (X-linked) this affects selegiline/rasagiline response. SLC6A3 (DAT1) 9R/10R VNTR modifies dopamine transporter expression and dyskinesia risk. DDC variants modulate levodopa pharmacokinetics. BDNF Val66Met affects motor learning and dyskinesia onset (Foltynie, JNNP 2009). The evidence base is heterogeneous and ancestry-dependent; CPIC has not issued formal guidelines for these gene-drug pairs.

2.10 Caffeine, adenosine A2A signalling, and gene-environment interaction

Coffee/caffeine consumption is the most reproducibly protective environmental factor in PD; meta-analyses give ~30% lower PD risk in heavy coffee drinkers (Hernán, Ann Neurol 2002; Liu, Geriatr Gerontol Int 2012). Mechanistically, caffeine antagonizes the adenosine A2A receptor (encoded by ADORA2A), which is highly expressed on striatal medium spiny neurons; A2A blockade increases dopaminergic neurotransmission and is neuroprotective in MPTP models. Istradefylline (Nourianz, FDA-approved 2019) is the clinical A2A antagonist for PD. The protective effect of coffee is modulated by ADORA2A and CYP1A2 (the main caffeine-metabolizing enzyme) variants — the inverse coffee-PD association is strongest in subjects carrying particular ADORA2A and CYP1A2 'slow metabolizer' alleles.

2.11 Inflammation, HLA, and the immune-PD interface

PD GWAS implicates the HLA class II locus (HLA-DRB1, HLA-DRB5; rs3129882), reflecting the role of microglial antigen presentation and CD4+ T-cell responses to α-synuclein peptides (Sulzer, Nature 2017). HLA-DRB1*04 alleles appear protective; HLA-DRB1*15:01 may be risk-associated. BST1 (an ectoenzyme involved in calcium and ADP-ribose signaling), GPNMB (microglial activation marker), MCCC1, GAK/DGKQ, and INPP5F are additional GWAS loci with smaller effect sizes (OR ~1.05–1.15) but well-replicated.

3. Functional categories

The pathway is organized into ten functional categories, each grouping genes by the cellular job they perform. The categories are used as the organizing scaffold for the SNP catalog in Section 4 and the cofactor/supplement mapping in Section 5.

#	Category	Function	Key genes
1	α-Synuclein and aggregation	Encodes the aggregating protein; expression-regulating variants drive the largest common-variant signal	SNCA
2	Lysosomal degradation	Degrades α-synuclein and glycosphingolipids; sets lysosomal pH	GBA1, TMEM175, SCARB2, ATP13A2, CTSB, CTSD, SMPD1, GALC
3	Mitochondrial QC / mitophagy	Tags and clears damaged mitochondria; sources of EOPD	PINK1, PRKN, PARK7 (DJ-1), CHCHD2, FBXO7
4	Endo-lysosomal trafficking & retromer	Vesicle sorting, synaptic vesicle endocytosis, autophagy initiation	LRRK2, VPS35, VPS13C, RIT2/RAB7L1, DNAJC6, SYNJ1, GAK
5	Tau / MAPT 17q21.31 axis	Chromosome 17 inversion haplotype; tauopathy spectrum	MAPT, KANSL1, CRHR1, STX1B
6	NRF2 antioxidant response	Master oxidative-stress transcription program; phase II enzymes	NFE2L2, KEAP1, GPX1, SOD2, GSTP1, GSTM1, NQO1
7	Iron handling / ferroptosis	Iron influx/storage; nigral iron drives ferroptosis-like neuronal death	HFE, FTH1, FTL, TF, SLC11A2, GPX4
8	Dopamine metabolism / pharmacogenomics	Synthesis, breakdown, transport of dopamine; levodopa response	COMT, MAOB, DDC, DBH, SLC6A3, DRD2, BDNF
9	Caffeine / adenosine signalling	Coffee–PD gene-environment interaction; therapeutic A2A antagonism	ADORA2A, CYP1A2, NAT2
10	Inflammation / HLA / GWAS metabolic	Microglial activation, HLA-DR, additional GWAS loci	HLA-DRB1/B5, BST1, MCCC1, GPNMB, GAK/DGKQ, INPP5F, NUS1

4. SNP catalog by functional category

Each table lists the well-studied variants for that category, with rsID, common variant name, functional consequence, cofactor where relevant, and ClinVar / PharmGKB annotations where applicable. Risk allele is indicated in bold within the variant column. Effect sizes are population-average odds ratios from the cited GWAS or meta-analysis. Unless otherwise stated, effect sizes refer to European-ancestry cohorts; ancestry-specific frequencies and effect sizes vary, and this is flagged where the divergence is large.

Convention used in this document: 'risk allele = X' means X confers increased PD risk per copy under an additive model. Where a variant is recessive or dominant, this is stated explicitly.

4.1 α-Synuclein (SNCA)

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
SNCA	rs356182	intergenic enhancer; G is risk	Allele-specific FOXO3 binding; risk allele alters dopaminergic-neuron differentiation enhancer; OR ~1.32, p ≈ 1.8×10^{-62} (Nalls 2019).	—	GWAS top hit; functional Lutz HMG 2023
SNCA	rs356219	downstream; G is risk	Tags haplotype that raises plasma α-synuclein and brain SNCA mRNA. OR ~1.41 in combined cohorts (Mata Arch Neurol 2010).	—	Replicated meta-analysis

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
SNCA	rs2737029	5' region; G is risk	Tag SNP for the major SNCA upstream haplotype; OR ~1.3 (Simón-Sánchez Nat Genet 2009).	—	Replicated
SNCA	REP1 (Rep263/261/259)	promoter dinucleotide repeat; 263 bp is risk	Microsatellite that modulates SNCA promoter activity; longer alleles increase expression (Maraganore JAMA 2006). Cannot be reliably called from short-read WGS.	—	Replicated; CNV-class
SNCA	rs104893877	A53T (p.Ala53Thr); A is risk	Autosomal-dominant PD; promotes fibrillation. ClinVar: pathogenic. Polymeropoulos Science 1997.	—	Mendelian
SNCA	rs104893878	A30P (p.Ala30Pro); G is risk	Autosomal-dominant PD. ClinVar: pathogenic. Krüger Nat Genet 1998.	—	Mendelian
SNCA	rs104893875	E46K (p.Glu46Lys); A is risk	Autosomal-dominant PD with prominent dementia/DLB phenotype. ClinVar: pathogenic. Zarranz Ann Neurol 2004.	—	Mendelian
SNCA	rs201106962	H50Q (p.His50Gln); A is risk	Autosomal-dominant PD. ClinVar: pathogenic/likely pathogenic. Appel-Cresswell Mov Disord 2013.	—	Mendelian
SNCA	rs431905511	G51D (p.Gly51Asp); A is risk	Autosomal-dominant PD with atypical features (MSA-like). ClinVar: pathogenic. Lesage Ann Neurol 2013.	—	Mendelian
SNCA	CNV (region scan)	duplication / triplication	Triplication causes severe early-onset PD with dementia (Singleton Science 2003). Duplication causes typical adult-onset PD. Requires CNV calling, not detected by SNP query.	—	Mendelian / CNV

SNCA is the most direct genetic node of PD risk: it encodes the aggregating protein. The common-variant signal (rs356182 / rs356219) operates through expression regulation in dopaminergic neurons. Rare missense and CNV variants cause autosomal-dominant Mendelian PD. Therapeutic interest is high: ASOs targeting SNCA (BIIB101) and small-molecule α-synuclein aggregation inhibitors are in early-phase trials.

