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The global population genetics of GPNMB-associated amyloidosis cutis dyschromica: ancestry-specific variation and likely underdiagnosis

Alan Garcia-Elfring

alangarciaelfring87@gmail.com

PyType Laboratorio https://orcid.org/0000-0002-2093-4041

Research Article

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The global population genetics of *GPNMB*-associated amyloidosis cutis dyschromica: ancestry-specific variation and likely underdiagnosis

Alan García-Elfring

PyType Laboratorio, Morelia Michoacán, México

pytype.lab@gmail.com

Abstract

Amyloidosis cutis dyschromica (ACD) is a rare recessive pigmentary disorder caused by biallelic loss-of-function (LoF) variants in *GPNMB*. Almost all reported patients are East or Southeast Asian, and it is unknown whether this reflects allele distribution or ascertainment. Using gnomAD v4.1, I identified 114 high-confidence predicted LoF (pLoF) variants on the MANE Select transcript and estimated carrier frequencies and expected biallelic prevalence across ancestry groups. Carrier frequencies were highest in Ashkenazi Jewish (1 in 251) and East Asian (1 in 261) individuals, followed by non-Finnish Europeans (1 in 358) and Admixed Americans (1 in 422). Under Hardy–Weinberg proportions, about 183 people in Mexico (95% interval 141–344) and about 40 Ashkenazi Jews worldwide (25–68) are expected to carry biallelic pLoF alleles. A literature audit found no reported ACD cases of Latin American or Ashkenazi Jewish origin, against at least 100 reported patients worldwide. The Ashkenazi burden is driven by a single founder splice-donor allele, c.367+2T>C (57 of 80 gnomAD copies). In Admixed Americans, 70% of pLoF alleles are shared with Europeans and 30% come from four alleles essentially absent elsewhere. Heterozygous pLoF carriers in 394,841 UK Biobank exomes showed no association across 4,529 traits, consistent with recessive inheritance. Variants that disrupt the essential MITF binding site of the *GPNMB* proximal promoter (MCS3) were rare, but one, 7-23246653-A-T, is confined to African and Admixed American chromosomes and is a candidate for functional testing. These results indicate that ACD is likely underdiagnosed in Latin America and among Ashkenazi Jews, and that *GPNMB* belongs on diagnostic panels for pigmentary disorders beyond East Asia.

Keywords: human genetics; amyloidosis cutis dyschromica; *GPNMB*; pigmentation; rare diseases; loss of function; carrier frequency; founder variant; underdiagnosis; MITF; promoter; Latin America; Ashkenazi Jewish; population genetics; gnomAD

Introduction

Glycoprotein non-metastatic melanoma protein B (GPNMB; also known as osteoactivin, DC-HIL and HGFIN) was first identified in 1995 as *nmb*, a transcript showing higher expression in poorly metastatic than in highly metastatic human melanoma cell lines [1]. Orthologues were later described independently as osteoactivin in rat and DC-HIL in mouse, reflecting expression in bone, macrophages and dendritic cells [2], and the human protein was also characterized as HGFIN (hematopoietic growth factor-inducible neurokinin-1 type) [3]. Beyond pigment cells, GPNMB has been implicated in osteoblast differentiation [4], inhibition of T-cell activation through syndecan-4 [5], neuroprotection in models of amyotrophic lateral sclerosis [6] and macrophage-mediated cardiac repair and angiogenesis after injury [7,8]; these roles depend on tissue context, and on whether the protein is membrane-bound or cleaved and soluble, as has been recently reviewed [9]. GPNMB is also a candidate therapeutic target in cancer [2], with GPNMB-directed CAR T cells shown to be active in mouse models of leukemia, melanoma and colorectal cancer [10]. Human *GPNMB* maps to chromosome 7p15 and encodes a type I transmembrane glycoprotein. Alternative splicing yields isoforms of 560 and 572 amino acids that differ by 12 residues in the extracellular region [11,12]. GPNMB shares about 33% amino-acid identity with the melanocyte protein PMEL (Pmel17/gp100/Silver), both having the same domain layout: a signal peptide, an N-terminal domain, a polycystic kidney disease (PKD) domain, a kringle-like domain, a single transmembrane segment and a short cytoplasmic tail [1,13,14]. The two proteins diverge in a key respect. PMEL fragments assemble into the functional amyloid fibrils on which melanin is deposited, whereas GPNMB lacks PMEL's repeat domain and its PKD domain is heavily N-glycosylated; it traffics to different compartments and is largely absent from fibrils [14].

In pigment cells, GPNMB is a melanosome protein. Proteomic studies place it in all stages of melanosome maturation, with enrichment in mature melanosomes, and its ectodomain is released by proteolytic cleavage [13,15,16]. Its expression in melanoblasts and the retinal pigment epithelium depends on the microphthalmia-associated transcription factor MITF, which acts through a conserved proximal enhancer [17]. Knockdown of *GPNMB* in human PIG1 melanocytes sharply reduced the number of early melanosomes and lowered TYR, TYRP1, PMEL and OA1 expression [12]. The link to pigmentation extends beyond mammals: in the European fire salamander, GPNMB is differentially expressed and differentially m6A-methylated among yellow, brown and black colour morphs [18]. Outside pigment cells, GPNMB is an endo-lysosomal protein. Lysosomal stress induces it in macrophages through the MiT/TFE transcription factors, including MITF and TFEB, and lysosomal exocytosis then delivers it to the cell surface, where ADAM proteases cleave a soluble ectodomain into plasma and cerebrospinal fluid [19–21]. GPNMB therefore links two lysosome-related systems: melanosome biogenesis in pigment cells and the lysosomal stress response in phagocytes.

