

Hypomorphic *IDUA* genotypes are associated with retinitis pigmentosa in individuals without syndromic mucopolysaccharidosis type I

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Hypomorphic variants in *IDUA* are associated with attenuated mucopolysaccharidosis type 1, including apparent non-syndromic retinitis pigmentosa. Functional experiments are used to characterize the impact of variants on expression and enzyme activity and to predict the residual level of function that may contribute to sparing of systemic disease.

Hypomorphic *IDUA* genotypes are associated with retinitis pigmentosa in individuals without syndromic mucopolysaccharidosis type I

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Summary

Bi-allelic variants in *IDUA* classically cause mucopolysaccharidosis type I (MPS I), a multisystem lysosomal storage disorder. This study describes 14 individuals from 12 families presenting with retinitis pigmentosa, later attributed to bi-allelic *IDUA* genotypes. Notably, seven individuals, despite comprehensive systemic assessments, showed no features consistent with MPS I at last assessment (aged 46–73 years). Leukocyte α -L-iduronidase activity was reduced but not abolished across all individuals assessed ($n = 9$), supporting a shared mechanistic basis for the mild, retina-predominant, or exclusively retinal phenotype. No individual carried bi-allelic null genotypes; most had a loss-of-function allele paired with a missense variant, consistent with an overall hypomorphic genotype. Variant-level functional assays, using a cell-based expression platform assessing enzyme activity and protein abundance to derive relative specific activity (RSA), showed that several missense alleles confer very low residual activity and/or impaired abundance/processing, with RSA typically in the ~0.5%–1.5% range. The recurrent missense c.298A>G (p.Arg100Gly) variant showed no protein or catalytic effect; targeted long-read transcript analysis instead demonstrated predominant loss-of-function mis-splicing with a small fraction of correctly spliced transcript (~1%–2%), explaining residual activity *in vivo*. Together, these data expand the phenotypic spectrum of *IDUA*-associated disease to include late-onset retinal-predominant or apparently isolated retinitis pigmentosa and indicate that residual enzyme activity likely contributes to systemic sparing, highlighting the value of integrated genomic, biochemical, and functional analyses to advance understanding in attenuated metabolic disease.

IDUA (MIM: 252800) encodes the enzyme α -L-iduronidase, which is essential for the degradation of the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate within lysosomes. Bi-allelic loss-of-function (LoF) variants in *IDUA* cause mucopolysaccharidosis type I (MPS I), an autosomal-recessive lysosomal storage disorder.¹ In MPS I, deficient or absent α -L-iduronidase activity leads to the accumulation of partially degraded GAGs

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within lysosomes, causing progressive disease with involvement of multiple tissues and organ systems.¹ Ocular manifestations include corneal clouding, pigmentary retinopathy, optic nerve abnormalities such as glaucoma, papilledema, and optic atrophy, as well as ocular motility and refractive issues.²

MPS I is classically divided into three phenotypes: the severe Hurler syndrome (MPS IH; MIM: 607014), the attenuated Scheie syndrome (MPS IS; MIM: 607016), and the intermediate Hurler-Scheie syndrome (MPS IH/S; MIM: 607015). However, the clinical spectrum is continuous, and classification is frequently complex.^{1,3} At the severe end, affected individuals typically present in early childhood and develop progressive coarse facial features, dysostosis multiplex, visceromegaly, hearing loss, cardiac involvement, restrictive lung disease, and cognitive and developmental delays, with life expectancy significantly reduced without treatment. At the attenuated end, individuals typically have near-normal cognitive function and life expectancy, with features such as joint contractures, corneal clouding, and cardiac valvular disease typically emerging in the first or second decades of life.⁴ Broad genotype-phenotype correlations exist, with the attenuated phenotype strongly associated with the presence of at least one missense *IDUA* variant.⁵

This study presents the clinical, biochemical, and molecular characterization of 14 individuals from 12 families, aged between 19 and 73 years, all of whom initially presented to ophthalmology services with retinitis pigmentosa (RP [MIM: 268000]). Subsequent genetic testing identified bi-allelic *IDUA* variants, prompting comprehensive systemic and enzymological evaluation where feasible. Notably, seven individuals showed no systemic abnormalities consistent with MPS I even after detailed reassessment and were considered to have apparently isolated or non-syndromic RP (nsRP) up to their last review. This series therefore highlights a distinct presentation of *IDUA*-related disease, expanding the recognized phenotypic spectrum beyond the classic syndromic forms of MPS I.

This study adhered to the tenets of the Declaration of Helsinki and received relevant local research ethics approval (see [supplemental methods](#)). Written informed consent was obtained from all participants and their relatives. Individuals were recruited from inherited retinal disease (IRD) cohorts across the United Kingdom, Ireland, Italy, the Netherlands, and the United States, all of whom initially presented to ophthalmology services and underwent genome or exome sequencing through accredited clinical or research pipelines ([supplemental methods](#)).^{6–10} For all individuals, initial variant analysis excluded pathogenic genotypes in other known IRD-associated genes; bi-allelic *IDUA* variants were identified as the only plausible candidate disease variants. Pseudodeficiency alleles were excluded where sequencing data were available for interrogation (individuals 1–6, 8, 9, and 11–14; [Table S1](#)). Functional characterization of missense var-

iants and long-read transcript analysis were performed as described in the [supplemental methods](#).

The *IDUA* genotypes and biochemical findings are summarized in [Table 1](#), while detailed ocular and systemic clinical data are provided in [Note S1](#), [Table S3](#), and [Figures S1–S3](#). [Table 2](#) provides information on the *IDUA* variants identified in this study. Family pedigrees and segregation data are shown in [Figure 1](#). The variant phase for each individual, where established by segregation analysis, direct read phasing, or inferred from population cosegregation data (gnomAD), is summarized in [Table 1](#).