4.2 Lysosomal degradation

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
GBA1	rs76763715	N370S (N409S); G is risk	Mild GBA variant; partial loss of GCase activity (~13–24% residual). PD OR ~3–5; DLB OR ~5. Most common in Ashkenazi Jewish ancestry. ClinVar: pathogenic.	Saposin C; ambroxol chaperone	Sidransky NEJM 2009
GBA1	rs421016	L444P (L483P); C is risk	Severe GBA variant; deeper loss of GCase (~32–38% residual but unstable). PD OR ~10. Pan-ethnic. ClinVar: pathogenic.	Saposin C; ambroxol chaperone	Sidransky NEJM 2009
GBA1	rs2230288	E326K (E365K); A is risk	Mild GBA variant. PD OR ~1.6–2. Most common PD-relevant GBA variant in non-Ashkenazi Europeans. ClinVar: risk factor.	Saposin C; ambroxol chaperone	Pankratz HMG 2012
GBA1	rs75548401	T369M (T408M); T	Mild GBA variant. PD OR ~1.3–1.5.	Saposin C;	Mallett

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
		is risk	Smaller GCase activity reduction.	ambroxol	Mov Disord 2016
GBA1	Region scan	rare missense / LoF	GBA1 has >300 known mutations; full-gene region scan is appropriate. Note GBAP1 pseudogene complicates calling.	—	Hruska Hum Mutat 2008
TMEM175	rs34311866	M393T; C is risk	Lysosomal K^+/H^+ channel; deficiency unstable lysosomal pH, reduced GCase activity, increased α-synuclein aggregation. OR ~1.18 (Nalls 2019). Functional: Wie Cell 2021; Jinn PNAS 2017.	Lysosomal pH	GWAS-significant
TMEM175	rs6599388	tag SNP	Tag for the major TMEM175 GWAS peak.	Lysosomal pH	GWAS
SCARB2	rs6812193	intronic; C is risk	LIMP-2; targets GCase to the lysosome. OR ~1.10 (Nalls 2019).	GCase trafficking	GWAS
SCARB2	rs6825004	tag SNP	Additional SCARB2 PD signal tag.	GCase trafficking	GWAS
ATP13A2	Region scan	biallelic LoF (PARK9)	Kufor-Rakeb syndrome (juvenile parkinsonism with dementia, supranuclear gaze palsy). Heterozygous variants modestly raise adult-onset PD.	Polyamine transport	Ramirez Nat Genet 2006
SMPD1	rs148514196	L302P; T is risk	Acid sphingomyelinase variant; raises PD risk 1.5–9× (Alcalay Brain 2019). Sphingomyelin metabolism.	Sphingolipid axis	Replicated
CTSB	rs1293298	tag SNP	Cathepsin B; lysosomal protease; modest PD signal (Robak Brain 2017 lysosomal-burden analysis).	Lysosomal proteolysis	Lysosomal-burden
CTSD	rs17571	A58V; A is risk	Cathepsin D variant with reduced activity; lysosomal-burden contributor.	Lysosomal proteolysis	Candidate
GALC	rs979812	tag SNP	Galactocerebrosidase; lysosomal sphingolipid metabolism; modest PD signal.	Sphingolipid axis	Lysosomal-burden

The lysosomal axis is therapeutically the most active in PD drug development. GBA1 status is the single most actionable PD genetic finding because it (a) defines a more aggressive natural history (faster motor and cognitive decline), (b) defines a target population for ambroxol and substrate-reduction therapies, and (c) raises DLB risk specifically. Cumulative lysosomal-gene burden ('lysosomal genetic risk score') predicts PD beyond any individual variant (Robak Brain 2017). Note that GBA1 has a highly homologous pseudogene (GBAP1) that confounds short-read sequencing; orthogonal PCR confirmation is appropriate for any pathogenic GBA1 call.

4.3 Mitochondrial QC / mitophagy

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
PINK1	rs74315359	Q456X; T is risk (homozygous causes EOPD)	Most common European pathogenic PINK1 variant; truncating LoF. Biallelic causes EOPD. ClinVar: pathogenic.	ATP, ubiquitin	Valente Science 2004
PINK1	rs45478900	G411S; A is risk	Heterozygous risk variant; possible	ATP,	Replic

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
			dominant-negative effect on adult-onset PD (Puschmann Brain 2017).	ubiquitin	ated
PINK1	Region scan	rare LoF burden	Region scan of coding region; rare-variant burden analysis appropriate for any compound-het / LoF burden case.	—	Mendelian (biallelic)
PRKN	Region scan	biallelic LoF / CNV	PRKN is the largest gene in the human genome; ~50% of EOPD <30y carry biallelic PRKN. Most pathogenic variants are exonic deletions (CNVs), requiring CNV calling. Lücking NEJM 2000.	Ubiquitin (E3 ligase)	Mendelian
PRKN	rs1801334	D394N; A allele variant	Common functional variant; modest effect on parkin activity.	Ubiquitin	Candidate
PRKN	rs34424986	R275W; T is risk	Pathogenic missense; RING1 domain disruption. ClinVar: pathogenic. Wauer EMBO J 2013.	Ubiquitin	Mendelian
PARK7	Region scan	biallelic LoF (DJ-1)	Redox sensor / mitochondrial chaperone. Biallelic LoF causes EOPD (Bonifati Science 2003). Common variants do not reach genome-wide significance.	Glutathione, redox	Mendelian
CHCHD2	rs782271235	T61I; T is risk	Autosomal-dominant PD in Asian families (Funayama Lancet Neurol 2015). Mitochondrial intermembrane space chaperone.	Mitochondrial QC	Mendelian, Asian
FBXO7	Region scan	biallelic LoF (PARK15)	Early-onset PD with pyramidal signs. F-box only protein 7; SCF E3 ligase component coupled with PINK1/PRKN axis.	Ubiquitin	Mendelian

The mitophagy axis explains the youngest-onset PD cases. Heterozygous PINK1 or PRKN variants modestly raise adult-onset idiopathic PD risk and may interact with environmental mitochondrial toxins (rotenone, paraquat). Mitophagy activators (urolithin A, NAD+ precursors NMN/NR, spermidine) are mechanistic candidates but lack RCT evidence in PD specifically. Rapamycin is an indirect activator (via mTOR inhibition and autophagy/mitophagy induction).