The lysosomal role connects GPNMB to neurodegeneration. A Parkinson's disease (PD) risk locus at 7p15.3 is associated with higher *GPNMB* expression in brain [22], and GPNMB is elevated in plasma and cerebrospinal fluid of people with PD, as well as in Gaucher disease, Niemann–Pick type C and amyotrophic lateral sclerosis [20,21,23]. LRRK2 mutation carriers show the highest cerebrospinal-fluid GPNMB concentration, consistent with LRRK2-modulated lysosomal exocytosis [20,21]. At the opposite end of the dosage range, loss of GPNMB causes amyloidosis cutis dyschromica (ACD; listed in OMIM as primary localized cutaneous amyloidosis 3, PLCA3, #617920), a disorder of mottled hyper- and hypopigmentation with dermal amyloid deposits. ACD was first described in Japan by Morishima in 1970

[24] and was long attributed to defective repair of ultraviolet-induced DNA damage, after fibroblasts from a Japanese patient proved hypersensitive to UV-B [25]. Its amyloid stains for the keratinocyte cytokeratins CK5/6 and CK34βE12, indicating that it derives from degenerating keratinocytes rather than from GPNMB itself [26], consistent with the non-amyloidogenic behaviour of GPNMB [14]. Yang et al. (2018) identified biallelic truncating *GPNMB* variants in nine affected individuals and established autosomal-recessive inheritance [27]. Inheritance is not uniformly recessive, however: Onoufriadis et al. (2019) described families in which a splice variant (c.700+5G>T) and a missense variant (p.Cys413Ser) caused disease in some heterozygotes, a pattern they termed semidominant [28,29].

ACD has been reported mainly in East and Southeast Asian families. A 2016 review of 48 cases found 63% of patients to be of East or Southeast Asian ancestry, and most genotyped families since then come from Taiwan, mainland China, Thailand, and the Philippines [29–32]. Whether this reflects the global distribution of *GPNMB* loss-of-function alleles or where clinicians have looked is unknown, and the frequency of such alleles in other ancestries has not been characterized. Large population databases now allow this question to be addressed directly. In this study I estimate the frequency of high-confidence predicted loss-of-function (pLoF) *GPNMB* alleles across gnomAD ancestry groups, compare the expected number of affected individuals with the reported literature, and test whether heterozygous carriers show any phenotype. I also examine the MCS3 element, an 89-bp conserved proximal enhancer of *GPNMB* identified by Loftus et al. (2009) [17], whose MITF binding site was required for enhancer activity in melanocyte cell lines, to ask whether regulatory variants add materially to the loss-of-function burden.

Methods

Variant data

All variants in *GPNMB* (ENSG00000136235) were exported from the gnomAD v4.1 browser (2,394 variants; exomes and genomes, GRCh38) [33]. Allele counts (AC) and allele numbers (AN) were taken per genetic ancestry group: African/African American, Admixed American, Ashkenazi Jewish, East Asian, Finnish, Middle Eastern, non-Finnish European, South Asian and Amish. A variant was considered to pass quality control if it passed the filters in either the exome or the genome dataset.

Loss-of-function classification

A variant was kept as a high-confidence predicted loss-of-function (pLoF) variant when all of the following held: (i) its consequence, as assigned by the Ensembl Variant Effect Predictor (VEP) in the gnomAD annotation, was stop_gained, frameshift_variant, splice_donor_variant, splice_acceptor_variant or start_lost; (ii) the consequence applied to the MANE Select transcript of GPNMB (ENST00000258733, NM_002510.3) [34]; (iii) it passed gnomAD quality filters in the exome or the genome dataset; (iv) it carried no low-confidence or LoF flag from LOFTEE, the loss-of-function filter applied by gnomAD [35]; and (v) it was not classified as benign or likely benign in ClinVar (variants with conflicting classifications were retained). The MANE restriction was necessary because the gnomAD export reports, for each variant, the most severe consequence across all transcripts of the gene. Eight variants had a loss-of-function consequence only on transcripts other than MANE, and all eight were excluded. LOFTEE also flagged six of them, so only two were excluded by the MANE restriction alone. One of these, 7-23261489-G-A (chromosome 7, position 23,261,489, G>A), is a stop-gained change on the alternative transcript ENST00000647578 but lies deep in an intron of the MANE transcript

(c.1018+716G>A). Had it been counted, the South Asian pLoF frequency would have been about 9.5 times higher, and it would have produced the only apparent pLoF homozygote in the data.

Carrier frequency and prevalence

For each ancestry group, the cumulative pLoF allele frequency was $q = \Sigma AC_i/AN_i$ over kept variants. Carrier frequency was 2q and expected biallelic prevalence was q^2, assuming Hardy–Weinberg proportions, random mating and no correlation between alleles. Uncertainty was estimated by Monte Carlo: for each variant with AC > 0 in a group, allele frequency was drawn from Beta(AC + 0.5, AN − AC + 0.5) and draws were summed across variants (4,000 iterations); 95% intervals are the 2.5th and 97.5th percentiles. Variants with AC = 0 in a group were not drawn, so that 114 Jeffreys priors did not add spurious mass. Expected numbers of biallelic individuals were population size × q^2, using approximate 2025 populations (China 1,410 million, Japan 124 million, South Korea 51.7 million, Taiwan 23.4 million, Mexico 130 million) with East Asian or Admixed American frequencies as proxies, and about 10 million Ashkenazi Jews worldwide.

Admixed American decomposition

pLoF alleles observed in Admixed Americans were split into those also present in non-Finnish Europeans and those absent from Europeans. For alleles concentrated in Admixed Americans, the probability of the observed distribution under equal frequency across groups was computed from the binomial distribution given the group allele numbers.