To determine the functional consequences of the missense variants in our cohort, variant-bearing *IDUA* vectors were transfected into an *IDUA*-knockout (KO) HEK293 cell line, and the resulting cell populations were investigated following an antibiotic selection to enrich for transfectants. The relative specific activity (RSA), defined as the enzyme activity per unit amount (relative to the overexpressed wild-type iduronidase), was calculated for each variant iduronidase ([supplemental methods](#)).

In addition to variants present in the primary study cohort, we also assessed two other missense alleles. Previous reports have identified c.956C>T (GenBank: NM_000203.5) (p.Ala319Val) ([Table 2](#), v13) homozygously in individuals with attenuated disease^{12,33}; this allele was therefore also included as a comparator to provide context for the RSA values observed for missense variants in the study cohort. The variant of uncertain significance (VUS) c.406G>A (p.Ala136Thr) ([Table 2](#), v14), identified in *trans* with the known pathogenic variant c.1469T>C (p.Leu490-Pro)^{23,30,36} in a previously published individual with suspected attenuated MPS I,³⁴ was evaluated to help determine its clinical significance.

As shown in [Figure 2A](#), the RSA values of some of these variant iduronidases, including c.271C>T (p.His91Tyr), c.956C>T (p.Ala319Val), and c.1148G>A (p.Arg383His) (shown in the green bars), were in the 0.5%–1.5% range, consistent with other previously investigated variants that contribute to attenuated MPS I.³⁷ As shown in [Figure 2B](#), these same variant iduronidases with low RSA values were also poorly processed and exhibited low stability and/or expression. Of note, we did not detect any measurable activity for the c.1045G>T (p.Asp349Tyr) iduronidase even though the enzyme was well expressed and processed in a manner similar to the wild-type enzyme ([Figure 2B](#)). Efficient proteolytic processing is an indication that the enzyme has reached the lysosomal compartment. Other variants, including c.406G>A (p.Ala136Thr) and c.590G>C (p.Gly197Ala), had an RSA similar to the wild-type enzyme and consistent with both c.298A>G (p.Arg100Gly) and c.299G>A (p.Arg100Lys) from our prior study.³⁷ Raw data are presented in [Figure S4](#).

Interpretation of the c.298A>G variant (v3, [Table 2](#)) was challenging. The variant had been previously reported in a newborn with deficient leukocyte iduronidase activity but normal urine GAGs¹¹ and in the current study was identified with a known pathogenic stop-gain variant in six

Table 1. Genetic and biochemical findings in individuals 1–14 with bi-allelic *IDUA* variants

Family	A (GC26137)	B (GC23127)	C	D	E	F (PN157)	G (CJ66)	H (NAP_1522)	I			J (OGI1526)	K (OGI2207)	L (OGI3554)
Individual	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Allele 1	c.271C>T (p.His91Tyr)	c.298A>G (p.Cys53_Arg100delinsTrp, Arg100Gly)	c.1598C>A (p.Pro533Gln)	c.386-2A>G (p.?)	c.794G>A (p.Gly265Asp)	c.794G>A (p.Gly265Asp)	c.794G>A (p.Gly265Asp)	c.1045G>T (p.Asp349Tyr)	c.208C>T (p.Gln70*)	c.208C>T (p.Gln70*)	c.208C>T (p.Gln70*)	c.208C>T (p.Gln70*)	c.794G>A (p.Gly265Asp)	c.208C>T (p.Gln70*)
Allele 2	c.1460G>A (p.Trp487*)	c.1205G>A (p.Trp402*)	c.1855C>T (p.Arg619*)	c.590G>C (p.Gly197Ala)	c.1205G>A (p.Trp402*)	c.1205G>A (p.Trp402*)	c.1205G>A (p.Trp402*)	c.1148G>A (p.Arg383His)	c.298A>G (p.Cys53_Arg100delinsTrp, Arg100Gly)	c.298A>G (p.Cys53_Arg100delinsTrp, Arg100Gly)	c.298A>G (p.Cys53_Arg100delinsTrp, Arg100Gly)	c.298A>G (p.Cys53_Arg100delinsTrp, Arg100Gly)	c.1205G>A (p.Trp402*)	c.298A>G (p.Cys53_Arg100delinsTrp, Arg100Gly)
Phase ^a	unresolved	inferred (gnomAD)	unresolved	confirmed (segregation)	inferred (gnomAD)	confirmed (segregation)	confirmed (segregation)	confirmed (direct read phasing)	confirmed (direct read phasing)	confirmed (segregation)	confirmed (direct read phasing)	inferred (gnomAD)	inferred (gnomAD)	confirmed (segregation)
Country of recruitment	UK	UK	UK	UK	UK	Ireland	Ireland	Italy	the Netherlands	the Netherlands	the Netherlands	US	US	US
Ethnicity	White British	NK	White British	White British	White British	White Irish	White Irish	White Italian	White Dutch	White Dutch	White Dutch	White (English-Irish-Scottish)	White (Irish-German)	White (European)
Sex	female	male	male	female	male	female	male	female	male	female	female	female	male	male
Age at last examination	73 years	57 years	58 years	46 years	56 years	62 years	40 years	59 years	62 years	67 years	68 years	54 years	42 years	19 years
Biochemical testing ^b														
α-Iduronidase (nmol/mg/hr)	3 (26–135)	1 (26–135)	0.4 (13–111)	1.0 (13–111)	0.2 (13–111)	NP	NP	0.9 (25–60)	1 (65–154)	1 (65–154)	1 (65–154)	NP	NP	NP
Urine GAG/creatinine ratio (mg/mmol/Cr)	2 (1–5)	8 (1–5)	6.8 (0–8)	1.6 (1–6)	7.6 (0–8)	NP	NP	NP	5.8 (1.5–3.8)	6.3 (1.5–3.8)	6.2 (1.5–3.8)	NP	NP	NP
Urine GAG electrophoresis	NP	presence of chondroitin sulfate, heparan sulfate, and large amount of dermatan sulfate	dermatan sulfate increased	presence of chondroitin sulfate present; small amounts of heparan sulfate and possible dermatan sulfate	heparan and dermatan sulfate increased	NP	NP	NP	increased dermatan sulfate, heparan sulfate, and chondroitin sulfate	presence of dermatan sulfate, heparan sulfate, and chondroitin sulfate	NP	NP	NP	NP

All variants described according to GenBank: NM_000203.5. GAG, glycosaminoglycan; gnomAD, Genome Aggregation Database v.4.1.0; NK, not known; NP, not performed; UK, United Kingdom; US, United States.

