REPORT

Mutations in *GPAA1*, Encoding a GPI Transamidase Complex Protein, Cause Developmental Delay, Epilepsy, Cerebellar Atrophy, and Osteopenia

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Approximately one in every 200 mammalian proteins is anchored to the cell membrane through a glycosylphosphatidylinositol (GPI) anchor. These proteins play important roles notably in neurological development and function. To date, more than 20 genes have been implicated in the biogenesis of GPI-anchored proteins. GPAA1 (glycosylphosphatidylinositol anchor attachment 1) is an essential component of the transamidase complex along with PIGK, PIGS, PIGT, and PIGU (phosphatidylinositol-glycan biosynthesis classes K, S, T, and U, respectively). This complex orchestrates the attachment of the GPI anchor to the C terminus of precursor proteins in the endoplasmic reticulum. Here, we report bi-allelic mutations in *GPAA1* in ten individuals from five families. Using whole-exome sequencing, we identified two frameshift mutations (c.981_993del [p.Gln327Hisfs*102] and c.920delG [p.Gly307Alafs*11]), one intronic splicing mutation (c.1164+5C>T), and six missense mutations (c.152C>T [p.Ser51Leu], c.160_161delinsAA [p.Ala54Asn], c.527G>C [p.Trp176Ser], c.869T>C [p.Leu290Pro], c.872T>C [p.Leu291Pro], and c.1165G>C [p.Ala389Pro]). Most individuals presented with global developmental delay, hypotonia, early-onset seizures, cerebellar atrophy, and osteopenia. The splicing mutation was found to decrease *GPAA1* mRNA. Moreover, flow-cytometry analysis of five available individual samples showed that several GPI-anchored proteins had decreased cell-surface abundance in leukocytes (FLAER, CD16, and CD59) or fibroblasts (CD73 and CD109). Transduction of fibroblasts with a lentivirus encoding the wild-type protein partially rescued the deficiency of GPI-anchored proteins. These findings highlight the role of the transamidase complex in the development and function of the cerebellum and the skeletal system.

Initially identified more than three decades ago,[1] glycophosphatidylinositol (GPI)-anchored proteins (APs) are emerging as a structurally diverse group of membrane-bound glycoproteins with important roles in cellular processes such as embryogenesis, fertilization, and neurogenesis. It is estimated that there are about 150 GPI-APs in the human proteome.