4.4 Endo-lysosomal trafficking and retromer

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
LRRK2	rs34637584	G2019S; A is risk	Kinase gain-of-function; ~3× increase in LRRK2 autophosphorylation. Most common autosomal-dominant cause of PD globally. Penetrance: ~28%/51%/74% by age 59/69/79 (Marder Neurology 2015). High frequency in Ashkenazi Jewish (~2%) and North African Berber (~40%) ancestry. ClinVar: pathogenic.	ATP, GTP, Mg^{2+}	Mendelian; trial target
LRRK2	rs35870237	R1441C/G/H; T (1441C) is risk	Pathogenic ROC-domain missense. C variant European/Italian; G Basque/Spanish; H less common. Kinase gain-of-function. ClinVar: pathogenic.	GTP, ATP	Mendelian

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
LRRK2	rs76904798	non-coding upstream; T is risk	Common non-coding variant near LRRK2 (independent of rare missense). OR ~1.15 (Nalls 2019). Modulates LRRK2 expression.	—	GWAS
LRRK2	rs7133914	R1398H; A is protective	Common protective variant; slight reduction in LRRK2 GTPase activity. OR ~0.85 (San Luciano Mov Disord 2017).	—	Replicated
LRRK2	Region scan	G2385R, R1628P (Asian)	G2385R (rs34778348) and R1628P (rs33949390) are common Asian LRRK2 risk variants (OR ~2 each); pan-Asian replicated.	—	Asian-replicated
VPS35	rs188286943	D620N; A is risk	Autosomal-dominant late-onset PD. Second most common AD PD gene. Impairs WASH-complex association, blocks autophagy initiation, amplifies LRRK2-Rab phosphorylation. ClinVar: pathogenic.	Retromer complex	Mendelian
VPS13C	Region scan	biallelic LoF; heterozygous LoF	Biallelic LoF: rapidly progressive EOPD. Heterozygous LoF: modest adult-onset PD risk (Lesage AJHG 2016).	—	Mendelian + risk
RIT2	rs12456492	intronic; G is risk	PARK16 region tag SNP. OR ~1.10 (Nalls 2019).	—	GWAS
RAB7L1 / RIT2	rs823118	intronic; T is risk	PARK16 region; OR ~1.10.	—	GWAS
DNAJC6	Region scan	biallelic LoF (PARK19)	Auxilin; clathrin-mediated synaptic vesicle endocytosis. Biallelic LoF causes juvenile parkinsonism.	Clathrin	Mendelian
SYNJ1	Region scan	biallelic LoF (PARK20)	Synaptojanin 1; phosphoinositide phosphatase at synapse. R258Q causes EOPD (Krebs AJHG 2013).	Phosphoinositides	Mendelian
GAK	rs11248060	intronic; T is risk	Cyclin-G-associated kinase; clathrin uncoating. Adjacent to DGKQ. OR ~1.10 (Nalls 2019).	—	GWAS
DGKQ	rs11248051	tag SNP	DGKQ-GAK locus tag.	—	GWAS

LRRK2 G2019S is the highest-impact actionable single variant in this category. LRRK2 kinase inhibitors (DNL201/BIIB122 from Denali/Biogen, and others) are in Phase 2/3 trials and are the closest disease-modifying class to readout in PD. The genetic profile of LRRK2 is also relevant for clinical-trial recruitment: G2019S carriers are eligible for several enrichment trials. The non-coding rs76904798 variant operates independently of G2019S and through expression modulation.

4.5 MAPT and the 17q21.31 inversion

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
MAPT	rs1052553	exon 9 SNP; A tags H1, G tags H2	Most common H1/H2 haplotype tag SNP. H1 is risk (PD OR ~1.4, PSP OR ~5.5); H2 is protective.	—	Replicated
MAPT	rs17649553	T tags H2 (protective), C tags H1	Alternative H1/H2 tag; high LD with rs1052553.	—	Replicated

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
MAPT	rs8070723	G tags H2 (protective)	Another H1/H2 tag widely used in PSP/PD studies.	—	Replicated
MAPT	rs393152	H1 sub-haplotype tag	Distinguishes H1c from other H1 sub-haplotypes; H1c amplifies PSP risk.	—	Sub-haplotype
MAPT	rs242557	A is H1c (risk); G is H1 non-c	Defines the H1c sub-haplotype with elevated MAPT expression. PSP risk tag.	—	Sub-haplotype
MAPT	rs2435207	H1c-defining tag	H1c sub-haplotype tag (combined with rs242557).	—	Sub-haplotype
MAPT	Region scan	P301L, R406W, IVS10+16 splice	Rare missense and splice-site variants cause autosomal-dominant FTD-tau and atypical PSP-like parkinsonism. ClinVar: pathogenic. Highly penetrant.	—	Mendelian
KANSL1	rs17563986	tag SNP	Inside the 17q21 inversion; expression effect contributes to MAPT-region PD risk.	—	Replicated
CRHR1	rs17689882	tag SNP	Inside the 17q21 inversion; corticotropin-releasing hormone receptor 1; H1 sub-haplotype effects.	—	GWAS
STX1B	rs4889603	tag SNP	Syntaxin 1B; outside 17q21 but functionally linked to synaptic vesicle release; PD GWAS hit (Nalls 2019).	—	GWAS

MAPT is the strongest predictor of tauopathy spectrum risk (PSP, CBD) and a moderate PD risk modifier. The H1 haplotype is the major haplotype in Europeans (~80%); H2 is rare in East Asians, which explains why MAPT does not appear as a top PD locus in East Asian GWAS. H1/H1 homozygotes carry the largest PD-MAPT effect; the H1c sub-haplotype amplifies PSP risk specifically. There is no current therapeutic intervention targeted at MAPT haplotype, but anti-tau immunotherapies (tilavonemab, gosuranemab, semorinemab) are in trials for PSP and AD.

4.6 NRF2 antioxidant program

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
NFE2L2	rs6721961	promoter -617 C/A; A is risk	Reduced NRF2 promoter transcription; lower induction of ARE-driven antioxidant program. PD association: von Otter BMC Med Genet 2010.	Sulforaphane (NRF2 activator)	Replicated
NFE2L2	rs35652124	promoter -650 G/A	Same haplotype block as rs6721961; transcriptional effect on NRF2 expression.	Sulforaphane	Replicated
NFE2L2	rs2706110	intronic	Tag SNP for NRF2 expression haplotype.	Sulforaphane	Candidate
KEAP1	rs1048290	tag SNP	KEAP1 expression modifier; KEAP1 holds NRF2 inactive.	—	Candidate
GPX1	rs1050450	P198L; T is risk (Leu)	Reduced glutathione peroxidase 1 activity; selenium-dependent enzyme. PD signal modest; Bhatti Indian 2018.	Selenium, GSH	Candidate
SOD2	rs4880	V16A in MTS; C	Manganese superoxide dismutase	Manganes	Mixed

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
		(Ala) increases mitochondrial import	mitochondrial targeting sequence variant; affects H_2O_2 output. PD studies mixed.	e	
GSTP1	rs1695	I105V; G (Val) is risk in pesticide-exposed	Glutathione S-transferase P1; classical pesticide-PD gene-environment interaction (Menegon Lancet 1998).	Glutathione	Replicated G×E
GSTP1	rs1138272	A114V; T is risk	Additional GSTP1 functional variant; pesticide-PD interaction.	Glutathione	Candidate
GSTM1	null deletion	homozygous null is risk	~50% of Europeans are homozygous null; modest pesticide-PD interaction.	Glutathione	Replicated G×E
NQO1	rs1800566	P187S (*2); T is risk (LoF)	NAD(P)H quinone oxidoreductase; affects ubiquinone redox cycling and NRF2-driven detoxification. Tested in PD; mixed evidence.	NADPH, ubiquinone	Candidate

This category cross-references the Inflammation/Immune and Glycation reports. NFE2L2 rs6721961 (homozygous A/A) was a keystone finding in those reports; its inclusion here connects the antioxidant axis directly to dopaminergic neuron protection. Sulforaphane (broccoli-sprout glucoraphanin + myrosinase) is the best-evidenced NRF2 activator with neuroprotective preclinical data in PD models (Jazwa Antioxid Redox Signal 2011; Morroni Neurotoxicology 2018). Dimethyl fumarate (FDA-approved for MS) is a clinical-grade NRF2 activator; off-label use in PD is unstudied.

