Konarbayeva *et al. Human Genomics* (2026) 20:102
https://doi.org/10.1186/s40246-026-00975-2

Human Genomics

RESEARCH Open Access

Genotype–phenotype correlations and mutation spectrum of GBA1 in Gaucher disease across Asian populations: a systematic review

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Abstract

Background Gaucher disease exhibits substantial genetic heterogeneity across populations. Asian populations remain understudied despite representing diverse genetic backgrounds. The systematic review was conducted to identify GBA1 mutations and genotype-phenotype correlations in Asian populations.

Methods Following PRISMA guidelines, three databases were searched (January 2000 to December 2025) for studies reporting GBA1 mutations in Asian populations (World Bank classification). From 58 included studies, 419 patients were analyzed with complete genotype-phenotype data. Meta-analyses with Freeman-Tukey transformation estimated pooled proportions of GBA1 variants among reported Gaucher disease cases. Genotype-phenotype associations were assessed using Fisher's exact or chi-square tests. Logistic regression identified predictors of severe phenotype.

Results 162 distinct genotypes across 15 countries were identified, with 94% represented by ≤ 4 patients. The GBA1 variant L444P was the most prevalent (pooled proportion: 0.46), contrasting with Ashkenazi populations where the N370S variant predominates. N370S clustered in West Asia (Iraq 58%, Turkey 30%) but was present at very low frequencies or absent in East Asian countries.

Conclusion Gaucher disease in the Asian population exhibits distinct mutation spectra and geographic patterns requiring population-specific diagnostic strategies. Due to high genetic heterogeneity, broad sequencing approaches are more appropriate than limited targeted panels.

Keywords Gaucher disease, Lysosomal storage disorders, GBA1 gene, Genetic variation, Epidemiology, Genotype–phenotype correlation, Asia

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while L444P showed the highest frequencies in Southeast Asia (Thailand 75%). Four genotypes showed significant associations: N370S/N370S (100% Type 1), L444P/RecNciI (89% Type 2), D409H/D409H (88% Type 2/3), and L444P/L444P (70% Type 3). D409H homozygosity (OR = 15.74), F213I (OR = 10.59), and L444P homozygosity (OR = 6.77) independently predicted severe disease.

Introduction

Gaucher disease (GD) is a rare lysosomal storage disorder (LSD) caused by a deficiency of the enzyme β-glucocerebrosidase and the subsequent accumulation of its substrate, glycosylceramide, in macrophages. The human β-glucocerebrosidase is encoded by the gene GBA1, located on chromosome 1q22, consisting of 12 exons. Currently, around 400 known and registered mutations have been found on the GBA1 gene associated with Gaucher disease [1]. The most common GBA1 mutations include c.84dupG (84GG) and IVS2 + 1G > A (c.115 + 1G > A), which are highly prevalent in Ashkenazi Jewish populations; N370S (c.1226 A > G, p.Asn370Ser), which is the most frequent variant in this population, representing > 70% of Gaucher disease mutations in Ashkenazi Jews and is also the second-most common mutation in European non-Jewish populations [2–4], and L444P (c.1448T > C, p.Leu444Pro), which is more commonly associated with neuronopathic forms of Gaucher disease, particularly Type 3 [5, 6]. Like most LSDs, GD is an inherited autosomal recessive disorder that causes organomegaly and, in some cases, CNS damage [7]. In excess, glycosylceramide is deacylated to glucosylsphingosine (lyso-Gb1). Subsequently, its accumulation leads to accumulation of glucosylsphingosine; these two metabolites accumulate in the body and can eventually lead to brain cell death, manifesting as neurological disorders and skeletal abnormalities [8]. The GD is classified as a sphingolipidosis type of the lysosomal disorders and the most common LSD [9] (see Fig. 1).

Gaucher disease is traditionally classified into three clinical subtypes: Type I (chronic, non-neuronopathic) is the most common subtype of the disease, with occurrences of 1:40,000 people worldwide and accounting for 80% to 90% of all the cases [10]. GD Type I is classically considered non-neuronopathic, as it does not present with overt central nervous system involvement; however, it primarily affects the visceral organs such as the liver, spleen and bone narrow. Importantly, accumulating evidence suggests that patients with Type I GD, as well as heterozygous GBA1 carriers, have an increased lifetime risk of developing Parkinson's disease and Lewy body dementia, indicating a broader spectrum of neurological vulnerability rather than a complete absence of neurological involvement [11]. Type II (acute, neuronopathic) is the rarest form, accompanied by chronic neuronopathic pathologies, developmental delays, and organomegaly (enlargement of the visceral organs). The common treatment options for Gaucher, such as enzyme replacement therapy (ERT), are often unsuccessful in Type II GD as ERT cannot pass the blood-brain barrier, leaving CNS symptoms untreated [8]. Type III (sub-acute, neuronopathic) is the second most common subtype of disorder, which represents a highly heterogeneous group of patients who present with either mild to severe systemic disease associated with neurological impairment that begins in childhood or early adulthood.

The diagnosis of GD is based on the demonstration of severely reduced β-glucocerebrosidase activity in the cells and the identification of pathogenic variants in the GBA1 gene via genetic testing or newborn screening [1]. The worldwide incidence rate of LSDs is 1:7,000 to 1:8,000, making it an a rare disease with limited epidemiological *data*" and research on it [10]. The global prevalence of Gaucher diseases varies across populations and ethnic groups. The prevalence among European and Ashkenazi Jews has been relatively explored, as the common prevalence in these groups is higher. In contrast, the genotype-phenotype correlation of GD in Asian populations,

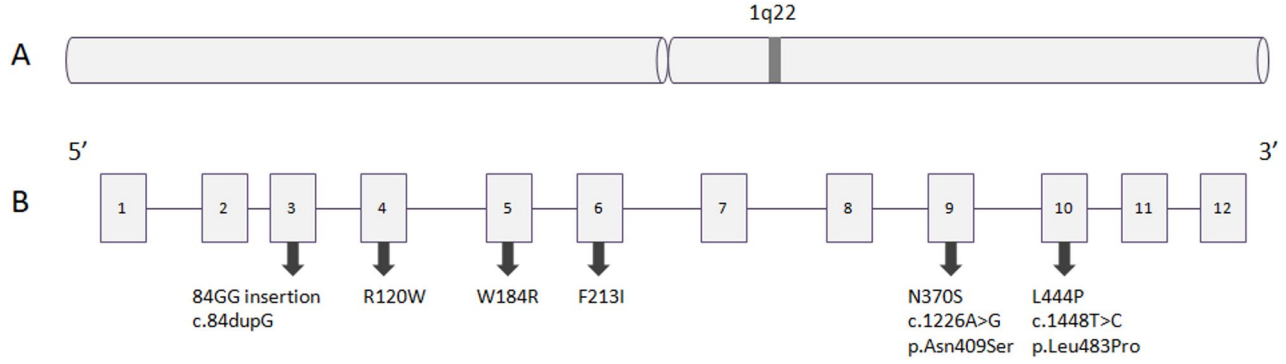

Fig. 1 (A) The position of the GBA1 gene on Chromosome 1 on 1q22. (B) Common Gaucher disease mutations and their positions within the GBA1 gene exons

specifically Central Asia, is generally lower due to an overall lower incidence rate, poor diagnosis, and limited access to advanced diagnostic and screening techniques. These genetic differences may influence clinical phenotype, disease severity, and response to enzyme replacement or substrate reduction therapies.