The attachment of a GPI anchor to a protein is a conserved posttranslational modification that occurs in the endoplasmic reticulum (ER) and requires at least 12 reactions. Proteins bearing the GPI anchor exit the ER and are shuttled to the Golgi, where they undergo fatty acid modification before being transported to the plasma membrane. Crucial in the GPI biosynthetic pathway are a group of enzymes (encoded by *PIGK* [MIM: 605087], *PIGS* [MIM: 610271], *PIGT* [MIM: 610272], *GPAA1* [MIM: 603048], and *PIGU* [MIM: 608528]) that form the GPI transamidase complex. These proteins mediate coupling of the synthesized GPI anchor to mature proteins with a C-terminal GPI-attachment signal peptide[2] in two principal steps: the cleavage of a C-terminal propeptide from the substrate protein and the formation of an amide bond between the C-terminal residue (ω-site) of the substrate protein and a phosphoethanolamine group of the GPI lipid anchor.[2] Among the five known subunits of the GPI-lipid-anchor transamidase complex, GPAA1 was the first to be discovered,[3,4] but its physiological role was demonstrated only recently.[5] This protein is composed of
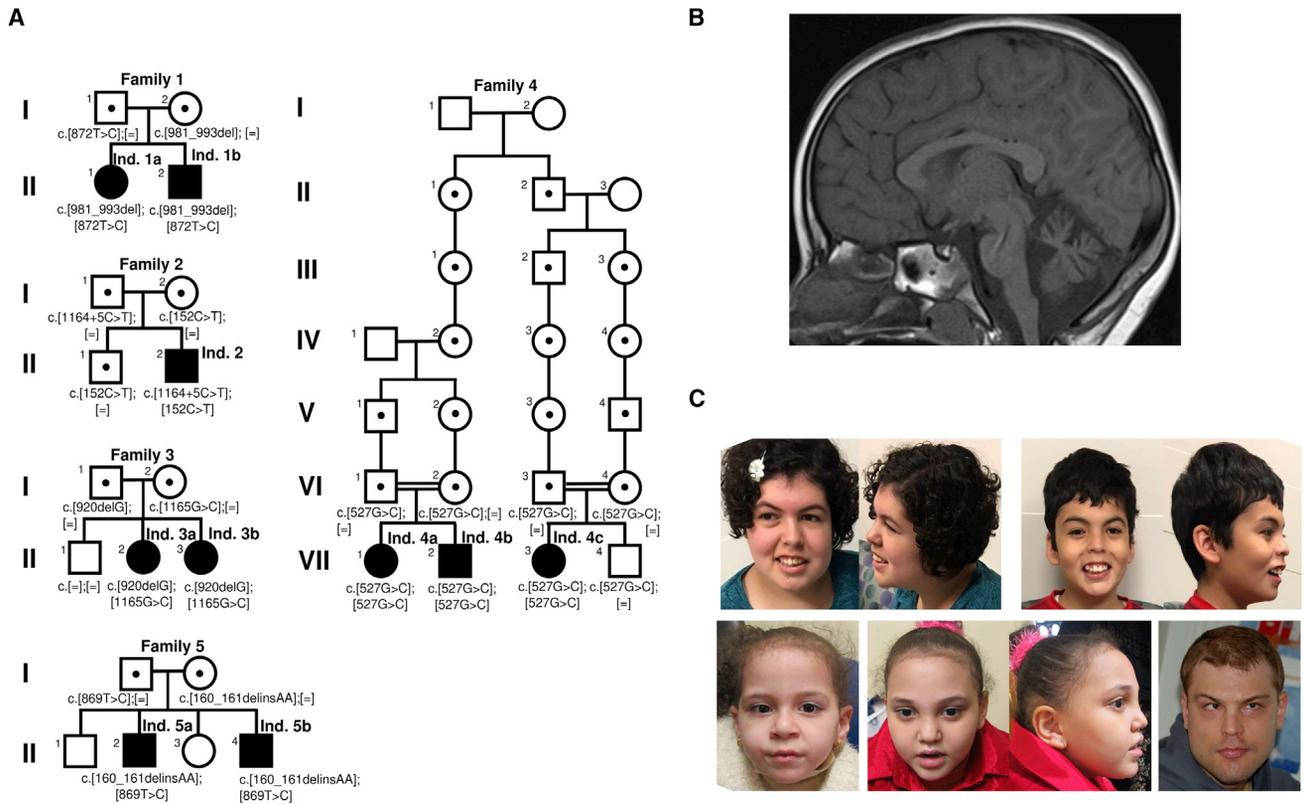
Figure 1. Pedigrees and Clinical Images

(A) Pedigrees of the five families affected by *GPAA1* mutations in this study.

(B) MRI of individual 4b (VII-2 of family 4) at 25 months. T1 sagittal image shows a marked reduction in cerebellar volume.

(C) Starting from the top right, photographs of individuals 1a (age 15 years), 1b (age 10 years), 3a (age 10 years), 3b (age 3 years), and 5 (age 25 years). A slightly broad and prominent root of the nose is noted in individuals 1b, 3b, and 5.

an N-terminal transmembrane domain, a luminal region, and a hydrophobic region containing six transmembrane domains in the C terminus. Recently, Eisenhaber et al. demonstrated that the luminal region of GPAA1 is similar to that of M28-type peptidases and that, like some of the peptidases in the M28 family, it might have one Zn-binding site. This protein was thus suggested to be a catalyst in the second step to complete the transamidation.[5] Several inherited disorders are known to be caused by GPI-biosynthesis defects.[6] However, mutations in *GPAA1* have yet to be reported in diseases other than cancer.[7–10] Here, we present functional characterization of *GPAA1* mutations in ten individuals with GPAA1 deficiency and clinical features (including developmental delay, hypotonia, and seizures) consistent with those of other inherited GPI-anchor deficiencies.