Literature audit

Reported ACD cases were compiled from PubMed-indexed, SciELO, LILACS/BVS and DOAJ records by web search in Spanish, Portuguese and English, and cross-checked against the country-by-country table of Del Villar et al. (2026) [32]. For each report I recorded country, stated ancestry, number of patients, familial status and *GPNMB* genotype (Table S1). Reported counts are lower bounds; overlap between series is possible, and Chinese-language literature (CNKI) could not be searched.

Phenotypes in heterozygous carriers

Gene-burden associations between *GPNMB* and 4,529 phenotypes in 394,841 UK Biobank exomes were taken from Genebass [36] for the pLoF and missense|LC masks (SKAT-O). Significance was judged against the Genebass threshold ($p < 2.5 \times 10^{-6}$) and a Bonferroni threshold across phenotypes ($p < 1.1 \times 10^{-5}$).

Proximal promoter (MCS3)

The 89-bp MCS3 element (hg18 chr7:23252780–23252868) [17] was located in GRCh38 by exact sequence match within chr7:23.20–23.30 Mb, using sequences from the UCSC API. MITF E-box (CACATG; full motif TCAYRTGA) and AP-1 (TGA[CG]TCA) motifs were located by pattern search. All gnomAD v4 variants within the element ± 50 bp, with per-group AC and AN, were retrieved through the gnomAD GraphQL API.

Results

High-confidence pLoF alleles in GPNMB

Of 2,394 *GPNMB* variants in gnomAD v4.1, 114 met all pLoF criteria: 38 stop-gained, 38 frameshift, 22 splice-donor, 13 splice-acceptor and 3 start-lost. They are spread along the whole coding sequence, and most are singletons or seen a handful of times (Figure 1). No pLoF homozygote was observed. Two exclusions illustrate the filters. The MANE restriction removed two variants that passed every other filter (eight non-MANE LoF annotations in total), including 7-23261489-G-A, which is intronic on MANE and had produced the only apparent homozygote. LOFTEE flagged 7-23274204-G-T (c.1663G>T), a stop at codon 555 near the C-terminus; it is classified benign in ClinVar and has 203 homozygotes in gnomAD, consistent with escape from nonsense-mediated decay.

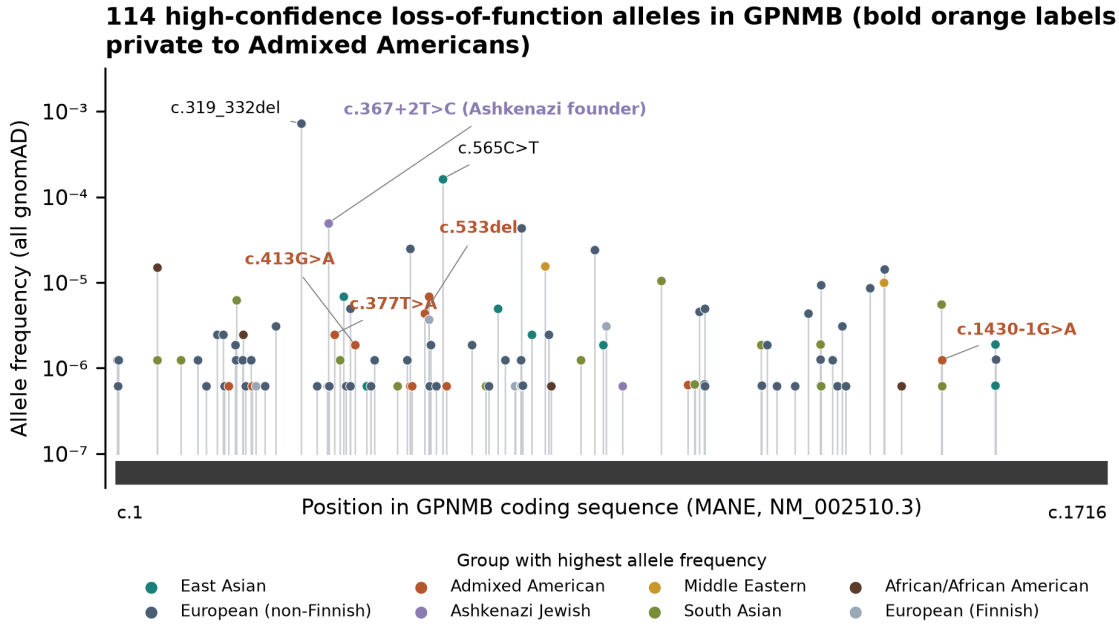


Figure 1. High-confidence pLoF alleles along the *GPNMB* coding sequence. Each lollipop is one of 114 pLoF variants on the MANE transcript (NM_002510.3), placed by coding position; height is its allele frequency across all of gnomAD v4.1 (log scale). Colour marks the ancestry group with the highest allele frequency. Labelled variants are discussed in the text; bold orange labels mark alleles essentially private to Admixed Americans, and the purple label the Ashkenazi founder allele.

Carrier frequency differs about tenfold across ancestries

The cumulative pLoF frequency was highest in Ashkenazi Jewish and East Asian individuals, with carrier frequencies of about 1 in 250, and lowest in African and Finnish individuals (Table 1, Figure 3a). Non-Finnish Europeans (1 in 358) and Admixed Americans (1 in 422) were intermediate. Intervals were widest for the Middle Eastern and Ashkenazi groups, which have the smallest samples.

Table 1. Carrier frequency and expected biallelic prevalence of *GPNMB* pLoF alleles by gnomAD ancestry group. Carrier frequency = 2q; prevalence = q^2 (Hardy–Weinberg, random mating). 95% intervals from Monte Carlo sampling of per-variant allele frequencies.