Methods

Literature search strategy

This systematic review and meta-analysis were conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and were registered in PROSPERO (CRD420261325080) [12]. Two authors [A.K. and S.A.] independently conducted a systematic search of the available peer-reviewed papers published from 2000 until 2025, using three online databases, including PUBMED, Web of Science, and Cochrane. The keywords for all databases were: "Gaucher disease", "glucocerebrosidase deficiency", "GBA1 gene", "genetic variation", "epidemiology", "Asia". A detailed literature search strategy was provided as Supplementary Table S1.

Eligibility criteria

The original research articles (observational studies, case reports, multicenter studies) with all of the following criteria met were selected: (1) conducted in countries classified as Asian according to the World Bank geographic classification or focused on Asian ethnic groups; (2) reported patients with confirmed Gaucher disease; (3) provided genetic data (GBA1 mutations, genotypes), epidemiological data (prevalence, incidence), genotype–phenotype correlations, or clinical characteristics associated with genetic variants; (4) published in English between 2000 and December 2025; and (5) included ≥ 1 patient. Studies with mixed populations were included only if Asian-specific data were reported separately.

Studies that fulfilled any of the following criteria were excluded: (1) studies focused exclusively on non-Asian populations; (2) reviews, meta-analyses, editorials, commentaries, letters, or protocols; (3) conference abstracts without full-text availability unless they provided sufficient genetic and patient-level data for extraction; (4) studies without patient data or purely theoretical works; (5) animal or in vitro studies; (6) studies on other lysosomal storage disorders without Gaucher-specific data; (7) studies reporting only treatment outcomes without genetic/epidemiological information; (8) non-English publications; (9) duplicate publications; and (10) studies with insufficient extractable data.

Quality assessment

Study quality was independently assessed by two reviewers (A.K. and S.A.). The disagreements were resolved through discussion or consultation with a third reviewer (B.S.). For the methodological assessment of studies quality, the following validated tools have been used according to the study design: the Newcastle-Ottawa Scale (NOS) for observational and cohort studies; the Joanna Briggs Institute (JBI) Critical Appraisal Checklists for case reports, case series, cross-sectional studies and experimental studies; the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for screening studies.

Data extraction

Data were independently extracted by two reviewers (A.K. and S.A.) using a standardized form. Extraction was performed in two stages based on the analytical objective. Primary extraction (all 58 studies): Author, year, country, study design, sample size, GBA1 mutations (nomenclature and frequency), and geographic data. All studies with reported GBA1 mutations were included to characterize the mutation spectrum and geographic distribution, regardless of phenotype data availability.

Secondary extraction (subset with genotype-phenotype data): For studies providing individual or clearly linked genotype-phenotype pairs, the following data were additionally extracted: Gaucher disease subtype (Type 1/2/3), zygosity status, and clinical characteristics. Studies reporting only aggregated mutations without phenotype linkage or without disease subtype classification were excluded from genotype-phenotype correlation analyses but retained in mutation frequency analyses. Variables not reported were recorded as "NR". Disagreements were resolved by consensus or third-reviewer consultation (D.A.). To ensure consistency, the standardization criteria were applied: recombinant alleles (e.g., RecNciI) were treated as single entities; only complete biallelic genotypes were included in quantitative analyses; Type 2/3 cases were classified as neuronopathic; and duplicate populations were excluded.

Data synthesis and analysis

Due to substantial heterogeneity in study design, predominance of case reports and small observational studies, a conventional quantitative meta-analysis was not feasible. Therefore, a multi-faceted analytical approach was employed.

Mutation distribution analysis

All 58 included studies contributed to mutation frequency characterization. The distribution of GBA1 mutations was characterized across the entire cohort and stratified by country. Geographic distribution was visualized using heat maps created in (StataMP ver.19.5) based on the most frequently reported GBA1 variants. Case reports and case series were included in this analysis to

maximize coverage of genetic diversity, acknowledging that these study designs may preferentially report rare or severe phenotypes.

Meta-analysis of mutation proportions

For the five most common mutations (L444P, N370S, D409H, RecNciI, F213I), meta-analyses of proportions using a random-effects model with Freeman-Tukey double arcsine transformation were performed to stabilize variances and account for between-study heterogeneity. The quantitative synthesis estimates the pooled proportion of GBA1 variants among published Gaucher disease cases and should not be interpreted as true population-level allele frequencies. The statistical unit was the country: for each mutation, allele counts were aggregated across all studies from a given country, with each country contributing one data point to the pooled analysis. Where studies from the same country reported overlapping patient populations, only the most comprehensive and recent dataset was retained to avoid duplication. Analyses were performed in R (version 4.5.2) using the *meta* package.

Genotype-phenotype correlation analysis

For studies with patient-level data ($n = 51$ studies, 419 patients), associations between genotypes and disease subtypes (Type 1/2/3) using Fisher's exact test (expected counts < 5) or chi-square test (expected counts ≥ 5) were assessed. To identify predictors of severe phenotype, a logistic regression model including five genetic predictors was fitted.: L444P homozygosity, N370S homozygosity, D409H homozygosity, presence of recombinant alleles, and presence of F213I alleles (all coded as binary variables).

Results

Study selection and characteristics

The systematic search identified 158 records from PubMed ($n = 98$), Web of Science ($n = 58$), and Cochrane Library ($n = 2$), searched up to December 2025 (Fig. 2). After removing studies by exclusion criteria, a total of 58 studies (18 countries) were included and then subjected to quality assessment. Studies were categorized as high (≥ 70% of criteria met), moderate (50–69%), or low risk of bias (< 50%) based on overall checklist completion. Based on the applied appraisal tools, 23 studies (39.6%) were judged to have a low risk of bias, 30 (51.7%) had a moderate risk of bias, and 5 (8.6%) were considered to have a high risk of bias. The details on the quality assessment of individual studies were reported in Table S2. All 58 studies contributed to mutation frequency analyses; 51 studies (419 patients) with individual- level genotype-phenotype data were included in correlation analyses. Seven studies were excluded from genotype-phenotype analysis.