Ten individuals from five unrelated families with bi-allelic *GPAA1* mutations (GenBank: NM_003801.3) were included in this study. We identified individuals by searching the Baylor Genetics Laboratory proband whole-exome sequencing database, DECIPHER,[11] and GeneMatcher[12] and contacting collaborators. Informed consent was obtained from all families according to protocols approved by the institutional review boards at the relevant institutions. Most individuals had global

developmental delay including late or absent independent walking and speech abilities. Among the more severely affected individuals, six from families 1–3 and 5 (ages 6 years and up) were unable to walk independently, and the individual from family 2 had not yet acquired speech as of age 6 years. Hypotonia was identified in all individuals at an early age. Seizures and cerebellar atrophy were each found in seven individuals (see MRI in Figure 1B), and osteopenia was present in five individuals. Further clinical features are summarized in Tables 1 and S1, and additional MRI images of family 4 can be found in Figures S1–S4.

Exome sequencing showed two compound-heterozygous mutations in siblings 1a and 1b (II-1 and II-2, respectively, from family 1, a Hispanic family from the US, in Figure 1A): missense mutation c.872T>C (p.Leu291Pro) inherited from the father and frameshift mutation c.981_993del (p.Gln327Hisfs*102) from the mother. Individual 2 (II-2 from family 2, a white family from the US, in Figure 1A) inherited missense mutation c.152C>T (p.Ser51Leu) from the mother and intronic splicing mutation c.1164+5C>T from the father. His unaffected sibling carried the c.152C>T (p.Ser51Leu) mutation but not the splicing mutation. Affected siblings 3a and 3b (II-2 and II-3, respectively, from Egyptian family 3 in Figure 1A) had frameshift mutation c.920delG (p.Gly307Alafs*11)

Table 1. Key Clinical Features

	Individual									
	1a	**1b**	**2**	**3a**	**3b**	**4a**	**4b**	**4c**	**5a**	**5b**
Gender	female	male	male	female	female	female	male	female	male	male
Age at last assessment (years)	15	10	6	10.7	3.8	8	5	4	30	25
Height (cm)	152.4 (8th %)	127 (4th %)	103.2 (59th %) at 4 years	125 (1st %, -2.3 SD)	95 (15th %)	109 (1st %, -3.3 SD)	98 (1st %, -2.3 SD)	93 (1st %, -2.2 SD)	165 (-2 SD)	167 (-1.8 SD)
Weight (kg)	54.4 (58th %)	27.8 (16th %)	15.4 (30th %)	35 (49th %)	14 (19th %)	23.6 (27th %)	17 (23rd %)	15 (31st %)	70 (48th %)	62.4 (31st %)
OFC (cm)	53 (14th %)	52 (27th %)	52 (87th %)	49.5 (1st %, -2.3 SD)	48 (19th %)	51 (31st %)	48.6 (4th %)	48 (18th %)	57.2 (50th %)	57.2 (50th %)
Developmental delay or intellectual disability[a]	++	++	++	++	++	++	++	+	++	++
Hypotonia	+	+	+	+	+	+	+	+	+	+
Seizures	GTC, myoclonic, atonic	GTC	GTC	GTC	GTC, myoclonic	no	no	no	GTC, myoclonic, atonic, absence	GTC, myoclonic
Cerebellar atrophy	+	+	− (age 1 year)	+	+	+	+	+	+	+
Nystagmus	+	+	− (but cortical visual impairment)	+	+	+	−	+	+	+
Dysarthria	NA	+	NA	+	NA	NA	NA	+	+	+
Dysmetria	+	+	NA	NA	NA	NA	+	+	+	+
Ataxic gait	+	+	NA	NA	NA	+	+	+	+	+
Spasticity	−	−	−	+	NA	+	+	+	−	−
Osteopenia	+	+	+	+ ($Z = -2.2$)	+ ($Z = -2.0$)	+	+	+	NA	NA
Dysmorphisms	none	slightly broad root of the nose	bitemporal narrowing, prominent forehead, antereveted nares	bitemporal narrowing, widely spaced eyes, prominent ears	slightly broad root of the nose	bitemporal narrowing, prominent forehead, antereveted nares	bitemporal narrowing, prominent forehead, antereveted nares	narrow prominent forehead, anteverted nares	none	slightly broad root of the nose
Plasma alkaline phosphatase (U/L)	155 (normal)	143 (normal)	223 (normal)	355 (normal)	624 (normal)	176 (normal)	183 (normal)	201 (normal)	serum alkaline phosphatase 465 (275–875) (normal)	180 (normal)

