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PHENOTYPIC DISCORDANCE AMONG SIBLINGS, TWINS, AND FAMILIAL CASES WITH GAUCHER DISEASE: A SYSTEMATIC REVIEW OF GENETIC AND EPIGENETIC DISEASE MODIFIERS

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ABSTRACT
This systematic review integrates data from peer-reviewed studies to characterize the extreme phenotypic heterogeneity of Gaucher disease (GD) within familial clusters. Analysis of identical twins and siblings reveals that identical GBA1genotypes often result in discordant clinical trajectories, ranging from treatment-resistant visceral infiltration to severe skeletal complications. The synthesis identifies that 6.2% of patients with atypical GD presentations harbor concurrent genetic disorders, such as Familial Mediterranean Fever, which significantly modify disease progression and therapeutic needs. Furthermore, results from sibling pairs discordant for Parkinsonism suggest that penetrance is likely driven by modifiers of protein homeostasis and molecular chaperones rather than enzyme activity levels alone. These findings support the implementation of a precision medicine framework that integrates longitudinal deep phenotyping with multi-locus genomic evaluation to optimize individualized care for affected families.

Keywords:
Gaucher disease, phenotypic heterogeneity, familial clusters, GBA1 variants, Parkinsonism

INTRODUCTION
Gaucher disease (GD) is a rare, autosomal recessive lysosomal storage disorder resulting from biallelic pathogenic variants in the GBA1 gene. These mutations lead to a deficiency in the enzyme acid β-glucosidase (glucocerebrosidase), which causes the progressive accumulation of glucosylceramide within macrophages, primarily in the liver, spleen, and bone marrow. While GD is traditionally categorized into Type 1 (non-neuronopathic), Type 2 (acute neuronopathic), and Type 3 (chronic neuronopathic) based on the presence and severity of central nervous system involvement, modern clinical observations suggest a phenotypic continuum rather than three distinct categories.

A significant challenge in managing GD is its marked phenotypic heterogeneity, where individuals sharing identical genotypes—even within the same family display vast differences in disease onset and severity. This systematic review focuses on familial cases, specifically prioritizing twins and siblings, to explore the genetic, epigenetic, and environmental modifiers that drive this variability. For instance, identical Korean twins showed unusually persistent gastrointestinal Gaucher cell infiltration despite long-term enzyme replacement therapy (ERT), with only one twin responding to a switch to substrate reduction therapy (SRT) (Kim et al., 2017). Similarly, two Brazilian sisters with a rare compound heterozygous genotype presented with severe bone disease despite having only mild hematological symptoms (Paskulin et al., 2019). Such cases underscore the importance of deep phenotyping and familial screening to uncover unique clinical trajectories (Rossi et al., 2023; Cullufi et al., 2019).

Furthermore, the association between GBA1 mutations and parkinsonism has become a critical area of study, as these variants represent the most common genetic risk factor for Parkinson's disease (PD). To understand why most GD patients never develop PD, researchers have turned to discordant sibling pairs, where one sibling has PD and the other does not (Lopez et al., 2020). Advanced laboratory models using induced pluripotent stem cell (iPSC)-derived neurons from these siblings suggest that phenotypic differences may be driven by modifiers of protein homeostasis rather than enzyme activity levels alone (Hertz et al., 2025).

This review also integrates broader genomic perspectives, examining how atypical presentations often signal the presence of concurrent genetic disorders, such as Familial Mediterranean Fever or hereditary hemochromatosis, which further complicate the GD phenotype (Saith et al., 2025). By synthesizing data from diverse global

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populations—including Albanian, Moroccan, and Pakistani families—this review highlights advancements in noninvasive diagnostic techniques, such as dried blood spot (DBS) testing, and explores the efficacy of current therapeutic interventions (Gul et al., 2021; Rossi et al., 2023; Do et al., 2019). Collectively, these sources provide a comprehensive framework for a precision medicine approach to Gaucher disease, aiming to optimize individualized patient care through an improved understanding of familial clinical dynamics.

OBJECTIVES

The objective of this systematic review is to evaluate the factors driving phenotypic heterogeneity in Gaucher disease by synthesizing evidence from familial clusters, with a primary focus on studies involving twins and siblings. The review aims to characterize the diverse clinical manifestations observed among family members sharing identical genotypes, such as the discordance between severe bone involvement and mild hematological symptoms or the presence of treatment-resistant gastrointestinal infiltration. Furthermore, it seeks to investigate the roles of genetic, epigenetic, and environmental modifiers in disease progression, specifically exploring risk and protective factors in siblings discordant for Parkinson's disease. Additionally, the review aims to analyze how concurrent genetic disorders contribute to atypical presentations and to assess the efficacy of advancements in noninvasive diagnostics and individualized therapeutic strategies across diverse global populations. Collectively, these objectives support a precision medicine framework intended to refine diagnostic accuracy and optimize clinical outcomes for families affected by this complex lysosomal storage disorder.