^aPhase: confirmed in *trans* by segregation analysis or direct read phasing of aligned sequencing reads; inferred in *trans* based on population co-occurrence data (gnomAD) where familial samples were unavailable.

^bFor biochemical tests, lab-specific normal reference ranges are shown in brackets below actual values.

Table 2. IDUA variants characterized in this study

Variant ID (family) ^a	Variant	In silico predictions ^c								
	Genomic coordinates (Chr4) ^b	Nucleotide	Protein	gnomAD AF	Revel	AlphaMissense	SpliceAI	ClinVar (ID)	Previously reported?	ACMG classification ^d
v1 (A)	g.987921C>T	c.271C>T	p.His91Tyr	0.000008135	deleterious (0.93)	deleterious (0.907)	benign (0.07)	absent	no	LPPS3(Su), PM2(Su), PM1(M), PP3(M)
v2 (A)	g.1003093G>A	c.1460G>A	p.Trp487*	0.0000006575	N/A	N/A	benign (0.03)	absent	no	LPPVS1(VS), PM2(Su)
v3 (B, I, J, L)	g.987948A>G	c.298A>G	p.Cys53_Arg100delinsTrp, Arg100Gly	0.00006097	uncertain (0.62)	benign (0.079)	splice altering (DL: 0.64)	LP/VUS (2058952)	yes ¹¹	PPVS1(VS),PM2(Su), PM3(M), PP4(Su)
v4 (B, E–G, K)	g.1002747G>A	c.1205G>A	p.Trp402*	0.001265	N/A	N/A	benign (0.01)	P (11908)	yes ^{12–22}	PPVS1(VS), PP4(Su), PM3(M)
v5 (C)	g.1003418C>A	c.1598C>A	p.Pro533Gln	0.0000006539	deleterious (0.67)	deleterious (0.91)	uncertain (0.15)	LP (1970157)	no	VUSPS3(Su), PM2(Su), PP3(Su)
v6 (C)	g.1004286C>T	c.1855C>T	p.Arg619*	0.00002235	N/A	N/A	benign (0.06)	P (280976)	yes ^{12,14,23,24}	PPVS1(M), PM3(VS), PM2(Su), PP4(Su)
v7 (D)	g.1000880A>G	c.386–2A>G	p.?	0.0001557	N/A	N/A	splice altering (AL: 0.61)	P (222994)	yes ^{13,19,25,26}	PPVS1(M), PM3(VS), PM2(Su), PP4(Su)
v8 (D)	g.1001679G>C	c.590G>C	p.Gly197Ala	0.00001249	deleterious (0.88)	uncertain (0.521)	splice altering (AL: 0.26)	absent	no	VUSPM2(Su), PP3(M), PM3(Su), BS3(Su)
v9 (E–G, K)	g.1001983G>A	c.794G>A	p.Gly265Asp	0.00004362	deleterious (0.83)	deleterious (0.906)	uncertain (0.11)	LP/VUS (2203496)	yes ¹⁴	LPPS3(Su), PM2(Su), PM5(Su), PP3(M), PM3(Su)
v10 (H)	g.1002341G>T	c.1045G>T	p.Asp349Tyr	0.000001240	deleterious (0.92)	deleterious (0.983)	benign (0.04)	P/LP (638075)	yes ^{27–29}	LPPM3(Su), PS3(Su), PM1(M), PM2(Su), PM5(Su), PP3(M)
v11 (H)	g.1002444G>A	c.1148G>A	p.Arg383His	0.00001608	deleterious (0.87)	uncertain (0.43)	benign (0)	P/LP (558189)	yes ^{13,24,28,30,31}	PPP4 (M), PP3(M), PM2 (Su) PM3(VS), PS3(M),PP1(M)
v12 (I, J, L)	g.987858C>T	c.208C>T	p.Gln70*	0.0004906	N/A	N/A	uncertain (0.13)	P (11909)	yes ^{12–19,21,22,32}	PPVS1(VS), PP4(Su), PM3(Su)
v13	g.1002145C>T	c.956C>T	p.Ala319Val	0.000003848	deleterious (0.9)	deleterious (0.779)	benign (0.03)	LP (1683230)	yes ^{12,33}	LPPM3(Su), PS3(Su), PM2(Su), PP3(M), PP4(Su)
v14	g.1000902G>A	c.406G>A	p.Ala136Thr	0.00008244	uncertain (0.45)	benign (0.099)	benign (0.07)	VUS (964816)	yes ³⁴	VUSPM2(Su), BS3(Su)

IDUA reference transcript Genbank: NM_000203.5. ACMG, American College of Medical Genetics and Genomics; AF, allele frequency; AL, acceptor loss; DL, donor loss; gnomAD, Genome Aggregation Database v.4.1.0; LP, likely pathogenic; P, pathogenic; VUS, variant of uncertain significance; N/A, not available.

^aVariant IDs correspond to labels used in Figure 1.

^bGenomic coordinates refer to GRCh38.