More details can be found in Table S1. Abbreviations are as follows: −, absent; +, present; NA, not available; GTC, generalized tonic-clonic seizure; OFC, occipitofrontal circumference; %, percentile; and SD, standard deviation from the mean.

[a]Intellectual disability: +, mild; ++, moderate; and +++, severe.

Table 2. Genetic Description of the GPAA1 Variants

Family	Genomic Variant[a]	cDNA Variant[b]	Protein Variant	Inheritance	ExAC Minor Allele Frequency
1	chr8: g.145139374T>C	c.872T>C	p.Leu291Pro	compound heterozygous	not present
	chr8: g.145139483_145139495del	c.981_993del	p.Gln327Hisfs*102	compound heterozygous	not present
2	chr8: g.145138104C>T	c.152C>T	p.Ser51Leu	compound heterozygous	not present
	chr8: g.145139783C>T	c.1164+5C>T	splicing	compound heterozygous	1.661e−5 total and 0.0001226 in South Asians; no homozygotes detected
3	chr8: g.145139422del	c.920delG	p.Gly307Alafs*11	compound heterozygous	not present
	chr8: g.145139946 G>C	c.1165G>C	p.Ala389Pro	compound heterozygous	8.681e−6 total and 7.592e−5 in South Asians; no homozygotes detected
4	chr8: g.145138854G>C	c.527G>C	p.Trp176Ser	homozygous	1.658e−5 total and 0.0001211 in South Asians; no homozygotes detected
5	chr8: g.145138112_145138113delinsAA	c.160_161delinsAA	p.Ala54Asn	compound heterozygous	not present
	chr8: g.145139371T>C	c.869T>C	p.Leu290Pro	compound heterozygous	not present

[a]UCSC Genome Browser hg19.
[b]GenBank: NM_003801.3.