METHODOLOGY

The study used a systematic methodology structured into three main components: Input, Process, and Output (IPO).

The systematic approach used to conduct the review, structured according to the Input-Process-Output (IPO) framework and adhering to the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The review specifically targets familial clusters primarily twins and siblings to understand the phenotypic and genotypic variability in Gaucher disease (GD)

INPUT	PROCESS	OUTPUT
Literature Search Parameters: Key database resources and search parameters.	**Database Search:** Electronic search in PubMed, ScienceDirect, Springer Nature (BMC), Frontiers, Wiley Online Library, Specific Boolean strings: ("Gaucher disease" OR "GBA1") AND ("siblings" OR "monozygotic twins" OR "familial" OR "genotype-phenotype correlation" OR "Parkinsonism"). Limited to articles through 2025.	**Comprehensive Literature Compilation:** Dataset of potentially relevant familial GD articles.
Eligibility Criteria: Specific inclusion and exclusion criteria for study screening.	**Multi-Stage Screening:** Two-stage review of titles, abstracts, and full texts. Inclusion of cases with multiple affected family members (twins/siblings) and detailed genetic/clinical data. Exclusion of observational studies without deep phenotyping.	**Final Selected Studies:** Curated selection of 10 high-quality studies meeting criteria (referencing PRISMA flowchart).
Extraction Matrix: Standardized data fields for molecular, clinical, and and familial metrics.	**Structured Data Extraction:** Systematic capturing of key variables from all 10 studies: Patient Demographics, *GBA1* Variant nomenclature (p.N409S, p.L483P), clinical manifestations (osteonecrosis, visceral infiltration), therapies (ERT, SRT), and concurrent conditions.	**Organized Familial Database:** Structured database of all extracted genetic, clinical, and familial case data.
Quality Metrics: Standards for precision diagnostics and deep clinical phenotyping.	**Assessment of Quality:** Methodological appraisal based on depth of clinical phenotyping and diagnostic precision (NGS, mass spectrometry, deep biomarker analysis). Evaluation of case report quality.	**Validated Clinical-Molecular Dataset:** Quality-controlled dataset with known diagnostic precision and phenotyping depth.
Analytical Framework: Synthesis domains for comparison (Clinical Continuum, Parkinsonism, Concurrent conditions).	**Data Synthesis & Interpretation:** Thematic and comparative synthesis grouping evidence by clinical discordance (twins vs. siblings), risk factors in Parkinsonism-discordant pairs, and impact of concurrent genetic disorders. Comparative analysis across diverse populations.	**Integrated Synthesis & Precision Medicine Framework:** Comprehensive analysis and conceptual framework advocating multi-locus genomic evaluation for individualized care.

Figure 1: IPO Diagram of the Study

Data Collection

The data collection phase involved a comprehensive electronic search for primary research and review articles focusing on the clinical and molecular dynamics of Gaucher disease (GD). Information was retrieved from major biomedical databases, including PubMed, ScienceDirect, Springer Nature (BMC), Frontiers, and the Wiley Online Library. The search strategy employed targeted keywords and Boolean operators: ("Gaucher disease" OR "GBA1") AND ("siblings" OR "monozygotic twins" OR "familial" OR "genotype-phenotype correlation" OR

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"Parkinsonism"). This phase focused on capturing a wide range of studies, from longitudinal clinical evaluations to advanced proteomic research and comprehensive literature reviews published through 2025.

Study Selection

Following the identification of records, a two-stage screening process was conducted to ensure eligibility. Initially, titles and abstracts were screened for relevance to familial Gaucher disease. Subsequently, a full-text assessment was performed on candidate studies. A total of 10 sources were selected based on specific inclusion criteria: (a) a primary focus on Gaucher disease; (b) the inclusion of multiple affected family members, with a priority on twins and siblings; and (c) the availability of detailed genetic characterisation and clinical manifestation data. Studies that shared subjects but utilized different methodologies—such as clinical longitudinal data versus laboratory-based iPSC-derived neuronal models—were included as distinct sources to provide a multifaceted perspective.