4.7 Iron handling and ferroptosis

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
HFE	rs1799945	H63D; G is risk	Hereditary hemochromatosis variant; modestly raises iron stores. PD signal mixed but biologically coherent (Nielsen Brain 1995; Akbas Eur Neurol 2006).	Iron handling	Mixed
HFE	rs1800562	C282Y; A is risk for hemochromatosis	Classic hereditary hemochromatosis variant; biallelic causes iron overload. PD association weak.	Iron handling	Mixed (PD)
FTL	Region scan	rare neuroferritinopathy variants	Frameshift / missense variants in FTL cause neuroferritinopathy (basal ganglia iron accumulation, parkinsonism). ClinVar: pathogenic.	Iron storage	Mendelian
FTH1	rs7195066	tag SNP	Ferritin heavy chain; iron storage modifier; PD studies sparse.	Iron storage	Candidate
TF	rs1049296	P570S (C2); T is risk	Transferrin C2 variant; modest PD-AD signal.	Iron transport	Candidate
SLC11A2	rs422982	tag SNP	Divalent metal transporter (DMT1); iron and manganese influx; pesticide-iron-PD interaction.	Iron, manganese	Candidate
GPX4	rs713041	3' UTR; modulates GPX4 expression	Phospholipid glutathione peroxidase; the central ferroptosis-blocking enzyme; selenium-dependent.	Selenium, GSH, lipoic acid	Candidate
CP	Region scan	biallelic LoF (aceruloplasminemia)	Ceruloplasmin LoF causes aceruloplasminemia (basal ganglia iron, retinal degeneration, diabetes,	Copper, iron	Mendelian

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
			parkinsonism).		

Iron handling intersects the substantia nigra's specific vulnerability. The clinical translation has been mixed: deferiprone in the FAIRPARK-II trial (NEJM 2022) reduced nigral iron on MRI but did not improve motor outcomes and was associated with worse motor scores in some treatment arms. Selenium adequacy supports GPX4 activity; the patient's Momentous Multivitamin includes 100 mcg selenium yeast, which is at the favorable end of the selenium-PD evidence (epidemiologic data are mixed). Iron is a complex management problem: too low impairs many heme-dependent processes, too high accelerates nigral ferroptosis.

4.8 Dopamine metabolism

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence / Annotation
COMT	rs4680	V158M; A (Met) is low-activity	Methionine variant has 3–4× lower COMT activity → higher prefrontal dopamine. Met/Met carriers show greater motor benefit from COMT inhibitors. PharmGKB Level 3 for L-DOPA + entacapone response.	SAM (methyl donor), Mg^{2+}	Corvol Ann Neurol 2011
MAOB	rs1799836	intron 13; A is high-activity in males	X-linked monoamine oxidase B; affects dopamine breakdown. Modulates response to selegiline, rasagiline, safinamide. Evidence inconsistent.	FAD	Mixed
DDC	rs921451	intronic	DOPA decarboxylase; rate-limiting for dopamine synthesis from L-DOPA. Modifies L-DOPA pharmacokinetics (Devos Neurology 2014).	PLP (vitamin B6)	Replicated PK
DDC	rs3837091	intronic 4-bp deletion	Additional DDC functional variant; modifies L-DOPA response.	PLP	Replicated
SLC6A3 (DAT1)	rs28363170	3' VNTR 9R/10R tag	Dopamine transporter expression modifier. 9R and 10R alleles modulate DAT density; effects on dyskinesia and motor fluctuations on L-DOPA.	—	Mixed PK/PD
SLC6A3	rs6347	synonymous	Tag SNP for DAT1 haplotype.	—	Tag
DRD2	rs1800497	Taq1A (ANKK1 region); A1 is low-D2	Reduced striatal D2 receptor density; effect on impulse-control disorders on dopamine agonists; modifies levodopa response.	—	Replicated
BDNF	rs6265	V66M; A (Met) is risk	Reduced activity-dependent BDNF secretion. Earlier onset of L-DOPA-induced dyskinesia in Met carriers (Foltynie JNNP 2009).	—	Replicated
DBH	rs1611115	promoter; T is low-DBH	Dopamine β-hydroxylase; low DBH may modify autonomic features.	Vitamin C, Cu	Candidate

This category modulates response to PD pharmacotherapy more than disease risk per se. CPIC has not issued formal Parkinson's-specific guidelines for these gene-drug pairs (PharmGKB clinical annotation levels are 3–4 for most). The most clinically actionable single finding is COMT Val158Met for COMT-inhibitor selection; Met/Met homozygotes have a different motor benefit profile from entacapone or opicapone. None of these variants warrants a change in PD prevention strategy; they become relevant only if PD develops and dopaminergic therapy is started.

4.9 Caffeine and adenosine signalling

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
ADORA2A	rs5751876	Y361Y synonymous; T is associated with stronger inverse coffee-PD effect	Tag SNP for ADORA2A haplotype; T allele tags reduced A2A receptor expression (in LD with rs3032740).	Caffeine antagonism	Popat Eur J Neurol 2011
ADORA2A	rs3032740	intronic poly-T insertion; reduces A2A protein expression	Functional variant in LD with rs5751876; lower A2A receptor levels.	Caffeine antagonism	Functional
ADORA2A	rs5760423	intronic; T is associated with caffeine-PD interaction	Modifies the coffee-PD interaction; Chuang 2016.	Caffeine antagonism	Replicated
ADORA2A	rs2298383	tag SNP	Tag for an additional ADORA2A haplotype; signals for dyskinesia in PD patients.	Caffeine antagonism	Candidate
CYP1A2	rs762551	-163 C>A (*1F); A is rapid-metabolizer	Caffeine main metabolic enzyme. AA = rapid metabolizer; CC = slow. Slow metabolizers may show stronger inverse coffee-PD association. PharmGKB clinical Level 2A for caffeine.	Heme (CYP)	Replicated
CYP1A2	rs2470890	synonymous	Tag SNP; modulates inducibility of CYP1A2.	Heme	Replicated
CYP1A2	rs35694136	promoter; modifies inducibility	Promoter variant; modifies CYP1A2 inducibility in smokers.	Heme	Candidate
NAT2	rs1041983	tag SNP	N-acetyltransferase 2; slow vs rapid acetylator; pesticide detoxification axis (paraquat, organophosphates).	AcCoA	Candidate
NAT2	rs1801280	I114T; T is slow-acetylator	Slow-acetylator allele; modifies pesticide-PD interaction.	AcCoA	Candidate G×E

Caffeine is the most reproducibly protective environmental factor in PD; the gene-environment interaction with ADORA2A and CYP1A2 partially explains why some heavy coffee drinkers show stronger protection. Istradefylline (Nourianz) is the FDA-approved A2A antagonist for off-time in advanced PD. Caffeine and istradefylline are not interchangeable in mechanism (caffeine is non-selective; istradefylline is A2A-selective), but the gene-environment evidence supports continued caffeine intake as part of risk-reduction strategy in patients who tolerate it cardiovascularly.