Mutation spectrum and geographic distribution

Heat map analysis revealed substantial geographic heterogeneity in GBA1 distribution of GBA1 mutations across 15 Asian countries (Fig. 3). The L444P variant was the most prevalent mutation but showed marked inter-country variation (range: 12%–80%). The N370S substitution demonstrated clustering in Turkey (30%) and Iran (19%), with lower frequencies in Thailand (2.2%) and China (0.6%). Additional recurrent variants, including p.D409H, RecNciI, and p.F213I, showed intermediate frequencies with distinct country-specific patterns. China, Japan, and South Korea demonstrated the most diverse mutation spectra (8–10 mutations per country), while countries with smaller cohorts exhibited lower genetic diversity. Several rare mutations (p.G241R, p.G46E, p.S405T) were country-specific, highlighting substantial genetic heterogeneity across Asian populations.

Meta-analysis of mutation proportions

The random-effects meta-analysis of proportions was performed to estimate the pooled pooled proportion of the five most reported variants across all selected countries. For each mutation, the allele counts, and total alleles were extracted according to the country. Due to the rarity of the disease and lack of studies, the Freeman-Tukey double arcsine transformation was implemented to stabilize the proportions. The I^2 statistic and τ^2 variables were found to account for statistical heterogeneity. The pooled estimate with 95% CI and prediction interval was accessed using a forest plot. Overall, the results of the meta-analysis showed considerable variability in the distribution of the L444P, N370S, D409H, F213I, and RecNciI recombinant allele. Among these variants, L444P showed the highest overall proportion among reported Asian cases, with a pooled proportion of 0.46 (95% CI: 0.36–0.57). According to the conducted meta-analysis, nearly half of the mutant alleles in the analyzed datasets among the Asian cohort correspond to the L444P mutation. Next, N370S variability showed a lower pooled proportion of 0.17 (95% CI: 0.02–0.40), but compared to L444P showed significant geographic variability. The remaining selected variants were less common: F213I had a pooled proportion of 0.10 (95% CI: 0.02–0.21), RecNciI 0.06 (95% CI: 0.02–0.10), and D409H 0.04 (95% CI: 0.02–0.07). The heterogeneity across all selected alleles was high, ranging from 71% to 97%. However, this heterogeneity was expected given the limited number of available studies, small sample sizes, prevalence of case reports\series, inclusion of family-based cohorts with high rates of consanguinity, and the rarity of Gaucher disease.

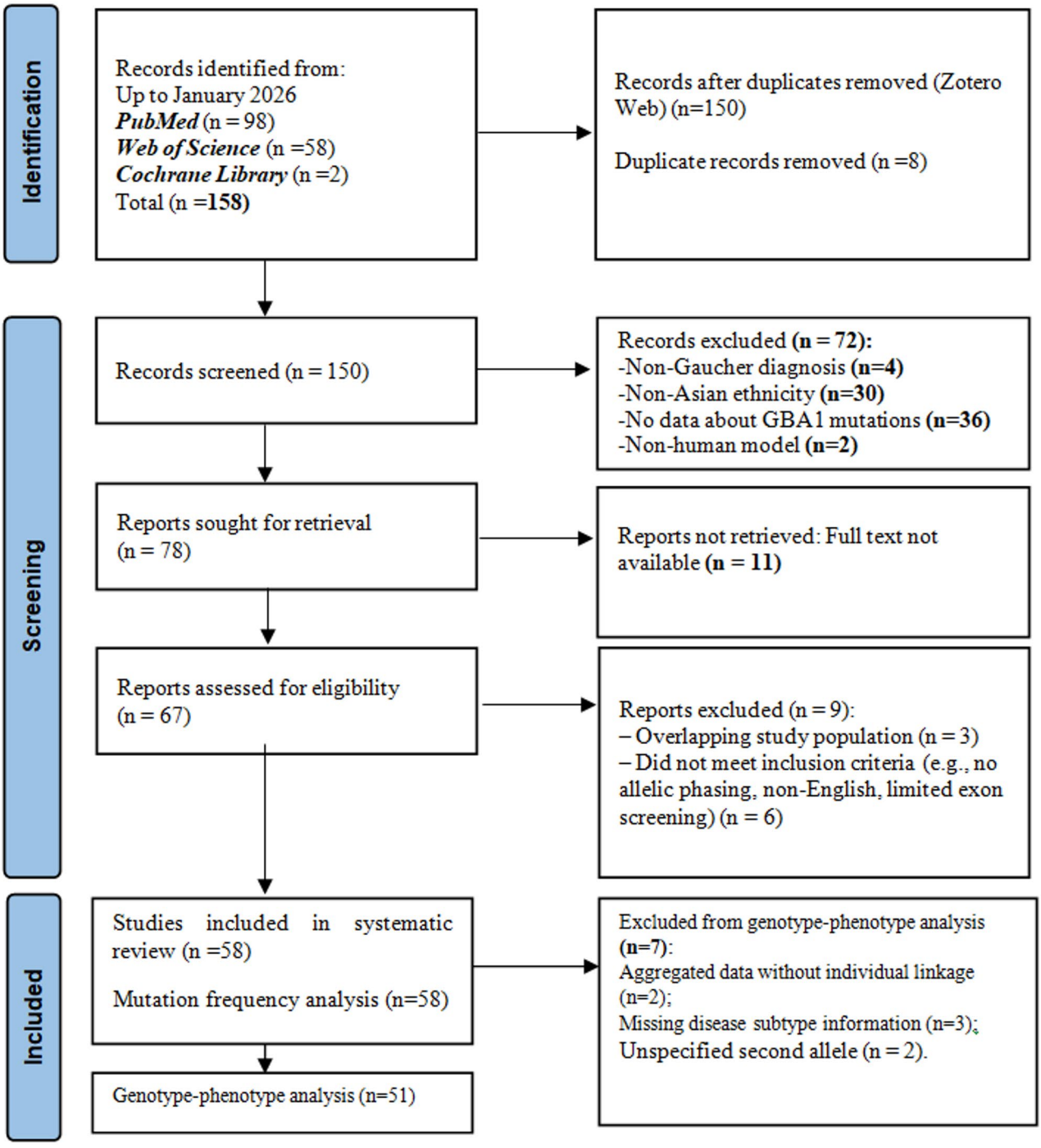

Fig. 2 Flow diagram of literature search and study selection according to PRISMA 2020 guidelines

The random-effect model with Freeman-Tukey transformation revealed the pooled proportion of the L444P allele was 0.46 (95% CI: 0.36–0.57). The frequency of the L444P allele varied considerably across the included countries (Fig. 4). The country-specific proportions ranged from 0.12 in Lebanon to 0.85 in Pakistan, giving substantial geographic variability and heterogeneity in the distribution (I^2 = 89.6%, τ^2 = 0.0275, $p < 0.0001$). The prediction interval of 0.11–0.83 suggests that the prevalence of the L444P allele varies widely in different populations.