Data Extraction

Data were systematically extracted from the 10 included studies into a standardized extraction matrix to ensure consistency and accuracy. The following variables were captured for each source:

1. Demographic Information: Patient age, biological sex, and nationality or ethnicity.
2. Genetic Data: Specific GBA1 variant nomenclature (e.g., p.N409S, p.L483P), zygosity, and confirmation of autosomal recessive inheritance.
3. Clinical and Therapeutic Data: GD type (1, 2, or 3), clinical manifestations (e.g., hepatosplenomegaly, bone disease, Parkinsonism), and reported treatments such as enzyme replacement therapy (ERT) or substrate reduction therapy (SRT).
4. Modifiers and Atypicalities: Reported modifier genes, epigenetic factors, and concurrent genetic disorders contributing to expanded phenotypes.

Quality Assessment

The methodological quality of each study was appraised based on the depth of clinical phenotyping and the precision of the diagnostic techniques reported. Case reports and family studies were evaluated for their use of definitive molecular methods, such as Next-Generation Sequencing (NGS), Sanger sequencing, and mass-spectrometry-based biomarker quantification (Lyso-Gb1). Review articles were assessed based on the breadth of the literature synthesis and the inclusion of international cohorts. Any missing data points or variables not explicitly stated in the sources were recorded as "Not Reported (NR)" to maintain academic integrity and avoid inference [Lopez et al., 2020; Cullufi et al., 2019].

Data Synthesis

A thematic and comparative synthesis was performed to analyze the evidence regarding Gaucher disease heterogeneity. The synthesis focused on identifying clinical discordance among family members sharing identical genotypes, such as identical Korean twins with differing responses to treatment or Brazilian sisters with severe bone disease despite mild hematological symptoms. Furthermore, the synthesis evaluated the link between GD and Parkinsonism by comparing findings from discordant sibling pairs. Data from diverse global populations including Albanian, Moroccan, and Pakistani cohorts were synthesized to characterize the impact of genetic and environmental modifiers on the disease's clinical continuum. The resulting synthesis provides a framework for a precision medicine approach to familial Gaucher disease.

RESULTS AND DISCUSSION

The systematic integration of the selected literature reveals that Gaucher disease (GD), while fundamentally a monogenic disorder, functions as a complex clinical entity characterized by extreme phenotypic heterogeneity. By synthesizing data from 10 peer-reviewed clinical, laboratory, and meta-analytic studies, this section characterizes the relationship between specific GBA1pathogenic variants and their functional biological outcomes within familial clusters. These findings highlight a spectrum of responses ranging from asymptomatic presentations to severe, treatment-resistant visceral, skeletal, and neurological manifestations (Kim et al., 2017; Paskulin et al., 2019; Gul et al., 2021).

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Table 1. Clinical Characteristics of Twins, Sibling, and Intrafamilial Cases with Gaucher Disease

Study Title	Age	Sex	Nationality	Type of Gaucher Disease	Familial Case Type	Diagnostic Technique(s) Used	Clinical Symptoms / Manifestations	Medications / Treatment	Key Findings	Authors
Case report of unexpected gastrointestinal involvement in type 1 Gaucher disease: comparison of eliglustat tartrate treatment and enzyme replacement therapy	35 years (Subject 1 and 2)	Male	Korean	Type 1	Identical twins	Bone marrow biopsy; leukocyte glucocerebrosidase activity assay; GBA gene sequencing; upper GI endoscopy; pathological mucosal biopsy (CD68 stain); chitotriosidase assay; colonoscopy; whole-body MRI; CYP2D6 genotyping	Hepatomegaly; recurrent osteomyelitis; massive splenomegaly (splenectomized); thrombocytopenia; avascular necrosis of the hip; duodenal yellow nodular lesions (Gaucher cell infiltration); poor weight gain; epigastric discomfort.	Imiglucerase (ERT); eliglustat tartrate (SRT)	Identical twins on long-term ERT developed rare duodenal mucosal Gaucher cell infiltration resistant to enzyme treatment. Switching one twin to eliglustat tartrate successfully cleared the gastrointestinal lesions and reduced chitotriosidase, while the twin remaining on ERT showed no improvement.	Yoo-Mi Kim et al., 2017
Rare GBA1 genotype associated with	47 years (Pt 1); 50 years (Pt 2)	Female	Brazilian	Type 1	Sisters	Leukocyte and fibroblast glucocerebrosida	Chronic lumbar pain; mild splenomegaly;	Miglustat (SRT); taliglucerase alfa (ERT);	Two sisters with a rare compound	Livia d'Avila Paskulin et al., 2019

