

Gene	Variant (single unless noted)	Penetrance Data	Citations	Summary Statements for Genetic Counseling (Important to compare risk estimate with lifetime background risk [typically to age 80 used])
GBA	ALL	a) 15% by age 80, UK, familial GD cohort b) 29.7% by age 80 (CI: 16-40%), France, familial PD cohort c) 10.9% ± 7.2% by age 85, mostly AJ N370S, familial GD cohort d) 7.7% ± 2.74 by age 80, mostly AJ N370S, familial GD cohort e) 19.4% (CI: 12-28%), Italy, PD kin-cohort	a) McNeil et al, 2012 b) Anheim et al, 2012 c) Rana et al, 2013 d) Alcalay et al, 2014 e) Balestrino et al, 2020	Disease risk depends on age, population, and type of variant (refer to specific variant when available) – range is likely 10% to 30% to age 80.
	N370S and other mild variants	a) 5.9% ± 3.14 by age 80, mostly AJ N370S, familial GD cohort b) OR 2.84 to 4.94 for mild variant carriers*	a) Alcalay et al, 2014 b) Gan-Or et al, 2015	Milder variants, in general, have lower disease risk, compared to severe ones.
	E326K	a) OR 1.97 (CI: 1.57-2.46) b) OR 1.99 (CI: 1.57-2.51), across total populations c) May be lower effect in AJ population, OR 1.07 (CI: 0.39-2.93), AJ PD cohort; additive effect suggested when occurring with another variant	a) Zhang et al, 2018 b) Huang et al, 2019 c) Goldstein et al, 2019	This is likely a low risk factor/susceptibility allele for PD.
	T369M	OR 1.78 (CI: 1.20-2.64), across all populations	a) Zhang et al, 2018	This is likely a low risk factor/susceptibility allele for PD.
	84GG, IVS2+1G>A, L444P (<i>severe variants</i>)	OR 9.92 to 21.29 for severe variants*	Gan-Or et al, 2015	Severe variants, in general, have and increased disease risk (lifetime risk of 30% or greater using general population risk of 3%), compared to mild variants.
	Gaucher disease (homozygous or compound heterozygous)	a) 9.1% ± 6.07 by age 80, AJ, N370S homozygous or compound heterozygous) b) approximately 9-12% by age 80, AJ, prevalent genotype N370S, (ICGGRegistry)	a) Alcalay et al, 2014 b) Rosenbloom et al, 2011	PD risk is slightly increased compared to that of single variant carriers.

*Initial review developed for the PDGENERation study

LRRK2	ALL	Reduced penetrance for common variants	GeneReviews: LRRK2	Disease risk depends on age, population, and type of variant (refer to specific variant when available).
	G2019S	a) 26% (CI: 18–36%) lifetime risk by age 80, AJ, PD kin-cohort b) 42.5% (CI: 26.3-65.8%) to age 80, non-AJ populations, PD kin-cohort Note: There was not a significant difference when comparing to AJ populations	a) Marder et al, 2015 b) Lee et al, 2017	There is approximately a 26% lifetime risk for European populations including AJ.
	R1441C (Norwegian variant)	Lower cumulative incidence compared with other <i>LRRK2</i> variants, n=27*, Kaplan-Meier method	Trinh et al, 2014	Numbers are too small to quantify risk but suggestion of lower penetrance compared with other <i>LRRK2</i> variants.
	R1441G (Basque variant)	a) 83.4% (CI: 41.9-95.3%) by age 80, familial PD cohort b) Lower cumulative incidence compared with other <i>LRRK2</i> variants, n= 104, Kaplan-Meier method*	a) Ruiz-Martinez et al, 2010 b) Trinh et al, 2014	Suggestion of lower penetrance compared with other <i>LRRK2</i> variants, however, studies show mixed results.
	Y1699C, N1437H	Penetrance may be increased compared to other variants, small numbers n=16; n=10, Kaplan-Meier method*	Trinh et al, 2014	Numbers are too small to quantify risk.
	I2020T	Similar cumulative incidence compared with to <i>LRRK2</i> G2019S, small numbers n=29, Kaplan-Meier method*	Trinh et al, 2014	Penetrance may be similar to <i>LRRK2</i> G2019S based on small numbers.
	R1628P, G2385R	OR 1.83 (CI: 1.57-2.13)*	Zhang et al, 2017	Considered to be risk factors in Asian populations (Chinese and related ancestries)
	Homozygous G2019S	Did not find a gene dosage effect for clinical features	Ishihara et al, 2006	Penetrance risk data limited.
GBA + LRRK2		a) OR 11.79 (CI: 5.23–26.61), AJ PD cohort b) Suggestion of “dominant association” of <i>LRRK2</i> on <i>GBA</i> expression	a) Goldstein et al, 2019 b) Omer et al, 2020; Ortega et al, 2021	It is not clear if there is an additive effect for age of onset and penetrance; so far, an additive harmful effect has not been observed for clinical features based on small numbers