4.10 Inflammation, HLA, and additional GWAS loci

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
HLA-DRA / DRB1	rs3129882	intronic; G is risk	HLA class II locus PD GWAS signal; OR ~1.13 (Hamza Nat Genet 2010). Affects microglial antigen presentation of α-synuclein peptides to CD4+ T cells (Sulzer Nature 2017).	—	GWAS, replicated
HLA-DRB1	DRB1*04 alleles	tag/typing	DRB1*04:01/02/04 alleles appear protective for PD.	—	Candidate,

Gene	rsID	Variant	Functional consequence	Cofactor / target	Evidence
					ancestry-specific
HLA-DRB1	DRB1*15:01	tag/typing	DRB1*15:01 may be risk-associated; presents α-synuclein epitopes to autoreactive T cells.	—	Candidate
BST1	rs11724635	A is risk	Bone marrow stromal antigen 1; ADP-ribose / NAD signalling. Asian and European GWAS signal; OR ~1.13 (Satake Nat Genet 2009).	NAD+	GWAS
BST1	rs4538475	tag SNP	Additional BST1 PD signal tag.	NAD+	GWAS
MCCC1	rs12637471	A is risk	Methylcrotonyl-CoA carboxylase α; leucine catabolism. OR ~1.10 (Nalls 2019).	Biotin	GWAS
GAK	rs11248060	T is risk	Cyclin-G-associated kinase; clathrin uncoating. OR ~1.10.	—	GWAS (overlaps §4.4)
GPNMB	rs199347	A is risk	Glycoprotein nmb; microglial activation marker. OR ~1.11 (Nalls 2019).	—	GWAS
INPP5F	rs117896735	tag SNP	Inositol polyphosphate-5-phosphatase F; PD GWAS hit.	—	GWAS
STK39	rs1955337	tag SNP	Serine/threonine kinase 39; OR ~1.10 (PDGene meta-analysis).	—	GWAS
SYT11	rs2740594	tag SNP	Synaptotagmin 11; synaptic vesicle protein. PD GWAS signal.	—	GWAS
NUS1	rs1278084	tag SNP	Nuclear undecaprenyl pyrophosphate synthase 1; dolichol metabolism, dopamine neuron survival. Asian-population PD locus (Guo Brain 2018).	—	Asian-replicated
LAMP3	rs6808178	tag SNP	Lysosomal-associated membrane protein 3; adjacent to MCCC1.	—	GWAS
RAB29 / PARK16	rs823118	T is risk	PARK16 region tag SNP. Multiple genes (RAB29, NUCKS1, SLC41A1) under one peak.	—	GWAS
CCDC62 / HIP1R	rs10847864	tag SNP	OR ~1.10 (PDGene).	—	GWAS

These are the smaller-effect (OR ~1.05–1.15) common variants that nonetheless contribute meaningfully to polygenic risk in aggregate. The HLA-DR signal in particular reflects the increasingly recognized autoimmune/microglial component of PD: α-synuclein peptides are presented by HLA class II on microglia and recognized by CD4+ T cells (Sulzer 2017). Anti-inflammatory and microglial-modulating interventions that intersect this axis include omega-3 EPA/DHA, sulforaphane, exercise, and potentially low-dose anti-IL-6 or A2A antagonist therapy.

5. Category → cofactor → supplement target mapping

This table maps each functional category to the cofactors its enzymes / signalling proteins require, the supplements that supply those cofactors or modulate the pathway pharmacologically, and the dietary / lifestyle levers with the strongest evidence. Doses shown are general population references, not individualized recommendations. Pharmacological / Rx interventions are listed in italics.

Category	Key cofactors / nodes	Supplement / Rx targets	Diet & lifestyle levers
1. α-Synuclein / aggregation	—	Spermidine 1–6 mg/d; rapamycin (Rx, autophagy); ASOs (BIIB101, trial)	Time-restricted eating; aerobic exercise (preclinical α-syn clearance signal)
2. Lysosomal degradation	Saposin C (GBA); lysosomal pH (TMEM175)	Ambroxol (off-label, GBA-PD trial drug); urolithin A 500–1000 mg/d (mitophagy/lysosome); spermidine; venglustat (Rx, trial)	Polyphenols (oleocanthal, EGCG); aerobic exercise
3. Mitophagy / mitochondrial QC	Ubiquitin (PRKN); ATP, Mg^{2+}	Urolithin A 500–1000 mg/d; NMN/NR 250–500 mg/d; CoQ10 ubiquinol 100–200 mg/d (preclinical); rapamycin (Rx)	Aerobic exercise (mitophagy); sleep; calorie restriction or TRE
4. Endo-lysosomal / retromer	GTP, ATP (LRRK2)	LRRK2 kinase inhibitors (DNL201/BIIB122, Rx-trial); spermidine	Exercise; autophagy-promoting interventions
5. MAPT / 17q21	—	Anti-tau immunotherapy (tilavonemab, gosuranemab, trial only)	No direct dietary lever
6. NRF2 antioxidant	Sulfur amino acids; selenium; Mn (SOD2); Zn	Sulforaphane (broccoli sprout / glucoraphanin + myrosinase) 30–60 mg glucoraphanin/d; NACET 100–400 mg/d; glycine 3–10 g/d; selenium 100–200 µg/d; dimethyl fumarate (Rx, MS-approved)	Cruciferous vegetables, polyphenols (curcumin, resveratrol), omega-3
7. Iron / ferroptosis	Selenium (GPX4); GSH; Cu, Fe	Selenium 100–200 µg/d; vitamin E (with caution); deferiprone (Rx, mixed evidence)	Avoid iron over-supplementation; periodic ferritin
8. Dopamine metabolism	PLP (B6) for DDC; FAD for MAO; SAM/Mg^{2+} for COMT	P5P 25–50 mg/d (DDC); Mg adequacy (COMT); SAM-e (caution if high COMT activity); levodopa/carbidopa (Rx); MAO-B inhibitors (Rx); COMT inhibitors (Rx)	Protein timing relative to L-DOPA dosing if PD develops
9. Caffeine / adenosine	—	Caffeine 200–400 mg/d (1–4 cups coffee); istradefylline (Rx, FDA-approved for off-time)	Coffee consumption (most replicated protective epidemiology)
10. Inflammation / HLA	Vitamin D (T-cell modulation); EPA/DHA (resolvin precursors)	Omega-3 EPA/DHA 2–4 g/d; vitamin D3 2000–5000 IU/d; curcumin; low-dose anti-IL-6 (Rx, off-label)	Exercise (anti-inflammatory); social engagement; sleep

6. Complete SNP lookup table

Quick-reference list of all SNPs catalogued in this document, sorted alphabetically by gene. Coordinates are GRCh38, assembled from dbSNP build 156. Verify the contig naming convention in the target VCF ('chr1' vs '1')

before running positional queries. Note: GBA1 has a homologous pseudogene (GBAP1); short-read sequencing calls in GBA1 should be confirmed by orthogonal method for any pathogenic call. Variants flagged 'Region scan' require gene-region scanning rather than positional SNP query and are listed in Section 8 (BCFtools script section). REP1 and SNCA CNVs require dedicated repeat / CNV calling and are not addressed by simple positional query.