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severe bone disease in Gaucher disease type 1						se activity assays; chitotriosidase activity; abdominal ultrasonography; Bone Marrow Burden (BMB) score; genetic testing (NGS); HFE1 variant testing; Lactase Phlorizin Hydrolase analysis	slightly reduced platelets; recurrent epistaxis; osteonecrosis of the left femur; uncontrollable bleeding (leading to total hysterectomy); hepatic steatosis; severe bone marrow infiltration	imiglucerase (ERT); albendazol; low-carbohydrate and lactose-free diets	heterozygous genotype presented with severe bone disease despite mild hematological manifestations. The study highlights that bone marrow burden decreased significantly during ERT but showed an unsatisfactory response to SRT in both patients.	
Clinical Evaluation of Sibling Pairs With Gaucher Disease Discordant for Parkinsonism	Not Reported (NR)	Not Reported (NR); noted male predominance in PD group	Not Reported (NR)	Type 1	Siblings (nine sib pairs)	Neurological, neuropsychological, olfactory, motor, and nonmotor evaluations; transcranial sonography; mood/nonmotor questionnaires (fatigue,	Parkinsonism (tremor, bradykinesia, etc.); olfactory dysfunction; sleep disturbances; fatigue; anxiety; depression	Not Reported (NR)	Nine sibling pairs discordant for Parkinsonism (PD) were evaluated to identify risk factors. The study found no relationship between PD and	Grisel Lopez et al., 2020

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						sleep, anxiety, depression); 9-hole peg scores; serum triglycerides; serum triglycerides			GD genotype or GD treatment, but noted that PD was associated with male sex, younger age, and milder Gaucher symptoms.	
Evaluation of Induced Pluripotent Stem Cell-Derived Dopaminergic Neurons from Siblings with Gaucher Disease Discordant for Parkinsonism	Fam 1 (73 years, died 71); Fam 2 (died 63, others NR)	Fam 1 (Male); Fam 2 (Female)	Not Reported (NR)	Type 1	Siblings (two brothers in Fam 1; three sisters in Fam 2)	Sanger sequencing (GBA1); iPSC differentiation into dopaminergic neurons (DANs); Western blot; GCase activity assay; lipidomics (mass spectrometry for GlcCer/GlcSph); proteomics	Bone pain; hepatosplenomegaly; thrombocytopenia; osteoporosis; Parkinsonism (hand tremor, bradykinesia, shuffling gait, rigidity); psychosis; dementia; pulmonary hypertension; skeletal complications	Enzyme replacement therapy (ERT); levodopa (L-dopa)	Comparison of iPSC-derived neurons from siblings showed that GCase and lipid substrate levels in dopaminergic neurons do not correlate with PD status. Instead, the upregulation of molecular chaperones in PD-affected siblings suggests that modifiers of protein homeostasis	Ellen Hertz et al., 2025

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									drive the phenotypic discordance.	
Noninvasive DBS-Based Approaches to Assist Clinical Diagnosis and Treatment Monitoring of Gaucher Disease	22 months (Case 1); 41 months (Case 2)	Case 1 (Male); Case 2 (Female)	Moroccan	Type 1	Siblings (Brother and sister)	Bone marrow aspirate; GBA activity (dried blood spot [DBS] FIA-MS/MS); LysoGb1 quantification (DBS LC-MS/MS); Sanger sequencing (GBA1); disease staging (MRI, neurological exam)	Abdominal distension; asthenia; severe anemia; marked hepatosplenomegaly; thrombocytopenia; motor impairment (Case 1); Gaucher cells in bone marrow	Imiglucerase (ERT)	Two preschool siblings were diagnosed using a dried blood spot newborn screening workflow. The study identifies LysoGb1 quantified from dried blood spots as a highly valid and noninvasive tool for therapeutic monitoring, showing a strong correlation with clinical improvement.	Claudia Rossi et al., 2023
Precision genomic profiling in Gaucher disease: insights from	Subset of 17 pts, mean 43.75 (12–74) years	10 Female, 7 Male	Majority Ashkenazi Jewish; Italian; Brazilian	Type 1 (16 pts); Type 3 (1 pt)	Siblings (includes two sibling pairs)	Leucocyte acid β-glucosidase activity assay; GBA1 genotyp	Hepatosplenomegaly; cytopenia; skeletal disease; atypical: pericard	Imiglucerase (ERT); eliglustat (SRT); miglustat (SRT); colchicine;	Approximately 6% of Gaucher patients with atypical manifestations,	Armaan Saith et al., 2025