^cREVEL is an ensemble score based on 13 individual scores for predicting the pathogenicity of missense variants. AlphaMissense scores can be interpreted as the approximate probability of a variant being clinically pathogenic. SpliceAI delta scores can be interpreted as the probability that the variant affects splicing at any position within a ± 500 bp window around it. Scores for REVEL, AlphaMissense, and SpliceAI range from 0 to 1, with higher scores indicating a higher probability of the variant being damaging or having a splice-altering effect.

^dACMG/AMP evidence codes are provided for each variant classification. Evidence strength is denoted in parentheses: VS, very strong; and M, moderate; Su, supporting. Pathogenic evidence codes: PVS, pathogenic very strong; PS, pathogenic strong; PM, pathogenic moderate; and PP, pathogenic supporting. Benign evidence codes: BS, benign strong. Variant classifications were performed in accordance with the ClinGen Lysosomal Diseases Variant Curation Expert Panel (VCEP) specifications for IDUA.³⁵

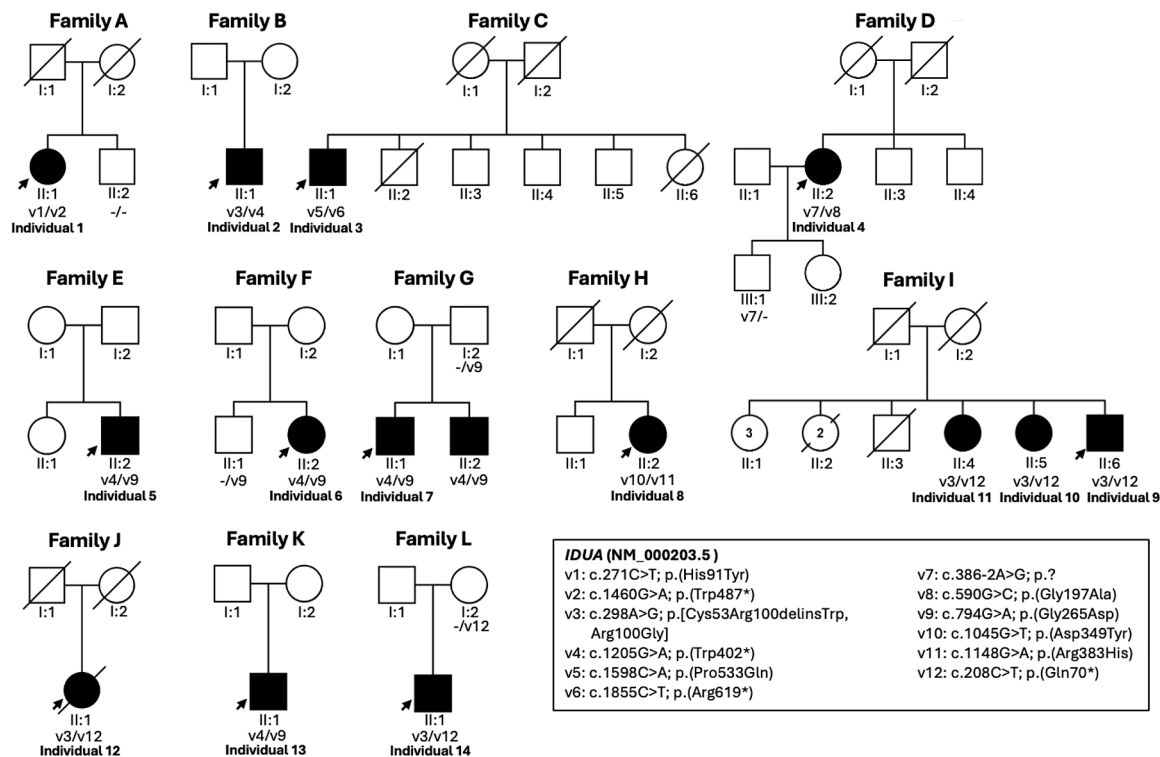


Figure 1. Pedigrees of families

(A–L) Pedigrees showing genotypes of affected individuals and segregation of *IDUA* variants where familial data were available.

affected individuals (individuals 2, 9–11, 12, and 14; Table 1). It is rare in population databases (96/1,574,498 alleles in gnomAD v.4), with conflicting VUS or likely pathogenic (LP) classifications in ClinVar, and *in silico* missense predictions for p.Arg100Gly suggested an uncertain or benign effect on the enzyme (Table 2). Cell-based functional assessment of the p.Arg100Gly missense alteration confirmed no measurable loss of iduronidase activity or abnormal protein aggregation due to the amino acid substitution (Figure 2A). However, given its location at the penultimate nucleotide of exon 2 and the potential splice-altering effect predicted by SpliceAI (Table 2), the variant was further assessed for possible splicing effects by RT-PCR followed by nanopore long-read sequencing.

The major effect of the variant, summarized in Figure 2C, was in-frame skipping of exon 2, p.Cys53_Arg100delinsTrp, observed on 388/456 reads (85.1%) derived from the c.298G allele, with lower-level detection of a frame-shifting alternate donor site usage 37 bp upstream of the variant, p.Val88Glyfs*31, observed on 58/456 reads (12.7%). In addition, 6/456 (1.3%) reads showed normal exon 2 splicing and confirmed the presence of the c.298A>G variant. The remaining four reads had inconclusive base calling at position c.298. The *trans* allele, encoding p.Gln70*, also located in exon 2, showed lower read depth overall (190/694 total reads), possibly due to nonsense-mediated decay triggered by premature termination. Exon 2 skipping was observed on 47/190 reads (24.7%) and the same cryptic splice-site usage leading to

p.Val88Glyfs*31 on 14/190 reads (7.4%), events observed at an average of 2.2% and 4.7% across five control subjects, respectively (a representative control is shown in Figure 2C). A summary of read depth data is shown in Table S2.