and missense mutation c.1165G>C (p.Ala389Pro). Homozygous missense mutation c.527G>C (p.Trp176Ser) was found in Pakistani siblings 4a and 4b (VII-1 and VII-2, respectively, from family 4 in Figure 1A) and a distant cousin (4c [VII-3]), all of whose parents are consanguineous. Affected siblings 5a and 5b (II-2 and II-4, respectively, from Finnish family 5 in Figure 1A) had two compound-heterozygous mutations: missense mutation c.869T>C (p.Leu290Pro) inherited from the father and missense mutation c.160_161delinsAA (p.Ala54Asn) from the mother. DNA from two unaffected siblings was not available for sequencing. These mutations were either not seen in the ExAC Browser or noted at a very low frequency without homozygotes (Table 2). See Figure 1 for the pedigrees and Figure 2 for the location and conservation of the substituted amino acids.
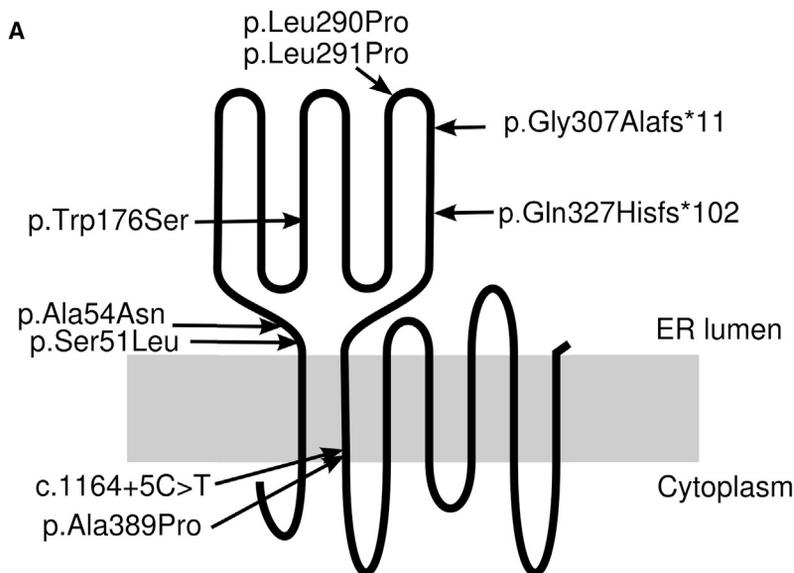
Frameshift or splicing mutations that introduce premature stop codons before the last 50 nucleotides of the penultimate exon usually trigger nonsense-mediated mRNA decay (NMD). To determine whether the mutations identified in our cohort triggered NMD, we performed real-time PCR on both fibroblasts and lymphoblastoid cell lines (LCLs) of individuals 1a and 1b, who had the frameshift mutation (c.981_993del) that introduces a stop codon at amino acid 428 (p.Gln327Hisfs*102). We observed a decrease in GPAA1 mRNA up to 50% in both fibroblasts and LCLs (Figures 3A and 3B). Similarly, individual 2, with the intronic splicing mutation c.1164+5C>T, also showed decreased mRNA expression of GPAA1 in LCLs (Figure 3B).

To assess whether these mutations could affect the amount of GPI-AP found at the cell surface, we performed flow-cytometry analysis on whole blood and LCLs of affected individuals from families 1, 2, and 4 (samples from families 3 and 5 were not available). Our results showed that all tested individuals had GPI-AP deficiency.

As shown in Figure 3C, decreased fluorescence-labeled aerolysin (FLAER) staining indicated that individuals 1a, 1b, and 2 presented with lower amounts of total GPI-AP in granulocytes, whereas lower amounts of CD16 were observed only in individuals 2, 4a, and 4b. In all LCLs examined, cell-surface staining also showed decreased FLAER abundance (Figure 3D). In addition, a moderate decrease in CD24 was observed in all individual cell lines (Figure S5).

Because fresh blood samples were not available for the affected individuals in family 3, we tested the effect of the mutations by transfecting GPAA1-knockout cells with plasmids encoding mutant cDNAs driven by a weak promoter with only a TATA box (pTA plasmid). GPAA1-deficient HEK293 cells were generated by CRISPR-Cas9 targeting of the gene. We previously generated a pME FLAG hGPAA1 plasmid,[13] in which we introduced the different variants by site-directed mutagenesis. The pME promoter was the SRα promoter (SV40 [Simian vacuolating virus 40] early promoter and HTLV LTR [human T-lymphotropic virus long terminal repeat] enhancer).[14] We also subcloned the constructs into plasmids with an intermediate-strength promoter (pTK with the herpes simplex virus thymidine kinase [HSV-TK] promoter) and a weak promoter (pTA with the TATA box from the HSV-TK promoter). The promoter activity of pTA was similar to that of a promoter-less plasmid. The promoter activities were estimated to be 1, 60, and 6,000 for pTA, pTK, and pME, respectively.