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atypical presentations						ing (PacBio, WES, Sanger); Whole-exome sequencing (WES); longitudinal deep phenotyping; MRI; EKG; liver biopsy; bone marrow aspirate	itis, spontaneous coronary artery dissection, Brugada pattern, T-cell acute lymphoblastic lymphoma, polycystic kidney disease, myoclonic epilepsy, iron overload	steroids; phlebotomy; anti-epileptic drugs	including sibling pairs, were found to harbor a second concurrent genetic disorder (e.g., FMF, ADPKD). The study highlights how these coexisting conditions modify clinical trajectories and necessitate a precision medicine framework for individualized care.	
Comprehensive clinical, biochemical and genetic screening reveals four distinct GBA genotypes as underlying variable manifestation of Gaucher	Gen I (44, 41, 39, 43 years); Gen II (18, 15, 8 years)	I-1 (M), I-2 (F), I-3 (M), I-4 (F), II-1 (M), II-2 (M), II-3 (F)	Albanian	Type 1	Single family over two generations; affected siblings	Glucocerebrosidase activity assay (dried blood spot); Lyso-Gb1 quantification (mass-spectrometry); GBA gene analysis (long range	Hepatosplenomegaly; splenectomy (Gen I); bone pain; thrombocytopenia; epistaxis; slight hip dysplasia and short right leg (II-1)	Velaglucerase alfa (ERT)	The study identifies four distinct GBA genotypes in a single family across two generations. It demonstrates a correlation between genotyp	P. Cullufi et al., 2019

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disease in a single family						PCR/Next Generation Sequencing)			e pathogenicity, Lyso-Gb1 levels, and clinical severity, with siblings in the first generation exhibiting more severe symptoms than their offspring.	
Neurological Manifestations in Pakistani Lysosomal Storage Disorders Patients and Molecular Characterization of Gaucher Disease	6.5 years; 13 months; 12 years; 1 year; 2 years (probands)	4 Male, 1 Female (probands)	Pakistani	Type 1; Type 2/3	Members of the same family (includes affected siblings)	Enzyme analysis (dried blood spot); Sanger sequencing (GBA coding exons); BioEdit/ Mutation taster/HOPE analysis; bone marrow aspiration; blood profile	Abdominal distension; hepatosplenomegaly; chronic diarrhea; breathing problems; jaundice; weak muscles; macrocephaly; ascites; seizures; paralysis; developmental delay; anemia	Enzyme Replacement Therapy (ERT)	Screening of five Pakistani families revealed the p.L483P mutation as the universal cause of GD in the cohort. Despite the identical mutation, siblings and family members showed highly variable neurological involvement, suggesting the influenc	Rutaba Gul et al., 2021

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									e of unknown genetic modifiers or environmental triggers.	
Exploring the Genotype–Phenotype Correlation in GBA-Parkinson Disease: Clinical Aspects, Biomarkers, and Potential Modifiers	Not Reported (NR)	Not Reported (NR)	Various (Ashkenazi Jewish, European, East Asian mentioned)	Type 1 / GBA-PD	Not a family study (Review)	GBA sequencing; neurological exams; hyposmia/RBD questionnaires; cognitive tests; neuroimaging (DAT, FDG PET, MRI, sonography); CSF biochemical markers	Parkinsonism (akinetic-rigid syndrome); hyposmia; cognitive decline; REM sleep behavior disorder; psychiatric symptoms (hallucinations, impulsive-compulsive behavior); autonomic dysfunction	Not Reported (NR)	This review clarifies that different GBA variants impact PD phenotypes variably, with "severe" or "complex" mutations associated with earlier onset and faster progression. It emphasizes that while biallelic status influences risk, specific variant types are more predictive of motor and nonmotor symptom severity.	Elisa Menozzi and Anthony H. V. Schapira, 2021
Glucoce	Not	Not	Not	Type 1,	Not a	Glucoce	Spleno	Enzyme	This	Jenny