Ancestry group	Cumulative pLoF frequency (q)	Carrier frequency (95% interval)	Expected prevalence per 100,000 (95% interval)
Ashkenazi Jewish	1.99×10^{-3}	1 in 251 (192–319)	0.40 (0.25–0.68)
East Asian	1.92×10^{-3}	1 in 261 (202–302)	0.37 (0.27–0.61)
Non-Finnish European	1.40×10^{-3}	1 in 358 (335–367)	0.20 (0.19–0.22)
Admixed American	1.18×10^{-3}	1 in 422 (307–480)	0.14 (0.11–0.27)
South Asian	8.04×10^{-4}	1 in 622 (445–688)	0.065 (0.053–0.13)
African/African American	3.47×10^{-4}	1 in 1,442 (879–1,774)	0.012 (0.008–0.032)
Middle Eastern	3.30×10^{-4}	1 in 1,515 (431–4,782)	0.011 (0.001–0.13)
Finnish	1.87×10^{-4}	1 in 2,668 (1,400–4,073)	0.0035 (0.0015–0.013)

A few alleles dominate each population's burden

The common alleles are distributed very differently across populations (Figure 2, Table 2). The variant most often reported in ACD patients, c.565C>T (p.Arg189*), is 6.9 times more frequent in East Asians (0.116%) than in non-Finnish Europeans (0.017%) and was seen in five of the eight major ancestry groups; it lies at a CpG site, which is the single most frequently mutated dinucleotide in vertebrate and mammalian genomes, so recurrent mutation and a shared founder are both possible. Two other East Asian–concentrated alleles, c.393T>G and c.660T>G, have also been reported in patients [27,29]. In contrast, c.319_332del (p.Lys107TrpfsTer6) is the most frequent pLoF allele in non-Finnish Europeans (0.090%) and Admixed Americans (0.077%) and is absent from East Asians. It is classified pathogenic/likely pathogenic in ClinVar (VCV001324506; four submitters) but has never been reported in a patient, and it lies in a tandem repeat flagged by gnomAD for discrepant frequencies.

The Ashkenazi Jewish burden comes from a single allele. c.367+2T>C (7-23254314-T-C), which destroys the +2 position of a splice donor, has an allele frequency of 0.19% in Ashkenazi Jews (57 of 29,584 chromosomes); 57 of its 80 copies in gnomAD are in this group, which makes up about 2% of the database. It passes all quality filters, carries no LOFTEE flag, is absent from ClinVar and accounts for about 97% of the Ashkenazi cumulative frequency, the pattern expected of a founder allele.

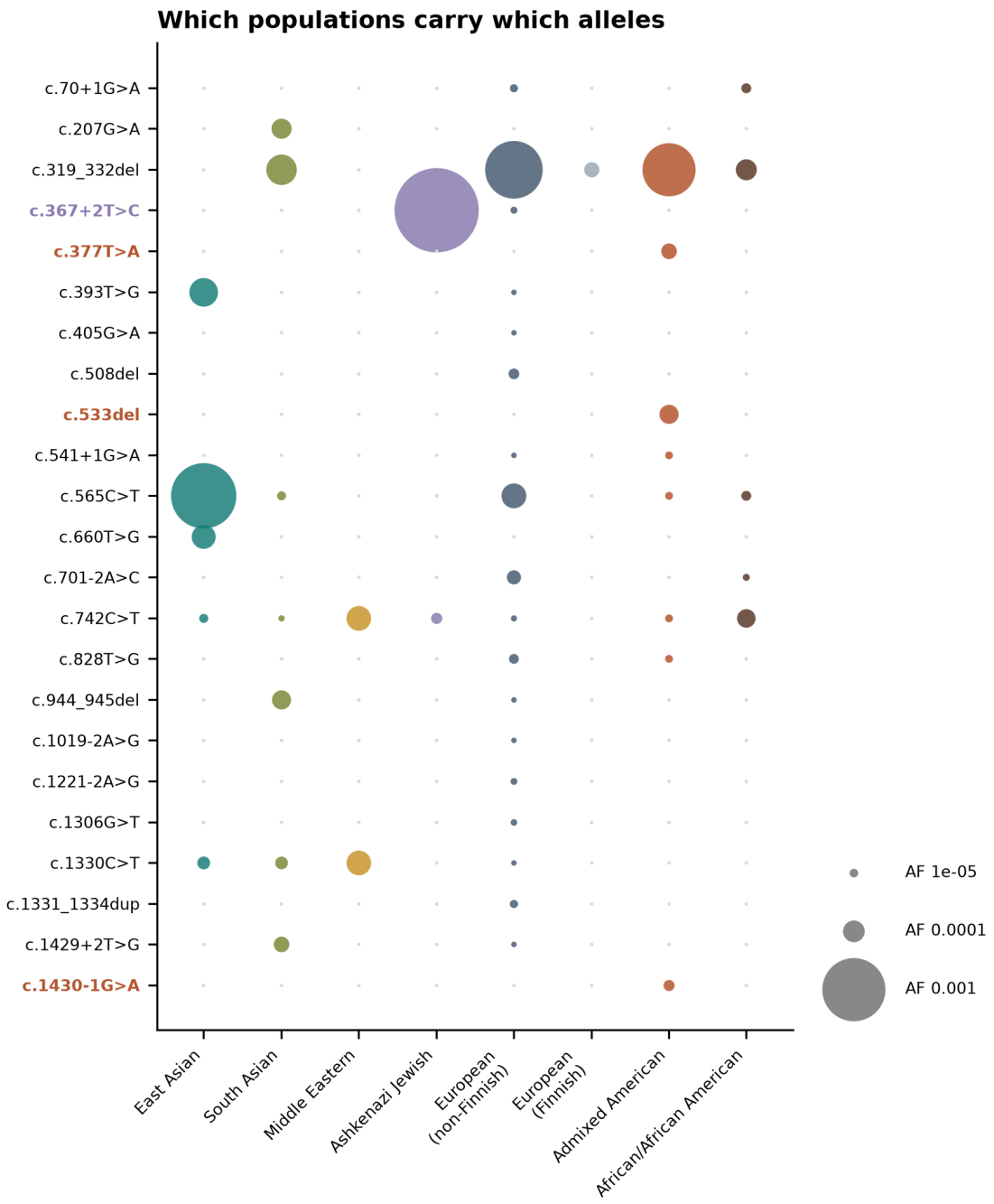


Figure 2. Population distribution of the most frequent *GPNMB* pLoF alleles. Rows are pLoF variants with at least 8 copies in gnomAD, plus alleles private to Admixed Americans with at least 2 copies, ordered by coding position. Columns are gnomAD ancestry groups; bubble area is proportional to allele frequency in that group, and grey dots mark absence. Orange labels mark Admixed American–private alleles; the purple label marks the Ashkenazi founder allele c.367+2T>C.

