GAUCHER INSTITUTE
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Genetics of Gaucher disease

*All terms shown in bold can be found within the **Glossary***

Which pathogenic variants occur in Gaucher disease?

Gaucher disease is a single-gene disorder caused by mutations or pathogenic **variants** in the *GBA1* **gene**, located on **chromosome** 1 (1q21).[1] As the *GBA1* gene is located on a numbered **autosomal** chromosome (rather than the X or Y sex chromosomes), males and females are affected by Gaucher disease in a similar manner.[2]

460

To date, almost 460 pathogenic variants in the autosomal *GBA1* gene have been identified.[3] These include **point** variants (**missense** or **nonsense**), **frameshift**, and **splice-site** variants, but also **deletions**, **insertions** and recombinant alleles.[4] Some variants also result from recombinant events between the functional *GBA1* gene and its **pseudogene**.[2] Most *GBA1* pathogenic variants are missense variants that lead to the synthesis of glucocerebrosidase enzyme with reduced catalytic function and/or stability.[5]

The four most common pathogenic *GBA1* gene variants are *N370S* (c.1226A>G; p.Asn4095er), *L444P* (c.1448T>C; p.Leu483Pro), *84GG* (c.84dupG; p.Leu29AlafsTer18) and *IVS2+1* (c.115+1G>A).[2] These account for approximately 90% of the pathogenic gene variants in Gaucher disease Type 1 in Ashkenazi Jews and 50–60% of variants in non-Jewish patients with Gaucher disease Type 1.[6,7] (**Table**)

Table. Proportion of individuals with GBA pathogenic variants using the panel of four common variants.[6,7]

Variants	Human genome variation society variant nomenclature	Proportion of affected individuals (%)
N370S/N370S	p.N409S	29
N370S/?	p.N409S/?	20
N370S/L444P	p.N409S/p.L483P	16
N370S/84GG	p.N409S/c.84dupG	12
L444P/L444P	p.L483P	6
L444P/?	p.L483P/?	3
N370S/IVS2+1	p.N409S/c.115+1G>A	3

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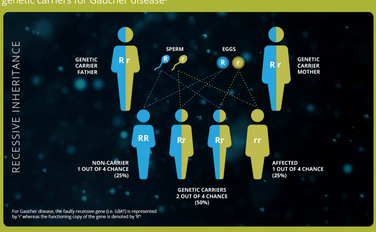
How is Gaucher disease inherited?

Gaucher disease is an autosomal **recessive** disease.[1] By following a pattern of autosomal recessive inheritance, two copies of the recessive pathogenic *GBA1* gene variant are required for an individual to develop the disease (i.e., **homozygous**);[2,8] one copy of the gene variant is passed from each parent.[2]

Not every generation of a family affected by a recessive genetic condition will necessarily display signs and symptoms of the disease.[8] Each parent of an affected person would generally be a **carrier**, having one working copy and one variant form of the gene.[2,8] Genetic carriers for many autosomal recessive genetic conditions usually lack any symptoms of the condition or fail to develop related health problems, as having only one gene variant is insufficient to cause the disease.[2]

Figure. Autosomal recessive inheritance when both parents are unaffected genetic carriers for Gaucher disease[2]



For autosomal recessive disorders, such as Gaucher disease, if both parents are **heterozygous** genetic carriers of the disease, there is a 1 in 4 chance that the child will inherit both copies of the recessive pathogenic *GBA1* gene variant and develop the disease (**Figure**).[2]

Is there a genotype–phenotype correlation in Gaucher disease?

Genotype-phenotype correlations in rare diseases supply clinicians with important data on which they base major therapeutic decisions and provide essential information for prognostic discussions with patients and at-risk relatives, and for pre-conceptional counseling.[9]

The *N370S* (c.1226A>G; p.Asn4095er) pathogenic *GBA1* variant is associated only with Gaucher disease Type 1 and appears to protect against the development of the neurological manifestations that are characteristic of neuronopathic Gaucher disease Types 2 and 3.[10]

Homozygosity for the *N370S* variant is not seen in individuals with neuronopathic Gaucher disease.[11] In general, individuals who are homozygous for the *N370S* gene variant are more likely to have milder disease than those with other genotypes, and some individuals may even remain asymptomatic for the disease.[7,11]

Individuals who are homozygous for the *L444P* gene variant are at a high risk of developing Gaucher disease Type 2 or Type 3 and are more likely to be severely affected by disease.[1,7]

Homozygotes for the rare *D409H* (c.1342) pathogenic variant present with calcification of aortic valves, hydrocephalus and impaired saccadic eye movements associated with Gaucher disease Type 3c.[4,12,13]

Despite some relationship between specific pathogenic *GBA1* gene variants and the clinical course of Gaucher disease, the correlation between genotype and phenotype in Gaucher disease remains limited.[4,11]

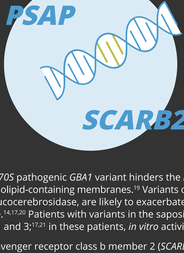
What role do genetic modifiers play in determining the phenotypic outcome of Gaucher disease?

There is significant phenotypic variability amongst patients with Gaucher disease who share the same genotype, suggestive of disease-modifying genetic modifiers.[14,15] For example, a study showed that 32 children who all shared the same *L444P/L444P* genotype had different levels of residual glucocerebrosidase enzymatic activity, and the associated phenotypic spectrum ranged from children with severe systemic and/or nervous system impairment leading to early death, to college students who were mostly asymptomatic for disease.[15]

Genetic modifiers are genetic variants that interact with the primary (disease-causing) gene variant through a variety of different mechanisms, leading to changes in gene expression and protein function, and resulting in varied phenotypic expression.[14]

Identifying such important modifiers of the Gaucher disease phenotype may help to decipher the complex relationship between genotype and phenotype and could potentially lead to improved treatment options for patients with Gaucher disease.[14]

Are there any candidate genetic modifiers for Gaucher disease?



The *PSAP* gene encoding saposin C is a potential genetic modifier for Gaucher disease.[14] In humans there are four saposins (A–D), derived from the precursor prosaposin, encoded by the prosaposin gene (*PSAP*).[16] Saposins A–D are enzymatic activators that assist lysosomal hydrolases in the degradation of sphingolipids.[17]

Saposin C functions by maximizing enzymatic activity of glucocerebrosidase and by protecting the enzyme against intracellular proteolysis; it may also help to extract glucosylceramide substrate from the lipid membrane, increasing its accessibility for hydrolysis.[17,18] Saposin C may be upregulated in patients with Gaucher disease in order to compensate for reduced glucocerebrosidase activity, and so helps to boost any residual enzyme activity that may be present.[17]

The *N370S* pathogenic *GBA1* variant hinders the *in vitro* ability of glucocerebrosidase to interact with saposin C and to bind to anionic phospholipid-containing membranes.[19] Variants of the *PSAP* gene that reduce expression or function of saposin C, or interaction of saposin C with glucocerebrosidase, are likely to exacerbate the effects of Gaucher disease pathogenic variants and so magnify the severity of disease.[14,17,20] Patients with variants in the saposin C domain have a rare variant form of Gaucher disease that resembles Gaucher disease Types 1 and 3;[17,21] in these patients, *in vitro* activity levels of glucocerebrosidase are normal.[17]

The scavenger receptor class b member 2 (*SCARB2*) gene that encodes lysosomal integral membrane protein type 2 (LIMP-2) is another potential genetic modifier of Gaucher disease.[14] *SCARB2* variants negatively impact trafficking of glucocerebrosidase to the lysosome by LIMP-2, reducing the enzyme's overall activity toward glucosylceramide.[14,17]

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