The second most common mutation was the N370S allele, which varied substantially across the included countries (Fig. 5). The proportions ranged from 0.01 (China) to 0.58 (Iraq). The intermediate frequencies were observed in Kazakhstan (0.20) and Turkey (0.30), and

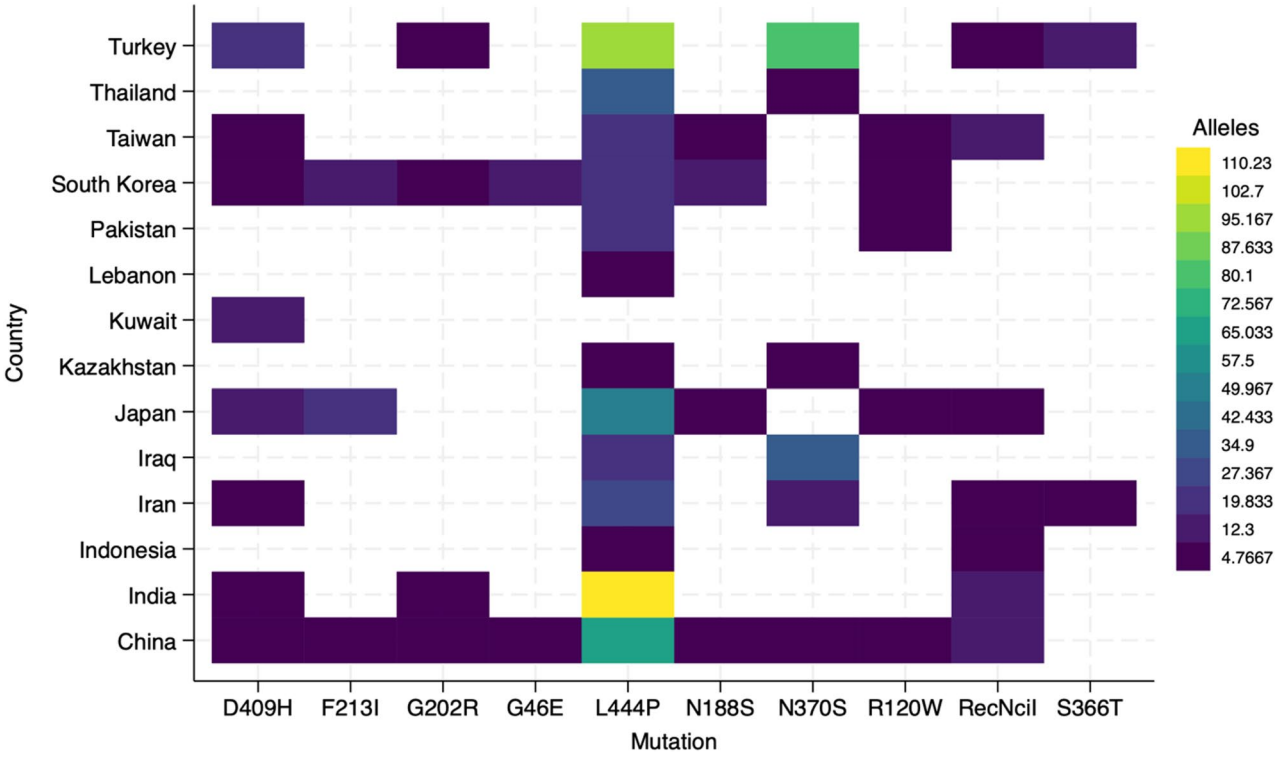

Fig. 3 Geographic distribution of the ten most common GBA1 mutations among reported Gaucher disease cases across 15 Asian countries. Heat map showing absolute allele counts of the top 10 GBA1 variants across included studies. Color intensity reflects the number of observed alleles, ranging from 4 to 110 (darker purple indicates lower counts; brighter yellow/green indicates higher counts)

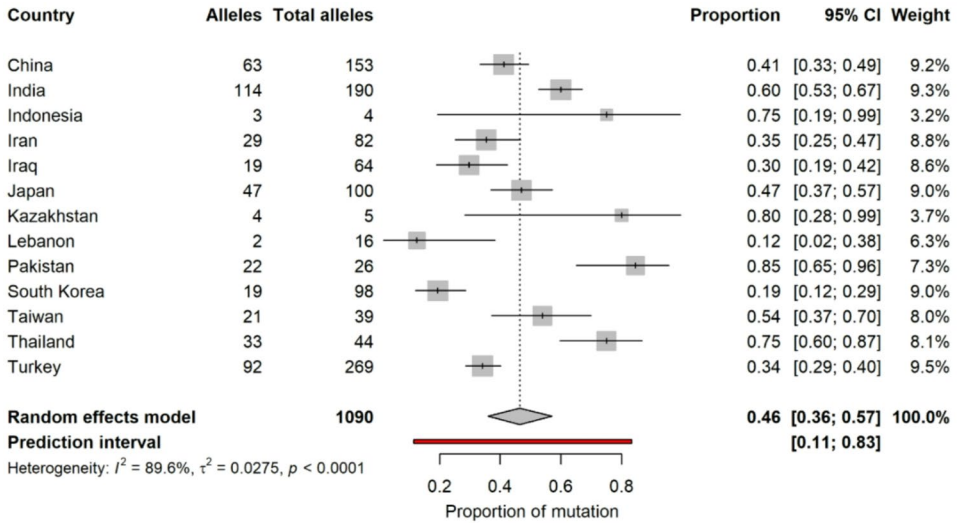

Fig. 4 Forest plot of the pooled proportion of the L444P variant among reported Gaucher disease cases

lower frequencies in Iran (0.20) and Thailand (0.02). The random-effects model with Freeman-Tukey transformation revealed the pooled proportion of 0.17 (95% CI: 0.02–0.40). Very high heterogeneity was observed (I^2 = 96.7%, τ^2 = 0.0834, $p < 0.0001$) with a prediction interval (0.00–0.92.00.92), suggesting considerable differences in allele frequencies among selected countries (Fig. 5).