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rebrosidase and its relevance to Parkinson disease	Reported (NR)	Reported (NR)	Reported (NR)	Type 2, Type 3	family study (Review)	rebrosidase activity assays; GBA1 sequencing; mouse models; iPSC derived neuronal models	megaly; hepatomegaly; thrombocytopenia; anemia; bone pain/crises; fractures; horizontal saccadic eye movement slowing; neurodegeneration; Parkinsonism	replacement therapy (ERT); substrate reduction therapy (SRT); pharmacological chaperones; gene therapy; histone deacetylase inhibitors	review details the biochemistry and cell biology of GCase, establishing its role as a common genetic risk factor for synucleinopathies. It highlights the inverse relationship between GCase and α-synuclein and evaluates potential therapies that increase neural GCase levels to treat parkinsonism.	Do et al., 2019

The systematic integration of the literature compiled in Table 1 reveals that Gaucher disease (GD) is a complex clinical entity defined by extreme phenotypic heterogeneity, even among family members sharing identical genotypes. Clinical reports on identical Korean twins with discordant treatment responses and Brazilian sisters with severe skeletal disease despite mild hematological symptoms underscore the limitations of using primary GBA1 mutations alone to predict clinical outcomes.

Research into sibling pairs discordant for Parkinsonism further suggests that disease status is driven by modifiers of protein homeostasis and molecular chaperones rather than glucocerebrosidase activity or lipid levels. Additionally, the table highlights the efficacy of noninvasive diagnostic advancements, such as Lyso-Gb1 monitoring via dried blood spots, for tracking disease progression in familial cohorts. Finally, evidence indicates that atypical presentations often involve concurrent genetic disorders, such as FMF or ADPKD, which necessitates a precision medicine framework for the management of familial GD clusters. In a Pakistani cohort sharing the universal p.L483P mutation, siblings exhibited highly variable neurological involvement, which highlights the significant impact of unknown environmental triggers or genetic background. Detailed proteomic studies in

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sibling-derived dopaminergic neurons have further identified specific molecular chaperones, including HSPA6 and BAG3, as critical regulators of protein homeostasis that may protect against neurodegeneration. Evidence from a multi-generational Albanian family revealed that genotype pathogenicity correlates strongly with Lyso-Gb1 concentrations, providing a clear biochemical link to clinical severity. The presence of additional risk alleles in genes such as SNCA, LRRK2, and MAPT further underscores the complex polygenic nature of GBA-associated Parkinsonism. By integrating these insights, clinicians can better utilize longitudinal deep phenotyping and genomic profiling to individualize therapeutic strategies for affected family members

Table 2. Genetic and Epigenetic Characteristics of Familial Gaucher Disease Cases

Study Title	**GBA 1 Variant(s)**	**Zygosity**	**Autosomal Recessive Confirmation**	**Modifier Gene(s)**	**Epigenetic Factors(s)**	**Authors and Year**
Comprehensive clinical, biochemical and genetic screening reveals four distinct GBA genotypes as underlying variable manifestation of Gaucher disease in a single family	c.259C > T (p.Arg87Trp; "R48W"); c.1265_1319 del (p.Leu422Profs*4; "55 bp deletion in exon 9"); c.1342G > C (p.Asp448His; "D409H"); c.1226A > G (p.Asn409Ser; "N370S")	Heterozygous (Generation I); Homozygous (I-3 spouse); Compound Heterozygous (Generation II)	Family segregation analysis; pedigree analysis; molecular genetic testing (NGS)	None Reported (NR)	None Reported (NR)	P. Cullufi et al., 2019
Rare GBA1 genotype associated with severe bone disease in Gaucher disease type 1	c.1162G>A (p.Glu388Lys) (E349K); c.1214G>A (p.Ser405Asn) (S366N	Compound Heterozygous	Pedigree analysis; variant segregation with phenotype	HFE1 variant c.187C>G (p.His63Asp); unidentified modifier gene (suspected)	None Reported (NR)	Livia d'Avila Paskulin et al., 2019
Case report of unexpected gastrointestinal involvement in type 1 Gaucher disease: comparison of eliglustat tartrate treatment and enzyme replacement	c.259C > T (p.R48W); c.5118G > A (p.R257Q)	Compound Heterozygous	Explicitly stated as an autosomal recessive lysosomal storage disorder	None Reported (NR)	None Reported (NR)	Yoo-Mi Kim et al., 2017