Table 2. *GPNMB* alleles highlighted in this study. AF, allele frequency in the named group; AC, allele count.

Variant (GRCh38)	HGVS (NM_002510.3)	Class	Population pattern	Note
7-23260003-C-T	c.565C>T (p.Arg189*)	Stop-gained	East Asian AF 0.116%; non-Finnish European 0.017%; five of eight groups	Most frequently reported ACD allele; CpG site
7-23254254-TAGATGCCAAAAGGA-T	c.319_332del (p.Lys107TrpfsTer6)	Frameshift	Non-Finnish European AF 0.090%; Admixed American 0.077%; East Asian 0	ClinVar P/LP; never seen in a patient; tandem repeat
7-23254314-T-C	c.367+2T>C	Splice donor	Ashkenazi Jewish AF 0.19% (57 of 80 copies)	Founder allele; not in ClinVar
—	c.533del	Frameshift	Admixed American: 6 of 7 copies	Admixed American–private; not in ClinVar
—	c.377T>A	Stop-gained	Admixed American: 4 of 4 copies	Admixed American–private; not in ClinVar
—	c.413G>A	Stop-gained	Admixed American: 2 of 3 copies	Admixed American–private; not in ClinVar
—	c.1430-1G>A	Splice acceptor	Admixed American: 2 of 2 copies (exomes)	Admixed American–private; not in ClinVar
7-23246653-A-T	promoter (MCS3, MITF(A) E-box)	Regulatory, not pLoF	African 18/56,958; Admixed American 12/49,388; 0 elsewhere	Breaks the essential MITF E-box core; untested

Admixed American alleles come from two sources

Admixed Americans carried 71 pLoF alleles across 16 variants (Figure 3b). Five of these variants, accounting for 50 alleles (70%), are also present in non-Finnish Europeans. Their combined frequency (8.3×10^{-4}) is 60% of the cumulative pLoF frequency in non-Finnish Europeans, consistent with these alleles having entered Admixed American genomes through European admixture. The remaining 21 alleles (30%) come from 11 variants absent from Europeans. Most of these 21 come from four alleles

that are largely restricted to Admixed Americans: c.533del, c.377T>A, c.413G>A and c.1430-1G>A (Table 2). All four pass quality filters and none is in ClinVar. If each allele were equally frequent across groups, these distributions would be very unlikely ($p \approx 1.9 \times 10^{-6}$ for c.377T>A; $p \approx 1.8 \times 10^{-8}$ for c.533del); for c.533del, about 118 copies would be expected among non-Finnish Europeans, against none observed. gnomAD provides no local-ancestry calls at these sites, and c.1430-1G>A was observed only in exomes, so the ancestral background on which these alleles occur could not be determined.

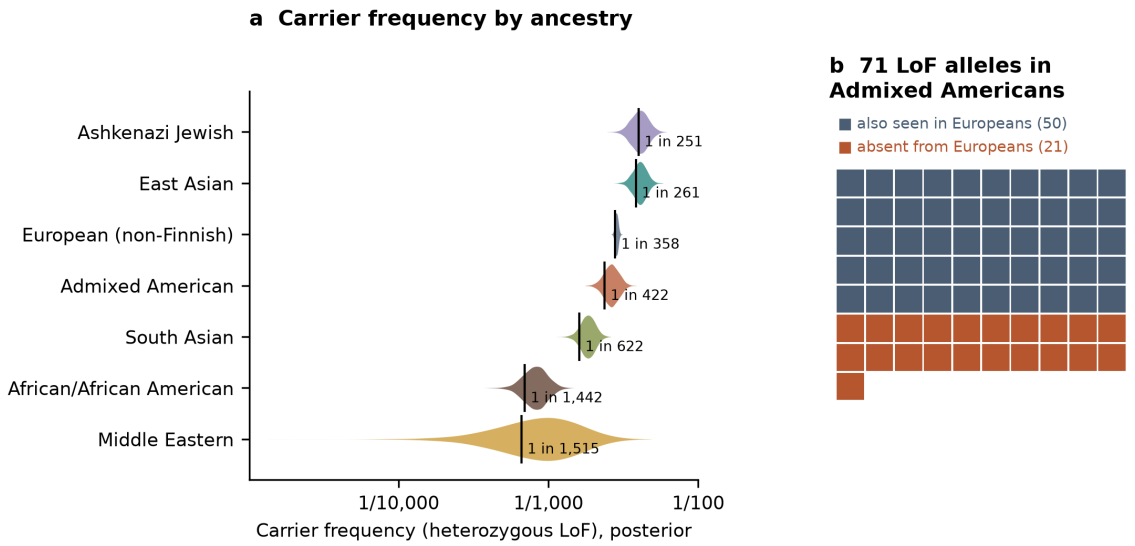


Figure 3. Carrier frequency by ancestry and the composition of the Admixed American burden. (a) Posterior distributions of *GPNMB* pLoF carrier frequency for each gnomAD ancestry group (log scale); vertical lines mark point estimates. (b) Each square is one pLoF allele observed in Admixed Americans (n = 71), coloured by whether the variant is also observed in non-Finnish Europeans (slate, 50 alleles) or absent from them (orange, 21 alleles).