The third most common mutation was D409H, and its frequency varied from 0.01 (South Korea and India) to 0.09 (Japan). Using a random-effects model with Freeman-Tukey transformation, the pooled proportion of the D409H allele was 0.04 (95% CI: 0.02–0.07). Overall, the heterogeneity was moderate among the included countries (I^2 = 71.2%, τ^2 = 0.0049, $p = 0.0020$). The prediction interval (0.00–0.15.00.15) suggests the expected

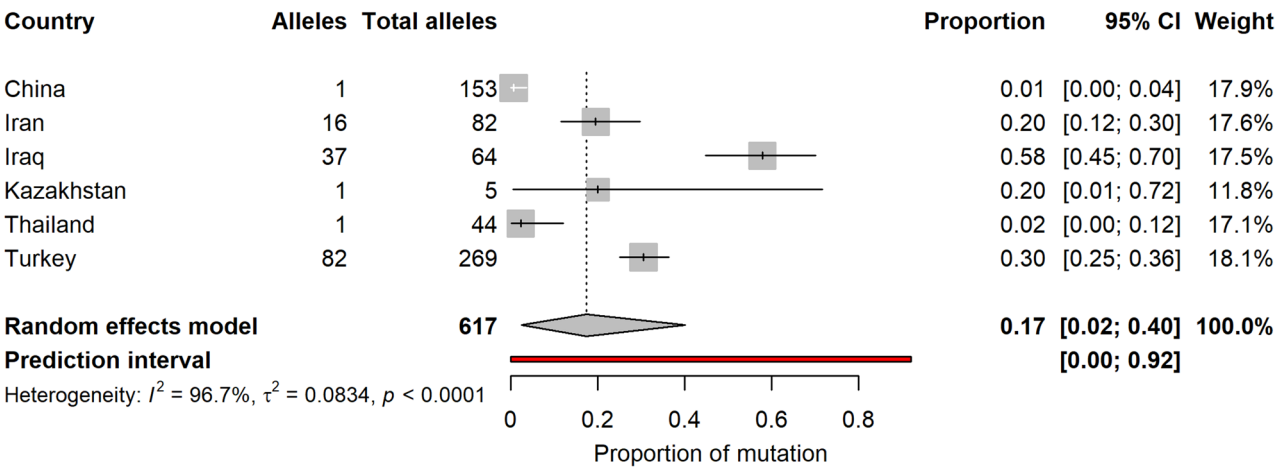

Fig. 5 Forest plot of the pooled proportion of the N370S variant among reported Gaucher disease cases

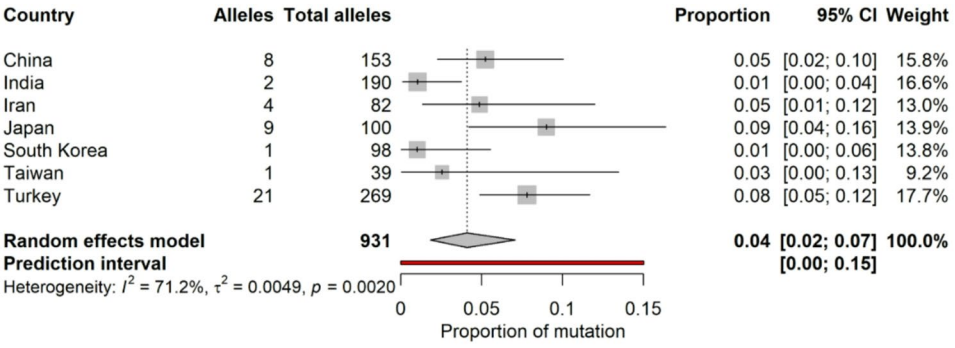

Fig. 6 Forest plot of the pooled proportion of the D409H variant among reported Gaucher disease cases

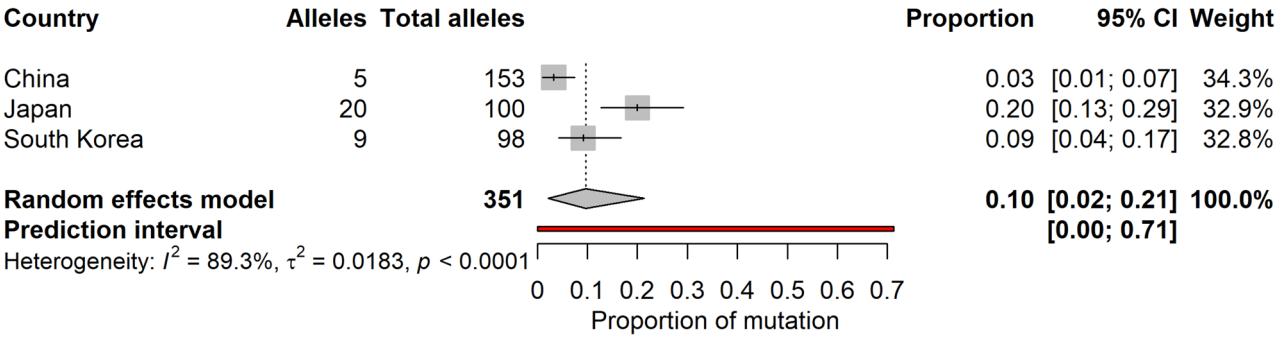

Fig. 7 Forest plot of the pooled proportion of the F213I variant among reported Gaucher disease cases

prevalence of the D409H allele among countries may vary but generally remains the same (Fig. 6).

The fourth most common mutation was F213I, with a pooled proportion being 0.10 (95% CI: 0.02–0.21). The country-specific proportions ranged from 0.03 (China) to 0.20 (Japan). The substantial heterogeneity was observed (I^2 = 89.3%, τ^2 = 0.0183, p < 0.0001) with a wide prediction interval (0.00–0.71.00.71) (Fig. 7).

The fifth most common RecNciI recombinant allele had a pooled proportion of 0.06 (95% CI: 0.02–0.10). The frequency across all included countries was relatively low overall (Fig. 8). The country-specific proportions ranged from 0.03 (Japan) to 0.25 (Indonesia). Moderate heterogeneity was observed (I^2 = 73.1%, τ^2 = 0.0062, p = 0.0011) with a prediction interval of 0.00–0.21.00.21, suggesting that RecNciI is an uncommon GBA1 recombinant allele (Fig. 8).