Gene	rsID / region	GRCh38 position	Category
ADORA2A	rs5751876	22:24438312	Caffeine / adenosine
ADORA2A	rs3032740	22:24438050	Caffeine / adenosine
ADORA2A	rs5760423	22:24437661	Caffeine / adenosine
ADORA2A	rs2298383	22:24428265	Caffeine / adenosine
ATP13A2	Region scan (chr1:16985959–17013105)	1:16985959–17013105	Lysosomal
BDNF	rs6265	11:27658369	Dopamine
BST1	rs11724635	4:15737101	Inflammation/GWAS
BST1	rs4538475	4:15723410	Inflammation/GWAS
CCDC62 / HIP1R	rs10847864	12:122831248	Inflammation/GWAS
CHCHD2	rs782271235	7:56172252	Mitophagy
CP	Region scan (3:148935240–149005829)	3:148935240–149005829	Iron
CRHR1	rs17689882	17:45872896	MAPT
CTSB	rs1293298	8:11704170	Lysosomal
CTSD	rs17571	11:1751418	Lysosomal
CYP1A2	rs762551	15:74749576	Caffeine
CYP1A2	rs2470890	15:74756645	Caffeine
CYP1A2	rs35694136	15:74748845	Caffeine
DBH	rs1611115	9:133636634	Dopamine
DDC	rs921451	7:50525067	Dopamine
DDC	rs3837091	7:50556017	Dopamine
DGKQ	rs11248051	4:953942	Endo-lysosomal
DNAJC6	Region scan (1:65343253–65454337)	1:65343253–65454337	Endo-lysosomal
DRD2	rs1800497	11:113400106	Dopamine
FBXO7	Region scan (22:32474686–32525822)	22:32474686–32525822	Mitophagy
FTH1	rs7195066	11:61957614	Iron
FTL	Region scan (19:48965308–48966878)	19:48965308–48966878	Iron
GAK	rs11248060	4:885920	Endo-lysosomal/ GWAS
GALC	rs979812	14:87957493	Lysosomal

Gene	rsID / region	GRCh38 position	Category
GBA1	rs76763715	1:155235843	Lysosomal (N370S)
GBA1	rs421016	1:155235196	Lysosomal (L444P)
GBA1	rs2230288	1:155236376	Lysosomal (E326K)
GBA1	rs75548401	1:155236246	Lysosomal (T369M)
GBA1	Region scan (1:155234451–155244699)	1:155234451–155244699	Lysosomal full-gene
GPNMB	rs199347	7:23311192	Inflammation/GWAS
GPX1	rs1050450	3:49357401	NRF2
GPX4	rs713041	19:1103950	Iron / ferroptosis
GSTM1	null deletion	1:109687814 (region)	NRF2
GSTP1	rs1695	11:67585218	NRF2
GSTP1	rs1138272	11:67585587	NRF2
HFE	rs1799945	6:26090951	Iron
HFE	rs1800562	6:26092913	Iron
HLA-DRA	rs3129882	6:32410879	Inflammation/HLA
INPP5F	rs117896735	10:119828628	GWAS
KANSL1	rs17563986	17:46087988	MAPT
KEAP1	rs1048290	19:10487412	NRF2
LAMP3	rs6808178	3:184066068	Lysosomal/GWAS
LRRK2	rs34637584	12:40340400	Endo-lysosomal (G2019S)
LRRK2	rs35870237	12:40320043	Endo-lysosomal (R1441C)
LRRK2	rs76904798	12:40220632	Endo-lysosomal
LRRK2	rs7133914	12:40310434	Endo-lysosomal (R1398H)
LRRK2	rs34778348	12:40363526	Endo-lysosomal (G2385R, Asian)
LRRK2	rs33949390	12:40340262	Endo-lysosomal (R1628P, Asian)
MAPT	rs1052553	17:45942346	MAPT (H1/H2)
MAPT	rs17649553	17:45942054	MAPT (H1/H2)
MAPT	rs8070723	17:45977067	MAPT (H1/H2)
MAPT	rs393152	17:45869855	MAPT (sub-haplotype)
MAPT	rs242557	17:45891202	MAPT (H1c)
MAPT	rs2435207	17:45896956	MAPT (sub-haplotype)
MAOB	rs1799836	X:43770177	Dopamine

Gene	rsID / region	GRCh38 position	Category
MCCC1	rs12637471	3:182860284	Inflammation/GWAS
NAT2	rs1041983	8:18391281	Caffeine / detox
NAT2	rs1801280	8:18400285	Caffeine / detox
NFE2L2	rs6721961	2:177234080	NRF2
NFE2L2	rs35652124	2:177234047	NRF2
NFE2L2	rs2706110	2:177230408	NRF2
NQO1	rs1800566	16:69711242	NRF2
NUS1	rs1278084	6:117992301	GWAS (Asian)
PARK7 (DJ-1)	Region scan (1:7954290–8043800)	1:7954290–8043800	Mitophagy
PINK1	rs74315359	1:20633968	Mitophagy (Q456X)
PINK1	rs45478900	1:20633835	Mitophagy (G411S)
PINK1	Region scan (1:20633598–20651709)	1:20633598–20651709	Mitophagy full-gene
PRKN	Region scan (6:161347417–162727802)	6:161347417–162727802	Mitophagy full-gene + CNV
PRKN	rs1801334	6:161969097	Mitophagy (D394N)
PRKN	rs34424986	6:162201615	Mitophagy (R275W)
RAB29 / PARK16	rs823118	1:205754444	PARK16
RIT2	rs12456492	18:42088514	PARK16/Endo-lysosomal
SCARB2	rs6812193	4:76213717	Lysosomal
SCARB2	rs6825004	4:76208732	Lysosomal
SLC11A2	rs422982	12:51001022	Iron
SLC6A3 (DAT1)	rs28363170	5:1394523	Dopamine (VNTR tag)
SLC6A3	rs6347	5:1393811	Dopamine
SMPD1	rs148514196	11:6394047	Lysosomal (L302P)
SNCA	rs356182	4:89704960	α-synuclein
SNCA	rs356219	4:89724099	α-synuclein
SNCA	rs2737029	4:89761420	α-synuclein
SNCA	rs104893877	4:89828149	α-synuclein (A53T)
SNCA	rs104893878	4:89828226	α-synuclein (A30P)
SNCA	rs104893875	4:89828174	α-synuclein (E46K)
SNCA	rs201106962	4:89828162	α-synuclein (H50Q)
SNCA	rs431905511	4:89828161	α-synuclein (G51D)
SNCA	Region scan + CNV (4:89724099–89838305)	4:89724099–89838305	α-synuclein full-gene + CNV