These results indicate less activity than the wild-type protein only for the p.Ser51Leu and the p.Ala389Pro variants (Figure 4A). In this overexpression experiment, the other variants (p.Trp176Ser and p.Leu291Pro) possibly had sufficient residual activity to provide a rescue. Similar results were obtained after transfection with plasmids encoding the cDNAs controlled by stronger promoters

A

p.Leu290Pro
p.Leu291Pro

p.Gly307Alafs*11

p.Trp176Ser

p.Gln327Hisfs*102

p.Ala54Asn
p.Ser51Leu

ER lumen

Cytoplasm

c.1164+5C>T
p.Ala389Pro

B

					Ser51			Ala290							Trp176				
Human	R	T	Y	M	S	E	N	A	M		G	Q	I	Y	W	A	K	D	I
Rhesus	R	T	Y	M	S	E	N	A	M		G	Q	I	Y	W	A	K	D	I
Mouse	R	T	Y	M	S	E	N	A	M		G	Q	I	Y	W	A	K	D	I
Dog	R	T	Y	M	S	E	N	A	M		G	Q	I	Y	W	A	K	D	I
Elephant	R	T	Y	M	S	E	N	A	M		G	Q	I	Y	W	A	K	D	I
Xenopus	R	S	Y	I	S	E	N	S	M		G	Q	I	Y	W	A	K	D	I
Zebrafish	R	T	Y	M	S	E	N	A	M		N	Q	V	Y	W	A	K	D	I

				Leu291									Ala389					
Human	L	Q	T	L	L	L	M	V	L		L	G	L	K	A	L	E	L	W
Rhesus	L	Q	T	L	L	L	M	V	L		L	G	L	K	A	L	E	L	W
Mouse	L	Q	T	L	L	L	M	V	L		L	G	L	K	A	L	E	L	W
Dog	L	Q	T	L	L	L	M	V	L		L	G	L	K	V	L	E	N	W
Elephant	L	Q	T	L	L	L	M	V	L		L	G	L	K	A	L	E	L	W
Xenopus	L	Q	T	M	L	I	M	M	L		L	I	L	R	-	-	-	-	-
Zebrafish	-	Q	T	M	M	L	M	V	L		-	-	-	E	-	-	-	-

Leu290

Figure 2. Mutation Localization and Residue Conservation
(A) Location of the protein variants in GPAA1 (for the splicing variant, the site affected by the exon-exon junction is shown).
(B) Amino acid conservation in vertebrates of the amino acids affected by substitution mutations.

GPI-AP deficiency, which most likely causes their clinical manifestations. The protein with the p.Trp176Ser variant might cause a milder biochemical effect given that it showed no decreased activity when it was overexpressed.

There is clinical overlap between these individuals and those with other GPI-biosynthesis defects. Inherited mutations in *PIGA* (MIM: 311770),[15–17] *PIGM* (MIM: 610273),[18] *PIGL* (MIM: 605947),[19] *PIGW* (MIM: 610275),[20] *PIGV* (MIM: 610274),[21,22] *PIGO* (MIM: 610274),[23,24] *PIGN* (MIM: 606097),[25] *PIGC* (MIM: 601730),[26] *PIGP* (MIM: 605938),[27] and *PIGG* (MIM: 616918)[28] have been identified as causes of GPI-biosynthesis disorders. Similar disorders can also be caused by mutations in *PGAP* (post-GPI attachment to protein) genes (notably *PGAP1* [MIM: 611655],[29] *PGAP2* [MIM: 615187],[30,31] and *PGAP3* [MIM: 611801]),[32] which code for a family of proteins involved in structural remodeling of the GPI anchor after its attachment to proteins. The phenotypes of the individuals with *GPAA1* mutations in the present study overlap those identified in other GPI-biosynthesis disorders, such as epilepsy, hypotonia, and developmental delay,[24,33,34] as well as the progressive cerebellar atrophy in individuals with *PIGT* and *PIGN* mutations.[25,35] The rate and severity of the progressive atrophy are comparable to those seen with PIGT and PIGN deficiency, although the finding is rarer in PIGN deficiency. The only reported GPI-transamidase-complex gene associated with GPI deficiency is *PIGT*, mutations in which cause multiple-congenital-anomalies-hypotonia-seizures syndrome (MIM: 615398),[4,33,34,36] characterized by hypotonia, developmental delay, seizures, dysmorphisms, and malformations of the heart, urinary tract, and gastrointestinal system. In relation to the condition we describe here, most of these individuals also have osteopenia.