In summary, these data suggest that while the impact of the c.298A>G variant is mis-splicing leading to in-frame exon skipping, there is low-level survival of correctly spliced transcripts (~1.3% reads) arising from this allele. In addition, we observed exon skipping consequent upon the stop-gain variant (24.7%) higher than that observed in controls samples (2.3%) and in keeping with the weak SpliceAI Δ scores for this variant. Out-of-frame splice junction usage was observed across all control samples at a low level (mean: 4.7%) but elevated for the c.298G allele (12.7% reads), also corresponding to a weak predicted splice acceptor motif at this position (SpliceAI raw score: 0.52).

The in-frame deletion c.298A>G (p.Cys53_Arg100delinsTrp) removes a region of the protein that, in the wild-type iduronidase, corresponds to one of eight β strands and one of eight α helices forming a TIM barrel structure, in which His91 is in direct contact with its substrate (i.e., iduronic acid) and Cys53_His58 forms a loop interacting with polymannose of its N-glycan at Asn372, which is known to be critical for enzyme activity. Consistent with the structural importance of this deleted region, biochemical analysis of a similar mutant protein (c.157_300del [p.Cys53_Arg100del]) confirmed that the

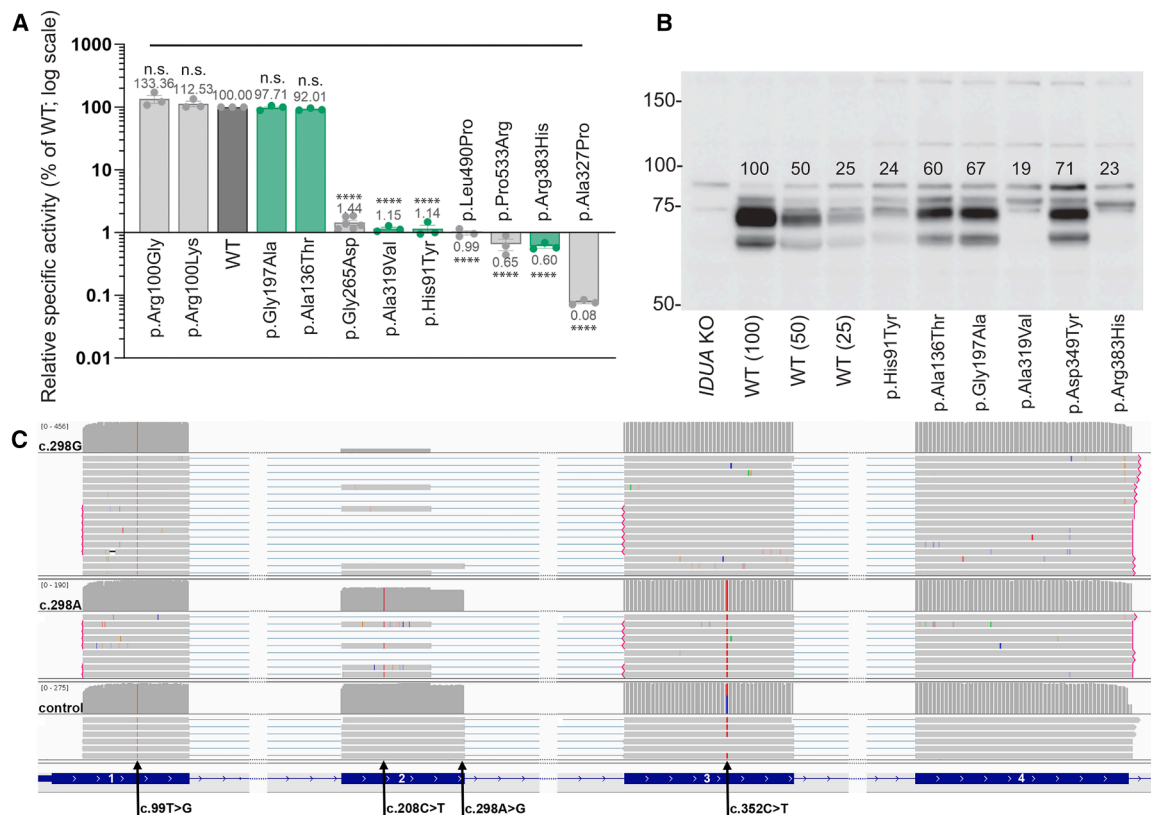


Figure 2. Functional characterization of missense *IDUA* variants in the cohort

(A) The relative specific activity (RSA) values of the missense variants within this cohort. Values are plotted on a log scale and represent the average of at least three independent analyses. Green bars represent new variants characterized in this study; light gray bars represent variants we previously characterized but related to genotypes within the cohort; the dark gray bar represents wild-type (WT) iduronidase. Variants p.His91Tyr, p.Arg383His, and p.Alal319Val have RSA values in the ~0.5%–1.5% range, consistent with RSA values of previously assessed variants known to be associated with attenuated mucopolysaccharidosis type I. Iduronidase RSA was determined for at least three independent biological replicates and the mean plotted; error bars represent the standard error of the mean. Statistical analyses were performed using one-way ANOVA followed by Dunnett's multiple comparison test; **** $p < 0.0001$; n.s. denotes not significant.

(B) Representative western blot of iduronidase from cells that express each WT or variant enzyme. Proteolytic processing of the enzyme to lower-molecular-weight forms is indicative of its transport to lysosomes. The relative abundance of the mutants by pixel densitometry is shown for each lane.