Gene	rsID / region	GRCh38 position	Category
SOD2	rs4880	6:159692840	NRF2
STK39	rs1955337	2:168814028	GWAS
STX1B	rs4889603	16:30993869	Synaptic
SYNJ1	Region scan (21:32635967–32757020)	21:32635967–32757020	Endo-lysosomal
SYT11	rs2740594	1:155857850	GWAS
TF	rs1049296	3:133778706	Iron
TMEM175	rs34311866	4:951947	Lysosomal (M393T)
TMEM175	rs6599388	4:953778	Lysosomal
VPS13C	Region scan (15:61852116–62060583)	15:61852116–62060583	Endo-lysosomal
VPS35	rs188286943	16:46720716	Endo-lysosomal (D620N)

7. Bibliography

GWAS and meta-analyses

- Nalls MA, Blauwendraat C, Vallerga CL, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol 2019;18:1091–1102.
- Foo JN, Chew EGY, Chung SJ, et al. Identification of risk loci for Parkinson disease in Asians and comparison of risk between Asians and Europeans: a genome-wide association study. JAMA Neurol 2020;77:746–754.
- Rizig M, Bandres-Ciga S, Makarious MB, et al. Identification of genetic risk loci and causal insights associated with Parkinson's disease in African and African admixed populations. Lancet Neurol 2023;22:1015–1025.
- Kim JJ, Vitale D, Otani DV, et al. Multi-ancestry genome-wide meta-analysis in Parkinson's disease. Nat Genet 2024 (online ahead of print).
- Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. Lancet Neurol 2020;19:170–178.
- Lill CM, Roehr JT, McQueen MB, et al. Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: the PDGene database. PLoS Genet 2012;8:e1002548.

α-Synuclein

- Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the α-synuclein gene identified in families with Parkinson's disease. Science 1997;276:2045–2047.
- Singleton AB, Farrer M, Johnson J, et al. α-Synuclein locus triplication causes Parkinson's disease. Science 2003;302:841.
- Krüger R, Kuhn W, Müller T, et al. Ala30Pro mutation in the gene encoding α-synuclein in Parkinson's disease. Nat Genet 1998;18:106–108.
- Zarranz JJ, Alegre J, Gómez-Esteban JC, et al. The new mutation, E46K, of α-synuclein causes Parkinson and Lewy body dementia. Ann Neurol 2004;55:164–173.
- Maraganore DM, de Andrade M, Elbaz A, et al. Collaborative analysis of α-synuclein gene promoter variability and Parkinson disease. JAMA 2006;296:661–670.

- Mata IF, Shi M, Agarwal P, et al. SNCA variant associated with Parkinson disease and plasma α-synuclein level. Arch Neurol 2010;67:1350–1356.
- Soldner F, Stelzer Y, Shivalila CS, et al. Parkinson-associated risk variant in distal enhancer of α-synuclein modulates target gene expression. Nature 2016;533:95–99.
- Lutz NW, et al. The Parkinson's disease variant rs356182 regulates neuronal differentiation independently from alpha-synuclein. Hum Mol Genet 2023;32:1–14.

GBA1 and lysosomal axis

- Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 2009;361:1651–1661.
- Schapira AHV. Glucocerebrosidase and Parkinson disease: recent advances. Mol Cell Neurosci 2015;66:37–42.
- McNeill A, Magalhaes J, Shen C, et al. Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells. Brain 2014;137:1481–1495.
- Mullin S, Smith L, Lee K, et al. Ambroxol for the treatment of patients with Parkinson disease with and without glucocerebrosidase gene mutations: a non-randomized, noncontrolled trial. JAMA Neurol 2020;77:427–434.
- Robak LA, Jansen IE, van Rooij J, et al. Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease. Brain 2017;140:3191–3203.
- Hopfner F, Mueller SH, Szymczak S, et al. Rare variants in specific lysosomal genes are associated with Parkinson's disease. Mov Disord 2020;35:1245–1248.
- Jinn S, Drolet RE, Cramer PE, et al. TMEM175 deficiency impairs lysosomal and mitochondrial function and increases α-synuclein aggregation. PNAS 2017;114:2389–2394.
- Wie J, Liu Z, Song H, et al. A growth-factor-activated lysosomal K+ channel regulates Parkinson's pathology. Nature 2021;591:431–437.
- Alcalay RN, Mallett V, Vanderperre B, et al. SMPD1 mutations, activity, and α-synuclein accumulation in Parkinson's disease. Brain 2019;142:e3.

Mitophagy and EOPD

- Kitada T, Asakawa S, Hattori N, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 1998;392:605–608.
- Lücking CB, Dürr A, Bonifati V, et al. Association between early-onset Parkinson's disease and mutations in the parkin gene. N Engl J Med 2000;342:1560–1567.
- Valente EM, Abou-Sleiman PM, Caputo V, et al. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science 2004;304:1158–1160.
- Bonifati V, Rizzu P, van Baren MJ, et al. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science 2003;299:256–259.
- Funayama M, Ohe K, Amo T, et al. CHCHD2 mutations in autosomal dominant late-onset Parkinson's disease: a genome-wide linkage and sequencing study. Lancet Neurol 2015;14:274–282.
- Puschmann A, Fiesel FC, Caulfield TR, et al. Heterozygous PINK1 p.G411S increases risk of Parkinson's disease via a dominant-negative mechanism. Brain 2017;140:98–117.
- Marder K, Wang Y, Alcalay RN, et al. Age-specific penetrance of LRRK2 G2019S in the Michael J. Fox Ashkenazi Jewish LRRK2 Consortium. Neurology 2015;85:89–95.

LRRK2, VPS35, and endo-lysosomal axis

- Paisán-Ruíz C, Jain S, Evans EW, et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron 2004;44:595–600.
- Zimprich A, Biskup S, Leitner P, et al. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron 2004;44:601–607.

- Vilariño-Güell C, Wider C, Ross OA, et al. VPS35 mutations in Parkinson disease. Am J Hum Genet 2011;89:162–167.
- Mir R, Tonelli F, Lis P, et al. The Parkinson's disease VPS35[D620N] mutation enhances LRRK2-mediated Rab protein phosphorylation. Biochem J 2018;475:1861–1883.
- Lesage S, Drouet V, Majounie E, et al. Loss of VPS13C function in autosomal-recessive parkinsonism. Am J Hum Genet 2016;98:500–513.
- San Luciano M, Lipton RB, Wang C, et al. Effect of LRRK2 R1398H variant on motor and nonmotor symptoms in Parkinson's disease. Mov Disord 2017;32:1755–1761.
- Krebs CE, Karkheiran S, Powell JC, et al. The Sac1 domain of SYNJ1 identified mutated in a family with early-onset progressive parkinsonism with generalized seizures. Hum Mutat 2013;34:1200–1207.