Expected patients far exceed reported patients outside East Asia

Published counts of ACD have grown slowly: 26 cases by 2012, when a single-centre series added 10 more [26], 48 cases in a 2016 review [30], and about 70 by 2021 [37]. The often-cited figure of about 50 reported cases traces to the 2016 review and has been repeated since. Genotyped series published from 2018 onward add more than 50 patients, and 29 *GPNMB*-genotyped pedigrees carrying 17 variants had been reported by 2024 [31], with additional Thai and Philippine families reported since [29,32]. At least 100 patients have therefore been reported worldwide, concentrated in China (at least 42 patients; e.g. [31,38]), Taiwan, Thailand, the Philippines, South Asia and the Middle East (Table S1). ACD was first described in Japan [24], where most early reports were published in Japanese [39]. These include Morishima's original description [24] and a later study of a 24-year-old woman evaluated for UV-induced DNA repair [25], establishing a minimum of two patients. Because these clinical diagnoses predate the identification of GPNMB and lack molecular confirmation—and because patient counts in the original Japanese-language literature could not be independently verified or comprehensively enumerated—two represents a conservative lower bound. A 2026 country-by-country review listed reports from 14 countries, including China, Taiwan, Japan, Thailand, India, Pakistan, Iran, Kuwait, Libya, Turkey and the United States, but none from South Korea or Latin America [32]. My own searches, including the Korean

ScienceON database, found none either; the only Korean ACD record was a Korean-funded genetic study of Pakistani families. The same review counted only five reports in patients it classed as of European descent, from the United States and Turkey [32]. The single case published in a Brazilian journal was a Turkish patient [40], and a case in a US journal previously of uncertain origin was Libyan [41]. I found no patient of Ashkenazi Jewish or Israeli origin. Two reviews also list two common synonymous variants, c.390G>A (allele frequency 39.5%; 128,805 homozygotes) and c.1461T>C (6.1%; 7,423 homozygotes), among causal alleles; neither can cause a rare recessive disorder.

The expected number of individuals with biallelic pLoF genotypes exceeds the number reported everywhere (Figure 4). The gap is largest where no case has been described: about 183 people in Mexico (95% interval 141–344) and about 40 Ashkenazi Jews worldwide (25–68). Even in Taiwan, where ACD is best documented, 12 reported patients compare with about 86 expected (64–143).

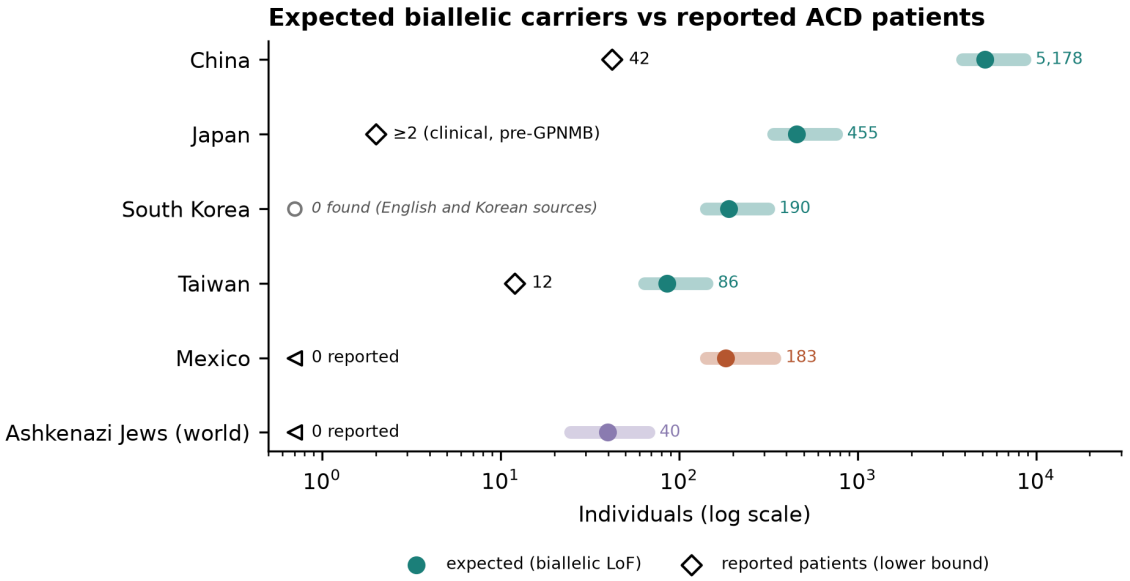


Figure 4. Expected individuals with biallelic *GPNMB* pLoF genotypes compared with reported ACD patients. Filled circles are point estimates of population size × q^2 with 95% intervals (bars), using East Asian frequencies for China, Japan, South Korea and Taiwan, Admixed American frequencies for Mexico and Ashkenazi Jewish frequencies for Ashkenazi Jews worldwide. Open diamonds are reported patients from the literature audit (lower bounds); arrows mark populations with no reported patient. For Japan, the diamond counts at least two patients, from the original description and one later report, both diagnosed clinically before GPNMB was known; further Japanese-language reports were not counted. The open circle marks South Korea, for which no ACD report was found in English- or Korean-language sources. Expected counts assume full penetrance and random mating.