Genotype-phenotype associations

Among the 419 patients with complete genotype and phenotype data from 51 studies, 162 distinct GBA1 genotypes were identified (Table S5). The genotype

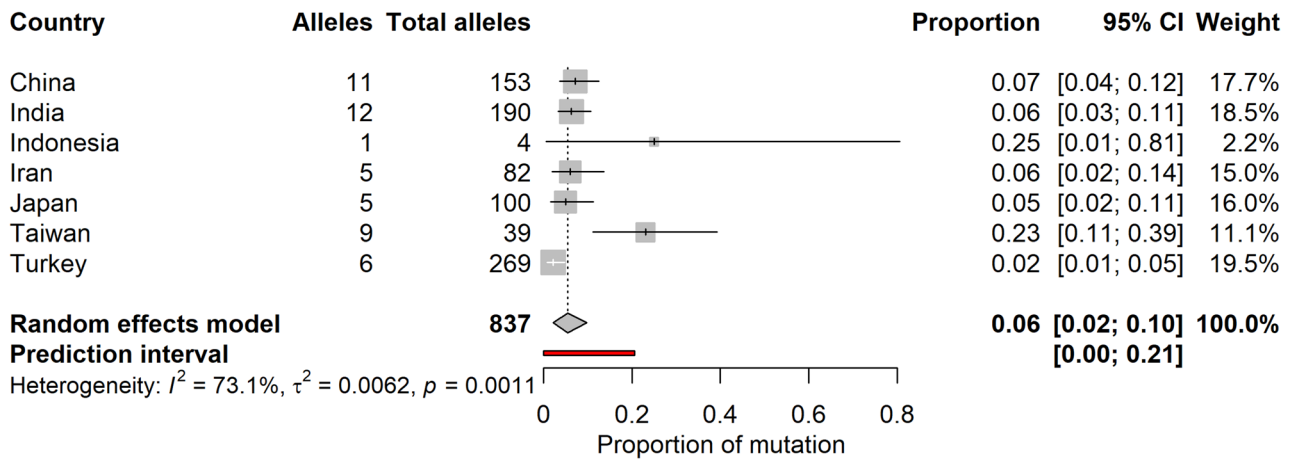

Fig. 8 Forest plot of the pooled proporion of the RecNcil variant among reported Gaucher disease cases

Table 1 Genotype-phenotype associations in asian gaucher disease patients

Genotype	Type 1	Type 2	Type 3	Total	Studies (*n*) [references]	Test	p_value	Adjusted *p*-value
L444P/L444P	22 (23.7%)	6 (6.5%)	65 (69.9%)	93	17 [8–24]	Chi-square	3.66E-18	5.92E-16***
N370S/N370S	50 (100%)	0 (0%)	0 (0%)	50	6 [12, 15–17, 25, 26]	Chi-square	3.74E-11	3.03E-09***
L444P/RecNcil	0 (0%)	8 (88.9%)	1 (11.1%)	9	5 [10, 11, 17, 23, 27]	Fisher	3.06E-07	1.65E-05***
D409H/D409H	2 (11.8%)	4 (23.5%)	11 (64.7%)	17	6 [10, 15–17, 21, 28]	Fisher	0.00062	0.0251*
N370S/L444P	13 (100%)	0 (0%)	0 (0%)	13	2 [12, 17]	Fisher	0.00194	0.0628
F213I/F213I	0 (0%)	0 (0%)	5 (100%)	5	2 [13, 21]	Fisher	0.00738	0.199
F213I/L444P	1 (11.1%)	2 (22.2%)	6 (66.7%)	9	4 [10, 13, 21, 29]	Fisher	0.0151	0.317
V460M+N370S/V460M+N370S	7 (100%)	0 (0%)	0 (0%)	7	1 [25]	Fisher	0.0654	0.466
L371V/L371V	6 (100%)	0 (0%)	0 (0%)	6	1 [30]	Fisher	0.124	0.466
N370S/RecΔ55	6 (100%)	0 (0%)	0 (0%)	6	1 [25]	Fisher	0.124	0.466

***p_adj < 0.001; *p_adj < 0.05. P-values adjusted using the Benjamini-Hochberg method. The chi-square test was applied to L444P/L444P ($n = 93$) and N370S/N370S ($n = 50$), while Fisher's exact test was used for all other genotypes. Only genotypes with ≥ 5 patients shown for brevity; complete analysis of all 162 genotypes in Supplementary Table S5

distribution was highly heterogeneous: 2 common genotypes (≥ 10 patients each) accounted for 143 patients (34.1%), 8 moderate-frequency genotypes (5–9 patients) for 69 patients (16.5%), and 152 rare genotypes (1–4 patients) for 207 patients (49.4%). This marked heterogeneity reflects the genetic diversity of Gaucher disease across Asian populations. Statistical analysis of genotype-phenotype associations was performed for all 162 genotypes. For each genotype, the distribution of disease subtypes (Type 1, Type 2, Type 3) was compared against all other genotypes combined. Fisher's exact test was applied for genotypes with small sample sizes, whereas Pearson's chi-square test was used for the most frequent genotypes (L444P/L444P, $n = 93$; N370S/N370S, $n = 50$), where expected cell counts were sufficient. P-values were adjusted for multiple testing using the Benjamini-Hochberg method. Four genotypes demonstrated statistically significant associations with specific disease phenotypes after multiple testing correction (adjusted $p < 0.05$) (Table 1).

L444P homozygosity was the most common genotype ($n = 93$, 22.2%) and showed the strongest association with disease phenotype (Fisher's exact test, $p\_adj = 5.92 \times 10^{-16}$). This genotype demonstrated pronounced phenotypic heterogeneity: Type 3 predominated (65/93, 69.9%), followed by Type 1 (22/93, 23.7%) and Type 2 (6/93, 6.5%). This distribution differed significantly from the overall cohort distribution (Type 1: 54.2%, Type 2: 14.1%, Type 3: 31.7%), indicating that L444P homozygosity is a strong predictor of neuronopathic disease, particularly Type 3, while still permitting substantial phenotypic variability.

N370S homozygosity ($n = 50$, 11.9%) exhibited complete phenotypic concordance, with all patients presenting Type 1 disease (50/50, 100%; Fisher's exact test, $p\_adj = 3.03 \times 10^{-9}$). No N370S homozygotes manifested neurological involvement, confirming the well-established non-neuronopathic character of this genotype and its protective effect against central nervous system manifestations.

L444P/RecNciI compound heterozygosity ($n = 9$) was associated with acute neuronopathic disease (chi-square test, $p\_adj = 1.65 \times 10^{-5}$), with 8 patients (88.9%) presenting Type 2 phenotype and 1 patient (11.1%) presenting

Table 2 Logistic regression analysis: predictors of severe phenotype

Genetic Predictor	OR	95% CI	*p*-value
L444P homozygote[a]	6.77	3.9–12.14	< 0.001
N370S homozygote[b]	Non-estimable	–	–
D409H homozygote	15.74	4.27–101.88	< 0.001
Recombinant allele	1.96	0.96–3.98	0.065
F213I allele	10.59	4.22–32.33	< 0.001

[a] Reference group: all other genotypes

[b]Complete separation observed: all N370S/N370S patients presented with Type 1 (non-neuronopathic) disease and none with Type 2/3. Under complete separation, maximum likelihood estimates are unreliable and the OR is non-estimable

OR = odds ratio; CI = confidence interval

Outcome: Severe phenotype (Type 2/3) vs. Mild phenotype (Type 1)

Model: Multivariate logistic regression with simultaneous entry

Type 3. This distribution significantly differed from the overall Type 2 prevalence (14.1%), underscoring the severe neurotoxic potential of RecNciI recombinant alleles when combined with L444P.