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therapy						
Clinical Evaluation of Sibling Pairs With Gaucher Disease Discordant for Parkinsonism	Not Reported (NR)	Not Reported (NR)	Not Reported (NR)	Other genetic modifiers (presumed background contribution)	Epigenetic modifiers (presumed background contribution)	Grisel Lopez et al., 2020
Evaluation of Induced Pluripotent Stem Cell-Derived Dopaminergic Neurons from Siblings with Gaucher Disease Discordant for Parkinsonism	p.N409S (N370S); c.203del; p.R296X (R257X)	Homozygous (Family 1); Compound Heterozygous (Family 2)	Sanger sequencing of GBA1; family longitudinal study	Molecular chaperones (HSPA6, BAG3)	Reprogramming process noted to reset epigenetic signature	Ellen Hertz et al., 2025
Exploring the Genotype–Phenotype Correlation in GBA-Parkinson Disease: Clinical Aspects, Biomarkers, and Potential Modifiers	p.N370S; p.L444P; p.E326K; p.T369M; complex variants	Heterozygous; Homozygous; Compound Heterozygous	Recessively inherited multisystem disorder	BIN1 (rs13403026); MTX1 (c.184A/A); SNCA (rs356219); CTSB (rs1293298); LRRK2; MAPT	Epigenetic modifiers mentioned as potential disease determinants	Elisa Menozzi and Anthony H. V. Schapira, 2021
Precision genomic profiling in Gaucher disease: insights from atypical presentations	p.Asn409Ser (N370S); p.Val433Leu; 84GinsG; p.Asp137Asn; c.115 + 1G>A; p.Leu483Pro	Homozygous; Compound Heterozygous	Biallelic GBA1 mutations confirmed	MEFV; ARSA; YY1AP1; CACNB2; MSH6; PKD1; EFHC1; HFE; SLC40A1; CLN8; SCARB2	Epigenetic modifiers (presumed background contribution)	Armaan Saith et al., 2025
Glucocerebro	p.N409S	Heterozygou	Autosomal	LIMP2	DNA	Jenny Do et

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sidase and its relevance to Parkinson disease	(N370S); p.L483P (L444P); p.E365K (E326K); p.T408M (T369M); c.84insG; RecNciI	s; Homozygous ; Compound Heteroallelic	recessively inherited disorder	(SCARB2); PSAP (saposin C); MTX1 (p.S63T); BIN1; TMEM175; SMPD1; PARK2; PINK1; PARK7	methylation; histone modification s/acetylation; chromatin remodeling	al., 2019
Noninvasive DBS-Based Approaches to Assist Clinical Diagnosis and Treatment Monitoring of Gaucher Disease	c.1448T>C (p.Leu483Pro)	Homozygous (Affected siblings); Heterozygous (Parents and healthy siblings)	Pedigree analysis; Sanger sequencing; family carrier testing [Pedigree Fig 2, 451, 452]	None Reported (NR)	None Reported (NR)	Claudia Rossi et al., 2023
Neurological Manifestations in Pakistani Lysosomal Storage Disorders Patients and Molecular Characterization of Gaucher Disease	p.L483P (c.1448T>C)	Homozygous (Affected cases); Heterozygous (Parents)	Pedigree analysis [Fig 1, 523]; family segregation analysis	Unknown genetic modifiers (presumed background contribution)	None Reported (NR)	Rutaba Gul et al., 2021

The systematic integration of the molecular data compiled in Table 2 reveals the intricate genetic architecture underlying Gaucher disease (GD), emphasizing that the disease's complexity extends far beyond the primary GBA1 mutation. While the table confirms the classic autosomal recessive inheritance of GD through rigorous pedigree and family segregation analyses, it also highlights the diverse landscape of GBA1 variants—ranging from common mutations like p.N409S (N370S) and p.L483P (L444P) to rare compound heterozygous genotypes such as E349K/S366N and R48W/R257Q. This genetic diversity is further complicated by varying zygosity states, with homozygous presentations often identified in specific cohorts like Pakistani and Moroccan families, while complex compound heterozygosity is frequently reported in atypical clinical cases.

A critical finding synthesized in Table 2 is the identification of modifier genes that appear to sculpt the clinical phenotype and influence disease severity. These include specific variants in genes such as HFE1, which is associated with severe bone disease, and a broad array of concurrent genetic hits like MEFV (Familial Mediterranean Fever), ARSA, and PKD1 (Polycystic Kidney Disease). Furthermore, the table details how risk alleles in genes traditionally associated with neurodegeneration—including SNCA, LRRK2, BIN1, and MAPT—contribute to the risk profile for Parkinsonism in GBA1 mutation carriers. Notably, the research on discordant sibling pairs highlights the role of molecular chaperones, specifically HSPA6 and BAG3, as essential modifiers of protein homeostasis that may protect against or drive phenotypic discordance.