(C) Representative IGV plots of nanopore long-read amplicons showing allele-specific splicing for *IDUA* exon 2 in individual 9 heterozygous for c.298A>G. Reads were phased into those carrying the c.298G (variant) allele (top) and those carrying the c.298A (reference) allele in trans (middle) and compared with a control sample (bottom). The c.298G allele shows predominant in-frame exon 2 skipping (p.Cys53_Arg100delinsTrp) with additional low-level cryptic donor site usage, while a small fraction of reads retain normal exon 2 splicing. Arrows indicate heterozygous SNVs used for read phasing (including c.298A>G and neighboring informative variants).

resulting enzyme had no detectable activity (this study, data not shown). Taken together, these data suggest a low level of transcript carrying the missense change is made and translated into an enzyme with essentially normal activity. *In vivo*, such a scenario would be predicted to contribute to low residual iduronidase activity.

Based on the SpliceAI score, c.590G>C corresponding to the p.Gly197Ala missense substitution may also primarily exert its functional consequence at the level of abnormal splicing (as opposed to a direct effect on enzymatic activity). Challenges in obtaining a sample from individual 4 precluded our ability to formally test this hypothesis. A different substitution at the same nucleotide position, c.590G>A (p.Gly197Asp), has also been reported in MPS I with a comparable SpliceAI prediction (acceptor loss:

0.19), although splicing was not formally assessed in that study either.²⁷ The proposed splice-mediated mechanism for c.590G>C is therefore based on *in silico* prediction alone and, without RNA confirmation, remains speculative.

In contrast, for c.406G>A (p.Alal36Thr), SpliceAI prediction was not supportive of an effect, and its near-wild-type RSA provides no evidence from this assay that the amino acid substitution is deleterious. While a splice-related effect not captured by the *in silico* prediction cannot be excluded, these findings suggest that p.Alal36Thr might be non-contributory in that individual, and alternative molecular explanations should be considered.

This study highlights a retinal-predominant presentation of *IDUA*-associated disease, including cases of apparently nsRP, which represent among the mildest clinical

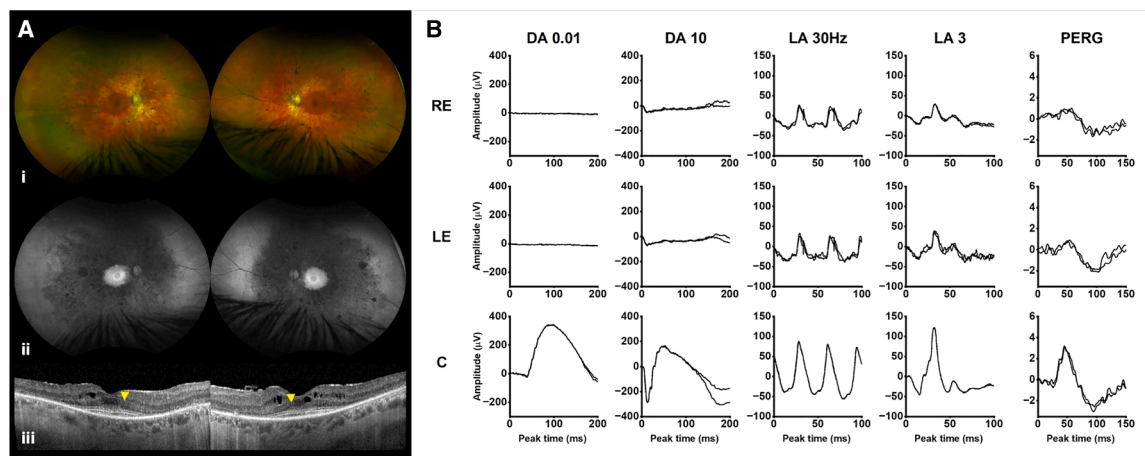


Figure 3. Representative retinal findings consistent with retinitis pigmentosa in individual 2

(A) Multimodal retinal imaging is shown for both eyes. Ultra-widefield pseudocolor fundus images (i) and autofluorescence (ii) (Optos, Dunfermline, UK) demonstrate disc pallor, arteriolar attenuation, perivascular atrophy, and pigment clumping in the posterior and mid-periphery, with relative sparing of the far peripheral retina bilaterally, with posterior pole hypo-autofluorescence sparing the macula, and a central hyper-autofluorescent ring bilaterally. Macular optical coherence tomography (iii) (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) demonstrates ellipsoid zone and outer retinal loss with central subfoveal preservation, mild intraretinal cysts, and subtle subfoveal hyperreflective material at the level of the external limiting membrane (yellow arrowheads).

(B) International-standard full-field and pattern electroretinograms (ERGs) recorded from individual 2. Right eye (RE) and left eye (LE) recordings are shown on the top and middle rows, respectively, with representative recordings from a healthy control individual (C) shown in the bottom row for comparison. In each image, waveforms are superimposed, demonstrating reproducibility. The DA 0.01 (dark-adapted dim flash) ERG is undetectable, indicating generalized rod system dysfunction. The DA 10 (dark-adapted strong flash) ERG a-waves are of severely subnormal amplitude, indicating rod photoreceptor dysfunction. The b-wave is severely subnormal, with the DA 10 ERG showing a “negative” appearance (here most likely reflecting a relatively preserved dark-adapted cone system response). LA 30 Hz (light-adapted flicker) and LA 3 (light-adapted single-flash) ERGs show subnormal amplitudes. The pattern ERG (PERG) is also subnormal (in keeping with macular involvement). The ERG findings are in keeping with rod-cone dystrophy.

manifestations reported to date. Through integration of genetic, biochemical, and functional data, the findings provide new insight into the mechanisms underlying attenuated disease, with implications for genotype-phenotype correlation, tissue-specific vulnerability, and diagnostic interpretation, with potential relevance to many other lysosomal storage diseases.