D409H homozygosity ($n = 17$) showed a significant association with neuronopathic phenotypes (chi-square test, p_adj = 0.025), with predominant Type 3 presentation (11/17, 64.7%), followed by Type 2 (4/17, 23.5%) and Type 1 (2/17, 11.8%). Unlike N370S homozygosity, D409H homozygosity demonstrated phenotypic heterogeneity, though with a marked shift toward neuronopathic subtypes (88.2% combined Type 2/3). Among the remaining 158 genotypes analyzed, no other genotype-phenotype associations reached statistical significance after correction for multiple testing (all p_adj > 0.05). However, several genotypes with smaller sample sizes showed trends toward specific phenotypes that warrant validation in larger cohorts. Notably, the high proportion of rare genotypes (93.8% of genotypes represented by ≤ 4 patients) limited statistical power for detecting associations with uncommon genotype-phenotype pairs. The overall distribution of disease subtypes in the cohort was: Type 1 (227/419, 54.2%), Type 3 (133/419, 31.7%), Type 2 (59/419, 14.1%).

This distribution differed substantially from that reported in predominantly Caucasian cohorts, where Type 1 typically accounts for > 90% of cases, highlighting potential ethnic differences in disease presentation or ascertainment bias favoring diagnosis of neuronopathic forms in Asian populations.

Genotype-phenotype correlations

Multivariable logistic regression was performed to evaluate independent genetic predictors of neuronopathic disease (Type 2/3 versus Type 1). Homozygosity for L444P was strongly associated with severe phenotype (OR = 6.77, 95% CI: 3.90–12.14). Homozygous p.D409H demonstrated an even stronger association (OR = 15.74, 95% CI: 4.27–101.88), although with wide confidence intervals reflecting limited sample size. Presence of p.F213I was also significantly associated with increased odds of severe disease (OR = 10.59, 95% CI: 4.22–32.33). The RecNciI allele showed a trend toward increased severity (OR = 1.96, 95% CI: 0.96–3.98), but did not reach statistical significance. In contrast, homozygous N370S was exclusively observed in non-neuronopathic cases, resulting in complete separation and an estimated OR approaching zero, consistent with its protective effect against neurological involvement (see Table 2).

Discussion

This systematic review provides the most comprehensive characterization of GBA1 variants and genotype-phenotype correlations in Asian Gaucher disease populations to date, encompassing 419 patients with complete phenotype data from 51 studies across 15 countries. Our analysis identified 162 distinct genotypes and four statistically significant genotype-phenotype associations, while also revealing substantial genetic heterogeneity and identifying key predictors of severe neuronopathic disease. Given that 94% of identified genotypes were represented by ≤ 4 patients, genotype-specific associations beyond the four most recurrent genotypes should be interpreted as exploratory and hypothesis-generating rather than definitive conclusions.

Mutation spectrum and geographic distribution

The mutation spectrum in Asian populations differs markedly from that reported in European and Ashkenazi Jewish cohorts [31–35]. While N370S predominates in Ashkenazi populations (50–60% of alleles) and is common in European cohorts [36–38], L444P emerged as the most prevalent mutation in our Asian cohort, consistent with previous regional studies from China [10], Japan [39], and Korea [18]. This distribution has important implications for genetic screening strategies and highlights the need for population-specific diagnostic approaches.

In contrast to the highly heterogeneous genotype distribution observed in our cohort (162 distinct genotypes), Gaucher disease in Ashkenazi Jewish populations is characterized by a founder mutation structure, where three recurrent variants (N370S, 84GG insertion, IVS2 + 1G→A) collectively account for > 90% of disease alleles [40]. This distribution likely reflects the complex demographic history and population structure of Asia, encompassing numerous ethnic groups with distinct evolutionary backgrounds.

The observed geographic heterogeneity in GBA1 mutation proportions among reported cases may reflect three distinct sources of variability: genuine population genetic differences arising from distinct demographic histories,

founder effects, and consanguinity patterns [41]; publication and ascertainment bias inherent to the included studies, which predominantly comprised case reports and clinically ascertained cohorts; and differences in diagnostic infrastructure and genotyping methods, as countries with limited resources may identify cases primarily when severe phenotypes prompt clinical investigation, and non-pseudogene-aware methods may affect accurate detection of certain variants such as recombinant alleles.

Despite these potential sources of bias, several consistent patterns emerged from the available data, most notably the predominance of L444P in East Asian populations and the relatively higher frequency of N370S in West Asian cohorts. These findings suggest genuine population-level differences in the genetic architecture of Gaucher disease across Asia.

Mutation spectrum heterogeneity

Substantial heterogeneity was observed across mutations (I^2 = 71–97%), reflecting population genetic differences. L444P was the most prevalent mutation (pooled proportion: 0.46), although the frequency varied between different geographic regions, in contrast to Ashkenazi populations, where N370S accounts for ~70% of alleles [40]. Wide prediction intervals (L444P:0.11–0.83) indicate considerable between-population variability in future studies.

N370S showed pronounced geographic variation, with frequencies ranging from 58% (Iraq) to 0% (Japan, Korea). This pattern is consistent with observations in Ashkenazi Jewish [40, 42] and Mediterranean [43] populations, where N370S is predominant, and may reflect limited historical gene flow and population-specific demographic histories. Consanguineous marriage practices in some populations may additionally increase the detection of homozygous genotypes.

D409H demonstrated more consistent frequencies across populations (I^2 = 71.2%). Kuwait was excluded from analysis as an outlier (10/10 alleles) likely representing single-family ascertainment. Other mutations (F213I, RecNciI) showed variable frequencies across countries, though interpretation is limited by small sample sizes.

These findings highlight the genetic diversity of Asian populations and suggest that mutation spectra vary substantially across countries. Comprehensive sequencing approaches may be preferable to targeted mutation panels in populations with diverse genetic backgrounds, particularly given the high proportion of rare genotypes observed.

Genotype-phenotype associations and predictors of severe disease

Analysis of genotype–phenotype relationships revealed four statistically significant associations between specific GBA1 genotypes and clinical presentation. Homozygosity for L444P demonstrated a strong association with neuronopathic forms of Gaucher disease, particularly type 3, although notable phenotypic variability was observed. In this cohort, the majority of patients presented with Type 3 disease (67%), while Type 1 and Type 2 phenotypes accounted for 24% and 7% of cases, respectively. Similar heterogeneity has been observed in Japanese (75% Type 3 among L444P/L444P) [44] and other populations [45], indicating that the L444P genotype alone is insufficient to predict phenotype with precision. Several mechanisms may contribute to this variability. L444P affects protein trafficking and stability but retains residual enzymatic activity (5–10% of wild-type), creating a phenotypic spectrum dependent on total residual activity [46]. Besides, environmental factors such as infectious exposures or metabolic stressors may trigger neurological manifestations in genetically predisposed individuals [45].