Heterozygous carriers show no detectable phenotype

In Genebass, *GPNMB* pLoF burden showed no association reaching significance across 4,529 UK Biobank phenotypes. The strongest result was “other and unspecified infectious diseases” (ICD-10 B99; $p = 2.3 \times 10^{-5}$), above both thresholds; the top results were unrelated (an operation code, brain-imaging measures, height with $\beta \approx -0.001$ SD), as expected under the null. The missense|LC mask was likewise null (top $p = 1.1 \times 10^{-5}$, platelet distribution width), including NMR metabolomic traits measured in

about 95,000 participants. *GPNMB* pLoF burden was not associated with the phenotypes most relevant to its biology: ICD-10 L81, other disorders of pigmentation (3,405 cases; p = 0.66), E85, amyloidosis (p = 0.24), or G20, Parkinson's disease (1,901 cases; p = 0.33). With about 1,100 expected carriers, these data exclude large effects in heterozygotes only, but they are consistent with recessive inheritance of truncating alleles.

Regulatory variants add little to the burden

MCS3 mapped exactly to GRCh38 chr7:23,246,636–23,246,724, with an identical sequence, immediately upstream of the first exon of the MANE transcript (Figure 5). It contains the AP-1 site (23,246,641–647), the MITF(A) E-box required for enhancer activity in melanocyte cell lines (23,246,652–658) and the MITF(B) E-box at the start of the 5′ UTR (23,246,712–719) [17]. The gnomAD database contained 120 variant records within the element. Six variants disrupted the MITF(A) E-box core, with a total of 46 alleles and a combined frequency of about 7×10^{-5}, or about 5% of the coding pLoF frequency in Europeans. Even if all were null, they would raise the pLoF burden by about 5% and expected prevalence by about 10%. The most frequent, 7-23246653-A-T (CACATG → CTCATG), was observed only in African (18 of 56,958 chromosomes; 3.2×10^{-4}) and Admixed American (12 of 49,388; 2.4×10^{-4}) individuals, and in none of 376,372 non-Finnish European chromosomes.

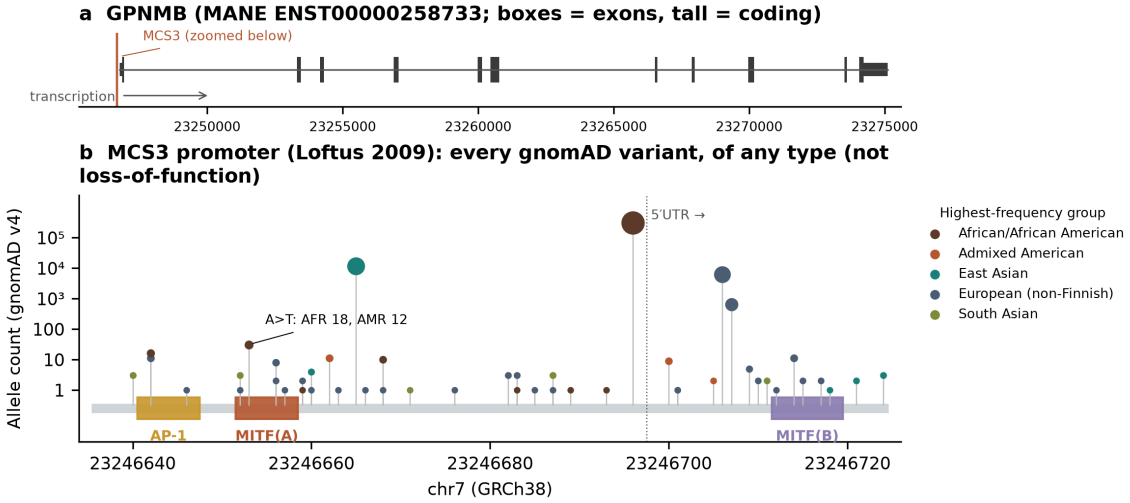


Figure 5. The *GPNMB* proximal promoter and its variation in gnomAD. (a) *GPNMB* (MANE transcript ENST00000258733, GRCh38); boxes are exons, with coding exons taller. The orange bar marks MCS3, the 89-bp conserved element of Loftus et al. (2009) [17], immediately upstream of exon 1. (b) All gnomAD v4 variants within MCS3, of any class; none is counted as pLoF. Height is allele count (log scale) and colour the ancestry group with the highest allele frequency. Boxes mark the AP-1 site and the two MITF E-boxes. Functional relevance of the motifs rests on cross-species conservation and enhancer assays [17]; human variation in this 89-bp window is too limited to test constraint directly.

Discussion

GPNMB pLoF alleles are not an East Asian peculiarity. Carrier frequencies in Ashkenazi Jews, non-Finnish Europeans and Admixed Americans are within a factor of two of the East Asian frequency, yet nearly all reported ACD patients are East or Southeast Asian. The simplest explanation is ascertainment: ACD has

been recognized and published where dermatologists know the diagnosis and where *GPNMB* was first linked to it, while elsewhere patients are likely misclassified among other reticulate or macular pigmentary disorders or not referred at all. Macular amyloidosis, which shares dermal amyloid deposits and mottled hyperpigmentation with ACD, is reported to be more frequent in adults of Asian and South American origin [42], so in Latin America an ACD patient could readily be diagnosed with this more familiar condition. Qiao et al. (2012) already noted that distinguishing the dyschromatoses is particularly difficult in populations where ACD is rarely seen [26]. The two largest gaps, about 183 expected patients in Mexico and about 40 among Ashkenazi Jews against none reported, are driven by different alleles, which makes a shared artefact less likely.

The expected counts assume recessive inheritance of truncating alleles, and the data support that model for the alleles counted here. Under a dominant model about 1 in 400 people would be affected, which is clearly not the case. The absence of pLoF homozygotes in gnomAD is also expected: across about 800,000 individuals, the predicted number with biallelic pLoF genotypes is about one, and most such people would be compound heterozygotes, invisible in per-variant homozygote counts. The Genebass results add that heterozygous carriers show no detectable phenotype. Semidominant effects have been described for specific splice and missense variants [28]; those classes were not counted, and including them could only raise the expected number of patients.