Pigmentary retinopathy is a recognized feature of MPS I and is thought to result from progressive GAG accumulation in the retinal pigment epithelium (RPE) and interphotoreceptor matrix, leading to photoreceptor loss and retinal degeneration.² In this cohort, RP (or rod-cone dystrophy) was the presenting feature in all 14 individuals, with the retinal degeneration predominantly affecting the mid-peripheral pericentric retina. Cystoid macular edema was a commonly associated finding. Subfoveal external limiting membrane thickening and electronegative electroretinogram were also observed in subsets of individuals, features that have previously been reported in metabolic retinopathies^{38,39} (Figure 3; Table S3). Nine individuals underwent comprehensive systemic evaluations; of these, seven (individuals 1, 3–5, and 9–11) had no features consistent with MPS I at last assessment (ages 46–73 years). Even the individuals with attenuated MPS in this cohort had a markedly later age of disease onset (20s–50s) than is typical for classical or attenuated MPS I.

Only a small number of cases of attenuated MPS I with predominantly retinal involvement have been reported.

These include a 65-year-old individual with retinal dystrophy and postlingual hearing loss but no other apparent systemic features who was homozygous for c.956C>T (p.Ala319Val) (Table 2, v13)³³; an adult in whom retinopathy diagnosed at age 34 was the presenting feature of attenuated MPS I and who was compound heterozygous for c.228T>A (p.Tyr76*) and c.1577T>C (p.Leu526Pro)⁴⁰; an individual with attenuated MPS I and pericentric RP, homozygous for c.1148G>A (p.Arg383His)⁴¹; and an individual reported with simplex RP with limited systemic details, with c.175del (p.Ser59Alafs*49) and c.400G>T (p.Gly134Cys).⁴²

No individual in this cohort harbored bi-allelic null *IDUA* genotypes; instead, most carried a presumed LoF (pLOF) allele in combination with a missense variant (Figure 1; Table 1). While genotype-phenotype correlations in MPS I remain difficult to establish in non-null genotypes,⁴³ the genotypes observed here suggest that the missense alleles are the key determinants of the attenuated, retinal-predominant presentation by permitting residual enzyme activity, consistent with the low-but-detectable leukocyte α -L-iduronidase activity observed across the cohort. In this study, c.271C>T, c.298A>G, c.794G>A (p.Gly265Asp), and c.1598C>A (p.Pro533Gln) were each observed in combination with a pLoF allele and were presumed hypomorphic variants associated with the milder phenotypes seen here. The recurrent alleles c.298A>G and c.794G>A, seen here in four not

knowingly related families each, are almost exclusively observed in individuals of European ancestry in population databases (gnomAD v.4), consistent with the predominantly European ancestry of the present cohort and suggesting these may represent ancestral European haplotypes. Another missense allele identified in this cohort, c.1148G>A, has been reported homozygously in an individual of Indian ethnicity with pericentric RP and attenuated MPS I.⁴¹ Additional hypomorphic alleles in both European and non-European populations may be identified with increasing recognition of *IDUA*-associated retinal disease.

For some of the presumed hypomorphic missense variants identified in this cohort, functional characterization using a cell-based expression platform assessing enzyme activity and protein abundance to derive RSA confirmed low residual enzyme activity: p.His91Tyr, p.Arg383His, and p.Pro533Gln showed RSA values in the 0.5%–1.5% range, comparable to other attenuated MPS I variants, including p.Gly265Asp, reported previously by the authors.³⁷ These RSA values place these variants at the high end of the attenuated range but still below all benign and pseudodeficiency variants reported in our prior study. Thus, the RSA values for the different variant iduronidases appear to align well with the unique, highly attenuated phenotype observed in this cohort. As more variants within this range are characterized, additional insight into the threshold that distinguishes apparently isolated RP versus attenuated MPS I is likely to emerge.

Resolution of the functional effect of the previously reported variant c.298A>G was only possible following the cell-based functional assay and nanopore-based transcript analysis, identifying a splice alteration with only very low-level wild-type splicing evident from the affected allele. These findings clarify the pathogenicity of this previously uncertain allele and support its hypomorphic effect, acting via low-level production of correctly spliced, catalytically competent transcripts rather than impaired enzyme function due to a deleterious missense effect. Similarly, the previously identified VUS affecting the same codon (c.299G>A [p.Arg100Lys]) may affect splicing in a similar way. By contrast, a splice-altering effect is also hypothesized but remains unconfirmed for c.590G>C (p.Gly197Ala), as participant RNA was not available to test this directly.

Clinical biochemical testing in this cohort supported the molecular findings, with leukocyte α -L-iduronidase activity consistently reduced, but not abolished, in all individuals tested. This finding suggests the variants do not exert their effect in a retina-specific fashion, such as a unique retinal isoform, but rather supports the hypothesis that the retina is more susceptible to low α -L-iduronidase function. Of note, urine GAG levels were only outside the normal range in half the cases where testing was performed, and when elevated, the increase was modest and well below the ~4-fold elevation above the upper limit of normal reported in classic MPS I.⁴⁴

Biochemical evaluation, including leukocyte α -L-iduronidase activity measurement and urine GAG analysis, should be considered as part of the clinical workup in individuals presenting with RP in whom bi-allelic *IDUA* variants have been identified. While enzymology can corroborate a suspected diagnosis, it cannot reliably predict disease severity,⁴³ and results are often atypical in attenuated disease.⁴⁵ Interpretation can be further confounded by pseudodeficiency alleles, which reduce α -L-iduronidase activity *in vitro* without causing clinical disease or altered GAG metabolism *in vivo*.^{46,47} In this cohort, screening for pseudodeficiency alleles (performed in 12/14 individuals) did not identify any carriers of the alleles assessed.