SNCA	A53T and other less common point mutations	a) 85% for A53T variant (Italian family cohort) b) 89.7% or > at age 70 for A53T variant (Italian/Greek family cohorts), Kaplan-Meier method	a) Polymeropoulos et al, 1996 b) Papadimitriou et al, 2016	Based on small numbers, likely reduced but highly penetrant
	Duplications	a) Incomplete penetrance in Korean and Japanese families although not formally assessed b) 43.8% (Japanese familial cohort) c) Similar cumulative incidence compared with SNCA point mutations, n=41, Kaplan-Meier method*	a) Ahn et al, 2008 b) Nishioka et al, 2009 c) Trinh et al, 2014	Based on small numbers, duplications show reduced penetrance - likely moderate to high.
	Triplications	Higher cumulative incidence compared with other SNCA variants, n= 15, Kaplan-Meier method*	Trinh et al, 2014	Numbers are too small to quantify but likely higher penetrance compared to duplications and other variants.
VPS35	D620N (primary variant identified)	Cumulative incidence >90% by age 70 (n=61)*	Trinh et al, 2014, GeneReviews: VPS35-Related PD	Numbers are too small to quantify but D620N appears to be of high penetrance.
PRKN	Homozygous or compound heterozygous (in trans) for variant	Follows AR inheritance	GeneReviews: Parkin Type of PD	Close to fully penetrant (age-dependent)
	Heterozygous for one variant	a) May act as a susceptibility allele in some families b) Observed in late-onset, familial PD cases c) Frequency of a heterozygous variant in PD pts vs “healthy” controls: 3.2% vs 3.1% d) Cases and controls were similar for single sequence variants whereas cases had increase in dosage variants. Suggest PRKN haploinsufficiency, esp. a dosage variant is a risk factor e) Copy number variants associated with PD risk in carriers (OR 1.60 and OR 2.11*), case-control cohort and pooled data	a) Oliveira et al, 2003 b) Foroud et al, 2003 c) Kay et al, 2007 d) Pankratz et al, 2009 e) Huttenlocher et al, 2015 f) Lubbe et al, 2021	One copy of a variant, especially if it affects dose, may represent a susceptibility factor for PD. However, there is the possibility of a “second-hit” that has not been identified confounding these results. Onset has been observed to be later than typical early-onset in some studies. Research still is ongoing to clarify risk.

*Initial review developed for the PDGENERation study

		f) >1.5 fold increased risk, case-control cohorts, OR 1.65 (CI: 1.36-2.00)*, evidence for greater risk with copy number variants (>2.5 fold)		
<i>PINK1</i> <i>or DJ1</i>	Homozygous or compound heterozygous (in trans) variant	Follows AR inheritance	GeneReviews: <i>PINK1</i> Type Young-Onset PD	Close to fully penetrant (age-dependent)
	Heterozygous for one variant	Several studies suggest that variants in these genes could result in PD and represent risk factors.	GeneReviews: <i>PINK1</i> Type Young-Onset PD Brooks et al, 2009 Sironi et al, 2013	Risk to heterozygotes is not fully known. May be similar to what is observed for <i>PRKN</i> single variants based on published literature. Research is ongoing.

These risks may be modified by other factors and should be used within the context of medical and family histories. Some of these variants have only been thoroughly studied in certain populations, often European. Thus, ancestry of the patient should be considered when relevant.

*Data derived from meta-analysis

Odds ratio to risk ratio (relative risk) calculator: <https://clincalc.com/Stats/ConvertOR.aspx>
(When the incidence of an outcome is low, <10%, the odds ratio is very similar to the risk ratio.)

AJ = Ashkenazi Jewish; AR = autosomal recessive; CI = confidence interval, 95%; GD = Gaucher disease; OR = odds ratio; PD = Parkinson’s disease

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