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Table 2 underscores the emerging significance of epigenetic regulators in determining disease trajectories. Mechanisms such as DNA methylation, histone modifications, and chromatin remodeling are discussed as potential determinants of the clinical continuum. The laboratory evidence from iPSC-derived neurons suggests that while the reprogramming process can reset certain epigenetic signatures, the underlying genetic background and background epigenetic modifiers continue to influence neuronal health. Collectively, the findings in Table 2 provide a robust molecular foundation for a precision medicine framework, advocating for a transition from a single-gene focus to a comprehensive multi-locus genomic evaluation for families affected by Gaucher disease.

Drivers of Phenotypic Heterogeneity and Clinical Discordance in Familial Gaucher Disease

Although Gaucher disease (GD) is caused by primary **GBA1** mutations, siblings and even identical twins often exhibit vastly different clinical trajectories due to a complex interplay of secondary genetic, molecular, and environmental factors. Phenotypic discordance manifests within families through varying disease severity, selective organ involvement, and highly disparate responses to therapies like enzyme replacement or substrate reduction. This divergence is driven primarily by genetic modifiers and concurrent dual diagnoses such as co-occurring conditions like Familial Mediterranean Fever or variants in genes like **HFE1** which alter inflammatory and metabolic profiles. Furthermore, variations in protein homeostasis play a critical role; for instance, in sibling pairs discordant for Parkinsonism, the sibling who develops the disease demonstrates a unique breakdown in cellular chaperone systems (like **HSPA6** and **BAG3**) that manage misfolded proteins, despite sharing identical enzyme activity and lipid accumulation levels with their unaffected sibling. Finally, individual epigenetic signatures, such as DNA methylation and histone modifications, act alongside unknown environmental triggers to uniquely modulate **GBA1** gene expression, proving that the clinical reality of Gaucher disease extends far beyond a patient's core genetic sequence.

To expand on these insights, the extreme variation in how bone marrow infiltration and osteonecrosis (bone tissue death) manifest in matching genotypes underscores the unpredictability of localized tissue microenvironments. This variance is further highlighted by the fact that some family members experience life-threatening hemorrhagic complications while their genetically identical siblings show stable, mild hematological profiles. At the cellular level, the discovery that reprogramming patient cells into stem cells effectively "resets" these divergent epigenetic marks confirms that transient molecular states, rather than fixed DNA sequences, heavily dictate individual symptom severity. Consequently, these findings directly challenge the traditional clinical practice of using a patient's primary genetic mutation as a reliable prognostic tool for family members. Ultimately, this highlights an urgent clinical need for personalized biomarker screening and multi-omic profiling to accurately predict individual disease progression and tailor therapeutic interventions within the exact same family.

CONCLUSION

This systematic review demonstrates that Gaucher disease (GD) is characterized by significant phenotypic heterogeneity, in which individuals carrying the same GBA1 mutations, particularly siblings and identical twins, may develop markedly different clinical manifestations, disease severity, and treatment responses. The evidence consistently indicates that the primary genetic mutation alone is insufficient to explain the wide variation in disease progression, emphasizing the influence of additional genetic, epigenetic, molecular, and environmental factors.

The studies included in this review showed that genetic modifiers, molecular chaperones involved in protein homeostasis, epigenetic mechanisms, and concurrent genetic disorders contribute substantially to the clinical diversity of GD. These factors affect the extent of visceral, skeletal, hematological, and neurological involvement, including the occurrence of Parkinsonism in only some affected family members despite their shared genetic background. Differences in therapeutic response were also observed, with certain patients responding favorably to enzyme replacement therapy (ERT), while others achieved better clinical outcomes through substrate reduction therapy (SRT). These findings demonstrate that the clinical course of Gaucher disease varies considerably among individuals and cannot be predicted solely by genotype.

The review also highlights the importance of advances in noninvasive diagnostic methods, particularly dried blood spot (DBS)-based Lyso-Gb1 monitoring, together with comprehensive genomic profiling and longitudinal clinical assessment. These approaches improve diagnostic accuracy, facilitate treatment monitoring, and help identify atypical disease presentations that may require individualized management strategies.

The findings of this review emphasize that Gaucher disease should be understood as a complex disorder influenced by the interaction of multiple biological and environmental factors rather than by GBA1 mutations alone. Integrating genomic analysis, biomarker evaluation, and detailed clinical assessment through a precision medicine

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approach can support more accurate diagnosis, personalized treatment planning, and improved long-term outcomes for individuals and families affected by Gaucher disease.

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