Together, these data suggest that hypomorphic *IDUA* alleles can act via diverse mechanisms—including direct reduction of enzyme activity, effects on protein processing, or leaky mis-splicing—to converge on a similar biochemical endpoint: low residual α -L-iduronidase activity contributing to an attenuated, retinal-predominant, or apparently isolated retinal phenotype. This highlights the need to integrate complementary functional approaches to resolve variant mechanism and improve interpretation of *IDUA* genotypes. What factors distinguish those with an apparently isolated retinal phenotype from those who will progress to attenuated MPS I, despite comparable residual enzyme activity, are not currently understood; this distinction was itself not always easy to establish in the present cohort, given variable depth of systemic assessment and the absence of longitudinal follow-up, meaning some individuals classified as having apparently isolated RP may yet develop systemic features over time. Differences in genetic background and the presence of genetic or environmental modifiers may contribute by altering how lysosomal GAG accumulation is managed in cells and tissues. Those individuals less affected (e.g., with apparently isolated RP) may possess an enhanced ability to reduce or clear any lysosomal storage within the skeletal system, for example. Defining such factors, supported by more comprehensive clinical and biochemical data in larger cohorts, will represent an important and therapeutically relevant area of future investigation.

Inborn errors of metabolism, including MPS I, feature prominently among the target disorders of several large-scale genomic newborn screening initiatives worldwide that are now sequencing the genomes of thousands of neonates, aiming to enable early detection of rare, treatable conditions.⁴⁸ In this context, the present data highlight an additional interpretative challenge: hypomorphic *IDUA* genotypes that may be associated with minimal or absent early multisystem disease, instead manifesting as late-onset, predominantly retinal disease for which there is currently no established treatment. It remains unclear how such findings should be managed within screening programs primarily designed to enable timely intervention for early-onset, treatable disease. The identification

of genotypes associated with apparently isolated RP through newborn screening efforts will present challenges in counseling and medical management that parallel current difficulties across the field in interpreting genotypes with highly variable outcomes in adult and highly attenuated individuals. At the same time, early identification may provide a window of opportunity for emerging retinal therapies before significant photoreceptor loss has occurred.

In recent years, there has been growing recognition that genes classically linked to severe multisystem lysosomal storage disorders, including neuronal ceroid lipofuscinosis (*CLN3* [MIM: 204200] and *MFSD8* [MIM: 611124]), MPS IIIA and IIIC (*SGSH* [MIM: 605270] and *HGSNAT* [MIM: 610453]), and multiple sulfatase deficiency (*SUMF1* [MIM: 607939]), can also cause highly attenuated, predominantly or exclusively retinal disease.^{49–53} Taken together, these observations across diverse lysosomal storage disorders support a model in which low residual enzyme activity may be sufficient to avert early multisystem disease; the retina, given its exceptionally high metabolic demand,⁵⁴ may, however, be particularly vulnerable to even modest reductions in lysosomal function and therefore be the first or only tissue affected. This has implications for therapeutic design in MPS I (and potentially other lysosomal storage disorders), suggesting that even modest enzyme restoration could confer systemic benefit, whereas higher and sustained activity may still be required to prevent progressive retinal degeneration.

This study provides a detailed characterization of the mildest end of the *IDUA*-associated disease spectrum, extending the recognized phenotype of MPS I to include apparently isolated RP. Variant classification for the hypomorphic alleles underlying such attenuated presentations presents particular challenges, as established gene-specific criteria and guidelines are primarily designed around classical disease phenotypes; by integrating genetic findings with enzymology and variant-level functional data, this approach offers a practical framework for interpreting *IDUA* variants of uncertain significance and highlights the need to update gene-specific classification guidelines to accommodate the full phenotypic spectrum.

Clinically, recognizing this attenuated presentation is important: *IDUA* and other MPS genes with retinal phenotypes should be included in IRD gene panels to support accurate molecular diagnosis, appropriate counseling, and timely referral to metabolic specialists for systemic surveillance, management of any systemic associations, and consideration of emerging therapies where appropriate.⁵⁵ More broadly, these findings show how distinct hypomorphic mechanisms converge on low residual lysosomal function, helping to explain how retinal-predominant or apparently isolated retinal disease can occur in the absence of overt early multisystem involvement and advancing mechanistic understanding of attenuated metabolic disease.

Data and code availability

- The functional data generated in this study are presented in full in the published article and its [supplemental information](#). No new code was generated in this study. Participant data supporting the findings of this study are confidential and subject to ethical restrictions. Access to data, including BAM files of RT-PCR amplicon ONT sequencing, can be requested from the corresponding author, subject to appropriate approvals and compliance with data protection regulations.
- Data from the National Genomic Research Library (NGRL) used in this research are available within the secure Genomics England Research Environment. Access to NGRL data is restricted to adhere to consent requirements and protect participant privacy. Data used in this research include whole-genome sequencing data (located in the /genomes/by_date folder) and associated phenotypic information extracted, using Participant Explorer, from participants enrolled in the Genomics England Rare Disease Program.
- Access to NGRL data is provided to approved researchers who are members of the Genomics England Research Network, subject to institutional access agreements and research project approval under participant-led governance. For more information on data access, visit <https://www.genomicsengland.co.uk/research>.

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Author contributions

Conceptualization, S.L., R. Steet, and G.A.; formal analysis, all authors; investigation, all authors; resources, S.B., S.R., R. Steet,

and G.A.; writing – original draft, S.L., R. Steet, and G.A.; writing – review & editing, all authors; visualization, S.L., R. Steet, and G.A.; supervision, G.A.; funding acquisition, R. Steet and G.A.

Declaration of interests

The authors declare no competing interests.

Web resources

ClinVar, <https://www.ncbi.nlm.nih.gov/clinvar>
GenBank, <https://www.ncbi.nlm.nih.gov/genbank/>
gnomAD, <https://gnomad.broadinstitute.org>
OMIM, <https://www.omim.org/>
RefSeq, <https://ftp.ncbi.nlm.nih.gov/refseq>

Supplemental information

Supplemental information can be found online at <https://doi.org/10.1016/j.ajhg.2026.09.008>.

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