All of the individuals we describe showed normal plasma and/or serum levels of alkaline phosphatase (ALP) (Table 1), which can be perturbed in other GPI-AP-synthesis-related
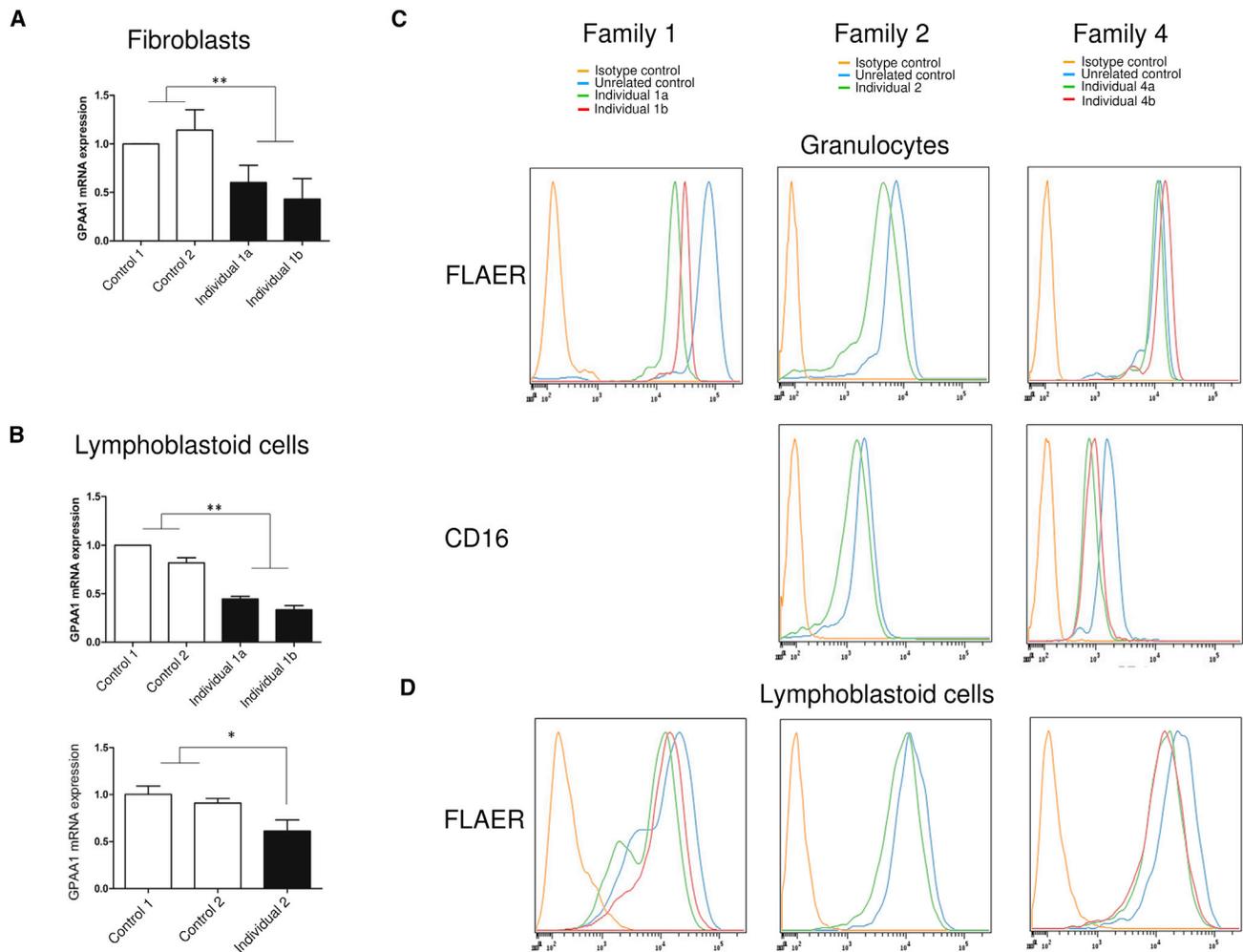
(see Figures S6 and S7). Western blotting of cell lysates after the transfection of cells with a strong promoter (pME) indicated that the p.Ala389Pro variant, located in the second transmembrane domain, leads to protein instability (Figure 4B). This could possibly be due to inadequate incorporation of the protein into the ER membrane.