In contrast, the N370S/N370S genotype was exclusively associated with the non-neuronopathic phenotype, consistent with its well-established protective effect against neurological involvement [47]. This complete separation precluded reliable estimation of the odds ratio by standard maximum likelihood methods; therefore, no quantitative OR is reported. This finding nonetheless provides strong qualitative evidence for the protective effect of N370S homozygosity against neurological involvement Mechanistically, N370S retains sufficient residual enzymatic activity to prevent neurological substrate accumulation while allowing visceral manifestations [48]. This finding has important implications for genetic counseling. Parents who are both N370S carriers can be reassured that affected children will not develop neurological disease, though visceral complications require monitoring [49]. However, the absence of N370S homozygotes with Type 2/3 in our cohort limits statistical power for detecting rare exceptions, if they exist.

The observed association with Type 2 disease suggests the severe neurotoxic potential of RecNciI recombinant alleles. RecNciI arises from homologous recombination between GBA1 and its pseudogene, creating a chimeric allele with severely compromised enzymatic function [50]. When combined with L444P, which itself shows reduced catalytic activity and markedly impaired activator responses, the resulting near-complete enzyme deficiency leads to acute neuronopathic disease [51]. This severe genotype-phenotype association has been consistently reported across populations [45]. Our findings in 9 patients from 5 Asian countries support this consistency. Recognition of RecNciI is clinically important as

recombinant alleles require molecular characterization beyond standard PCR-based point mutation screening and portend particularly poor prognosis, warranting early intervention.

D409H/D409H showed a significant association with neuronopathic phenotypes, though with less severe predictions than L444P/RecNciI. D409H encodes a severely compromised enzyme with < 0.5% residual activity [46], yet the phenotypic heterogeneity observed (Type 3 predominant; Type 2 and Type 1 present at lower frequencies) suggests D409H may permit broader variation in residual function or be more susceptible to modifying influences. D409H appears enriched in Asian populations (4% of alleles) compared to Caucasian and Ashkenazi Jewish cohorts, where it is rare or absent [45, 50], potentially representing an Asian-enriched variant warranting haplotype characterization.

These findings suggest a spectrum of genotype-phenotype predictability: N370S homozygosity deterministically precludes neurological disease, while L444P homozygosity strongly but incompletely predicts neuronopathic phenotypes. This heterogeneity indicates that the GBA1 genotype, though highly informative, represents only one determinant of clinical outcome. Total residual enzyme activity modulated by catalytic efficiency, protein stability, activator responsiveness, and modifier genes likely determine whether individuals cross the threshold for neurological involvement.

The N188S variant, although not among the five most frequent mutations in our cohort, warrants specific mention due to its association with progressive myoclonic epilepsy (PME), a severe and refractory Type 3 phenotype. This variant was identified in Japan, Taiwan, China, and South Korea (total allele count: 16), consistent with its previously reported enrichment in East Asian populations [52].

The genotype-phenotype associations identified in our Asian cohort are broadly consistent with those reported in European and Ashkenazi Jewish populations yet differ markedly in mutation frequencies. Grabowski et al. established in the Ashkenazi Jewish population that a single N370S allele is diagnostic of Type 1 GD, while L444P/L444P is strongly associated with neuronopathic variants [2]. In the Iberian Peninsula registry ($n = 436$), N370S and L444P together accounted for 67% of alleles, with mild-to-moderate phenotypes predominating, largely attributable to the high frequency of N370S [53]. Serrano-Gonzalo et al. further confirmed that non-N370S/L444P genotypes associate with more severe disease and higher Parkinsonism risk [54]. However, while the directional genotype-phenotype relationships are conserved, mutation frequencies differ substantially: N370S was largely absent in East Asian populations, and L444P dominated the Asian mutation spectrum (pooled proportion: 0.46), which likely underlies the higher burden of neuronopathic disease in our cohort compared to European registries.

Clinically, these associations enable risk stratification for genetic counseling and early intervention planning, though substantial minorities with "severe" genotypes presenting mild phenotypes (24% of L444P/L444P) preclude purely genotype-based prognostication. Future research should focus on identifying modifier genes through genome-wide association studies and developing integrated biomarkers combining genetic, biochemical, and imaging parameters to improve phenotype prediction and guide personalized management strategies.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, the included studies predominantly comprised case reports, case series, and retrospective clinical cohorts rather than population-based samples. Therefore, the reported distribution of GBA1 mutations among reported Gaucher disease cases is subject to ascertainment bias and likely overrepresents severe phenotypes and more frequently published variants. This limitation is difficult to avoid in rare disease research, particularly in populations with limited screening infrastructure. Second, the high proportion of rare genotypes (94% ≤4 patients) limited statistical power for detecting associations beyond the most common genotypes. Third, potential modifying factors such as SCARB2 variants, mitochondrial DNA polymorphisms, or environmental exposures were not accounted for, which may contribute to phenotypic heterogeneity. Fourth, language restriction to English publications may have excluded relevant Asian-language studies, potentially underestimating mutation diversity. Fifth, mutation proportions were estimated using country-level aggregation rather than individual study-level analysis, which may mask within-country heterogeneity between cohorts. Potential overlap between cohorts was addressed by excluding earlier or smaller datasets where duplicate populations were identified. A further limitation concerns genotyping methodology: not all included studies reported pseudogene-aware approaches and given the high sequence homology between GBA1 and its pseudogene GBAP1, some reported variants may warrant confirmation with more specific methods.

Conclusion

This systematic review provides a comprehensive overview of the distribution of GBA1 mutations across Asian populations and highlights substantial geographic variability in the distribution of GBA1 mutations among reported cases. L444P emerged as the predominant allele in East and South Asian cohorts, whereas N370S was

more frequently observed in West Asian populations. Despite considerable genetic heterogeneity and the high proportion of rare genotypes, consistent regional patterns were identified across multiple independent studies. These findings underscore the importance of population-specific genetic data for improving molecular diagnosis and genetic counseling in Gaucher disease. Future studies integrating functional assays, broader genomic data, and longitudinal clinical follow-up will be essential to refine genotype–phenotype prediction and improve precision in clinical management.

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s40246-026-00975-2.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Acknowledgements
Not applicable.

Author contributions
PT and BS conceived and designed the study. KA and AS collected data. KA and AS performed the data analysis. DA and PT drafted the manuscript. All the authors approved the final version of the manuscript.

Funding
This research has been funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. BR24992881).

Data availability
All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 18 March 2026 / Accepted: 24 April 2026
Published online: 04 May 2026

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