A human population perspective is particularly valuable for *GPNMB* because the mouse and human data disagree. Silencing *GPNMB* in human melanocytes largely abolished melanosome formation [12], whereas iris melanosomes of *Gpnmb*-mutant DBA/2J mice are ultrastructurally normal and differ only in chemical composition [43,44]. Mice also lack the MITF(A) E-box of MCS3 because of a 2-bp deletion [17]. Conclusions about GPNMB in human pigmentation therefore need human data, and the population frequencies reported here provide a baseline for clinical interpretation.

The Admixed American burden has two sources. Most alleles are shared with Europeans, consistent with European admixture, but 30% come from four alleles essentially confined to Admixed Americans. These alleles are absent from ClinVar and from the published patient literature, so a Mexican patient with ACD could carry a genotype never described before. The Ashkenazi founder allele c.367+2T>C is similarly unreported. Submitting these variants to ClinVar and adding *GPNMB* to gene panels used for pigmentary disorders in Latin America and in Jewish populations would make them visible to diagnostic laboratories.

One promoter variant is worth testing. 7-23246653-A-T breaks the core of the MITF(A) E-box, the only MITF site in MCS3 shown to be required for enhancer activity in melanocyte cell lines [17]. It is found only in African and Admixed American chromosomes and is absent from more than 376,000 European chromosomes and all Asian ones, so its presence in Admixed Americans most likely reflects African ancestry. By contrast, three of the four Admixed American–enriched coding alleles (c.533del, c.377T>A and c.1430-1G>A) have not been observed in African individuals; the fourth, c.413G>A, has a single copy in an African/African American genome. If the variant substantially reduces *GPNMB* expression, it would roughly double the effective loss-of-function burden in Africans (its frequency, 3.2×10^{-4}, is close to the coding pLoF frequency of 3.5×10^{-4}) and add about a fifth in Admixed Americans. It remains a candidate, not an established pathogenic allele. Deleting the MITF(A) site did not abolish expression in zebrafish [17], and a single heterozygous promoter variant could cause ACD only in trans with a coding pLoF allele. The main estimates therefore exclude it. A luciferase reporter assay comparing

MCS3 carrying the reference A with the T allele in a melanocyte line would resolve its effect quickly and cheaply.

The opposite end of the *GPNMB* dosage range is relevant to neurodegeneration. PD risk is associated with higher *GPNMB* expression and higher circulating GPNMB [22,23], whereas ACD results from its absence. Heterozygous pLoF carriers, at about half the normal dosage, sit at the low end of this range. Recent work points in both directions. Blocking GPNMB prevented α-synuclein pathology from spreading between cultured neurons, and genotypes that raise GPNMB were associated with more extensive α-synuclein pathology in 1,675 brains [45]; yet in human iPSC-derived microglia, GPNMB mediated trogocytic clearance of intraneuronal α-synuclein aggregates, and its knockdown impaired clearance [46]. Heterozygous carriers are therefore informative in either case. Whether their reduced GPNMB is protective or harmful for synucleinopathy cannot be tested with the roughly five PD cases expected among UK Biobank carriers (about 1,100 carriers × 1,901 G20 cases in 394,841 participants), but plasma GPNMB measured in carriers would test directly whether these alleles halve protein output.

Limitations

The 114 variants are predicted, not functionally tested, loss-of-function alleles. Some splice variants may allow partial normal splicing, start-lost variants may use an alternative start codon, and c.319_332del lies in a repeat where variant calling is less reliable, so carrier frequencies are best read as upper estimates of truly null alleles. gnomAD Admixed American samples are not a random sample of the Mexican population, and East Asian frequencies may not apply equally to China, Japan, South Korea and Taiwan. Expected counts assume full penetrance, random mating and Hardy–Weinberg proportions. Consanguinity would raise them, whereas incomplete penetrance or mild, unrecognised phenotypes would lower the number of clinically diagnosable patients. The literature audit relied on web searches rather than structured database queries. Korean-language sources were searched through ScienceON, but Chinese-language (CNKI) and Japanese-language literature could not be searched systematically, so additional reports in all three languages may have been missed and reported counts are lower bounds. The roughly 1,100 UK Biobank carriers exclude only large heterozygous effects, and a mild skin phenotype may not be captured by UK Biobank fields. Finally, gnomAD has no local-ancestry calls at the sites of the Admixed American–enriched alleles, so their ancestral background could not be determined.

Conclusion

Loss-of-function alleles of *GPNMB* are present at comparable frequencies in East Asian, Ashkenazi Jewish, European and Admixed American populations, yet amyloidosis cutis dyschromica has been reported almost exclusively in East and Southeast Asia. About 183 people in Mexico and about 40 Ashkenazi Jews worldwide are expected to carry biallelic loss-of-function genotypes, and none has been reported, which points to underdiagnosis rather than true absence. The alleles responsible differ by population, including a founder splice allele in Ashkenazi Jews and four alleles essentially private to Admixed Americans, none of which appears in ClinVar. Public population data are enough to reveal this gap, and including *GPNMB* in diagnostic testing for pigmentary disorders beyond East Asia, together with functional testing of the promoter variant 7-23246653-A-T, would be the next steps toward closing it.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org: Table S1: Reported cases of amyloidosis cutis dyschromica by country, with stated ancestry, number of patients, familial status, GPNMB genotype and source.

Data and code availability: All data are public: gnomAD v4.1 variant exports and GraphQL queries (gnomAD browser, accessed November 2026), ClinVar classifications as shown in gnomAD, Genebass gene-burden results (accessed November 2026) and genome sequences from the UCSC Genome Browser API. Scripts, configuration, the verification log and the figure-generation code are available at github.com/garfring/gpnmb-acd. Supplementary Table S1 gives the literature audit of reported ACD cases.

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Supplementary Files

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- TableS1ACDcasereports.csv