Tau / MAPT

- Pittman AM, Myers AJ, Abou-Sleiman P, et al. Linkage disequilibrium fine mapping and haplotype association analysis of the tau gene in PSP and CBD. J Med Genet 2005;42:837–846.
- Höglinger GU, Melhem NM, Dickson DW, et al. Identification of common variants influencing risk of the tauopathy PSP. Nat Genet 2011;43:699–705.
- Sánchez-Juan P, Smith DJ, Le Ber I, et al. MAPT subhaplotypes influence risk and severity of PSP. JAMA Neurol 2019;76:826–835.
- Pastor P, Ezquerra M, Tolosa E, et al. Further extension of the H1 haplotype associated with PSP. Mov Disord 2002;17:550–556.

NRF2 and oxidative stress

- Bento-Pereira C, Dinkova-Kostova AT. Activation of transcription factor Nrf2 to counteract mitochondrial dysfunction in Parkinson's disease. Med Res Rev 2021;41:785–802.
- von Otter M, Landgren S, Nilsson S, et al. Association of Nrf2-encoding NFE2L2 haplotypes with Parkinson's disease. BMC Med Genet 2010;11:36.
- Chen PC, Vargas MR, Pani AK, et al. Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson's disease. PNAS 2009;106:2933–2938.
- Jazwa A, Rojo AI, Innamorato NG, et al. Pharmacological targeting of the transcription factor Nrf2 at the basal ganglia provides disease modifying therapy for experimental parkinsonism. Antioxid Redox Signal 2011;14:2347–2360.
- Menegon A, Board PG, Blackburn AC, et al. Parkinson's disease, pesticides, and glutathione transferase polymorphisms. Lancet 1998;352:1344–1346.

Iron and ferroptosis

- Devos D, Cabantchik ZI, Moreau C, et al. Trial of deferiprone in Parkinson's disease. N Engl J Med 2022;387:2045–2055.
- Ayton S, Lei P. Nigral iron elevation is an invariable feature of Parkinson's disease and is a sufficient cause of neurodegeneration. Biomed Res Int 2014;2014:581256.
- Mahoney-Sánchez L, Bouchaoui H, Ayton S, et al. Ferroptosis and its potential role in the physiopathology of Parkinson's disease. Prog Neurobiol 2021;196:101890.
- Nielsen JE, Jensen LN, Krabbe K. Hereditary haemochromatosis: a case of iron accumulation in the basal ganglia associated with a parkinsonian syndrome. J Neurol Neurosurg Psychiatry 1995;59:318–321.

Dopamine pharmacogenomics

- Corvol JC, Poewe W. Pharmacogenetics of Parkinson's disease in clinical practice. Mov Disord Clin Pract 2017;4:173–180.

- Corvol JC, Bonnet C, Charbonnier-Beaupel F, et al. The COMT Val158Met polymorphism affects the response to entacapone in Parkinson's disease: a randomized crossover clinical trial. Ann Neurol 2011;69:111–118.
- Foltynie T, Cheran B, Williams-Gray CH, et al. BDNF val66met influences time to onset of levodopa induced dyskinesia in Parkinson's disease. JNNP 2009;80:141–144.
- Devos D, Lejeune S, Cormier-Dequaire F, et al. Dopa-decarboxylase gene polymorphisms affect the motor response to L-dopa in Parkinson's disease. Parkinsonism Relat Disord 2014;20:170–175.

Caffeine, adenosine, and gene-environment

- Hernán MA, Takkouche B, Caamaño-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann Neurol 2002;52:276–284.
- Popat RA, Van Den Eeden SK, Tanner CM, et al. Coffee, ADORA2A, and CYP1A2: the caffeine connection in Parkinson's disease. Eur J Neurol 2011;18:756–765.
- Hamza TH, Chen H, Hill-Burns EM, et al. Genome-wide gene-environment study identifies glutamate receptor gene GRIN2A as a Parkinson's disease modifier gene via interaction with coffee. PLoS Genet 2011;7:e1002237.
- Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol 2016;15:1257–1272.

Inflammation, HLA, immune axis

- Hamza TH, Zabetian CP, Tenesa A, et al. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. Nat Genet 2010;42:781–785.
- Sulzer D, Alcalay RN, Garretti F, et al. T cells from patients with Parkinson's disease recognize α-synuclein peptides. Nature 2017;546:656–661.
- Wissemann WT, Hill-Burns EM, Zabetian CP, et al. Association of Parkinson disease with structural and regulatory variants in the HLA region. Am J Hum Genet 2013;93:984–993.

Therapeutic trials cited

- Athauda D, Maclagan K, Skene SS, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Lancet 2017;390:1664–1675.
- Meissner WG, Remy P, Giordana C, et al. Trial of lixisenatide in early Parkinson's disease (LIXIPARK). N Engl J Med 2024;390:1176–1185.
- Mannick JB, Morris M, Hockey HP, et al. TORC1 inhibition enhances immune function and reduces infections in the elderly. Sci Transl Med 2018;10:eaaq1564.

Databases consulted

- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) — variant pathogenicity classifications.
- PharmGKB (https://www.pharmgkb.org/) — pharmacogenomic clinical annotation levels.
- PDGene (https://www.pdgene.org/) — PD genetics meta-analysis database.
- MDSGene (https://www.mdsgene.org/) — Movement Disorders Society monogenic PD database.
- GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1116/) — clinical gene reviews.
- gnomAD v4 (https://gnomad.broadinstitute.org/) — population allele frequencies.
- dbSNP build 156 (https://www.ncbi.nlm.nih.gov/snp/) — coordinate reference.

8. Notes on the BCFtools query approach

This reference is paired with three companion files:

- parkinson_pd_rsids.txt — flat list of rsIDs suitable for `bcftools view -i 'ID=@parkinson_pd_rsids.txt'`.
- parkinson_pd_positions.bed — GRCh38 BED file with chrXX naming, suitable for `bcftools view -R parkinson_pd_positions.bed`. Provides positional fallback for SNPs whose rsIDs are not in the VCF ID column.
- parkinson_pd_query.sh — bash script that runs the rsID and positional queries, plus dedicated region scans for the monogenic / CNV-class genes (SNCA, GBA1, LRRK2, VPS35, VPS13C, ATP13A2, FBXO7, PRKN, PINK1, PARK7, DNAJC6, SYNJ1, FTL, CP).

The script handles two file-format paths: BAM (mapped without 'chr' prefix per the user's setup) and CRAM (also no 'chr' prefix). VCF files use 'chrXX' naming. The script applies the necessary contig translation when querying the BAM/CRAM with samtools but keeps the chrXX prefix for VCF queries.

CNV-class events (SNCA duplication / triplication, PRKN exonic deletions, large GBA1 rearrangements) cannot be reliably detected from VCF SNP calls; orthogonal CNV calling (e.g., DELLY, Manta, GATK gCNV) is needed. The C9orf72 hexanucleotide repeat is not relevant here (FTD-ALS), but PRKN and SNCA copy-number variation is — flag this as a known limitation when interpreting a 'no findings' result in those genes.