We also assessed GPI-AP abundance on the cell surface of skin fibroblasts derived from individuals 1a, 1b, and 2 by using FLAER, CD73, and CD109 as GPI cell-surface markers (Figure S8). Because individuals 1a and 2 had significantly downregulated CD109 and CD73, respectively, we carried out rescue assays of these GPI-APs on fibroblasts from these individuals by using a GPAA1-encoding Lv105 lentiviral vector. As shown in Figure 5, CD109 in fibroblasts from individual 1a was completely rescued, and CD73 was partially rescued in fibroblasts from individual 2. Collectively, these findings demonstrate that individuals with *GPAA1* mutations have a

Figure 3. *GPAA1* Expression by qRT-PCR in Individuals from Families 1 and 2

(A and B) RNA extractions from fibroblasts (A) and LCLs (B) of individuals 1a, 1b, and 2 were subjected to qRT-PCR. Graphs show the results normalized to a reference gene (*TBP* for fibroblasts and *GAPDH* for LCLs) from quadruplicate experiments. Error bars represent standard deviations from the mean.

(C) GPI-AP abundance in granulocytes of individuals from families 1, 2, and 4. Fresh blood samples from these individuals and samples from healthy control individuals were fixed with 10% formaldehyde; red blood cells were lysed in 0.1% Triton X-100, and the samples were stained with GPI-AP markers (FLAER and CD16) for 1 hr at room temperature. Non-specific binding was washed before analysis by the BD FACScanto II system. Shown are representative results from experiments done in triplicate.

(D) GPI-AP abundance in LCLs of individuals from families 1, 2 and 4. LCLs were established by Epstein-Barr virus immortalization of peripheral-blood mononuclear cells. Cells were stained with a GPI-AP marker (FLAER) for 1 hr at room temperature. Non-specific binding was washed before analysis of the cell-surface abundance of GPI-APs by the BD FACScanto II system. Shown are representative results from experiments done in triplicate.

disorders. Previous data have suggested that the elevated serum ALP observed in some GPI-biosynthesis defects could be explained by cleavage of the signal peptide and secretion of soluble ALP as a result of abnormal GPI structure.[37] Because GPAA1 is a component of the GPI transamidase complex, decreased activity caused by mutations in the encoding gene might lead to a decrease in serum ALP. This was not observed in our cohort, perhaps because the remaining enzymatic activity was sufficient to maintain normal serum ALP. This hypothesis is supported by the fact that no individual with bi-allelic loss-of-function mutations was identified. With regard to the mechanism leading to osteopenia, perhaps decreased surface expression of ALP on osteoblasts affects its function and secondarily leads to the osteopenia seen in these individuals.

To date, GPI transamidase subunits have been proposed to function as oncogenes in breast and bladder cancers.[7–9] In addition, overexpression of *GPAA1* mRNA has also been found to be correlated with increased GPAA1 accumulation in samples from individuals with colorectal cancer.[10] It is thought that overexpression of GPI-biosynthesis genes might lead to increased uPAR (a GPI-AP), which in turn can lead to increased invasiveness and growth of tumor cells.[38]

Limited therapies are available for GPI-AP deficiency. Because alkaline phosphatase is essential for allowing pyridoxal-phosphate to pass through the blood-brain
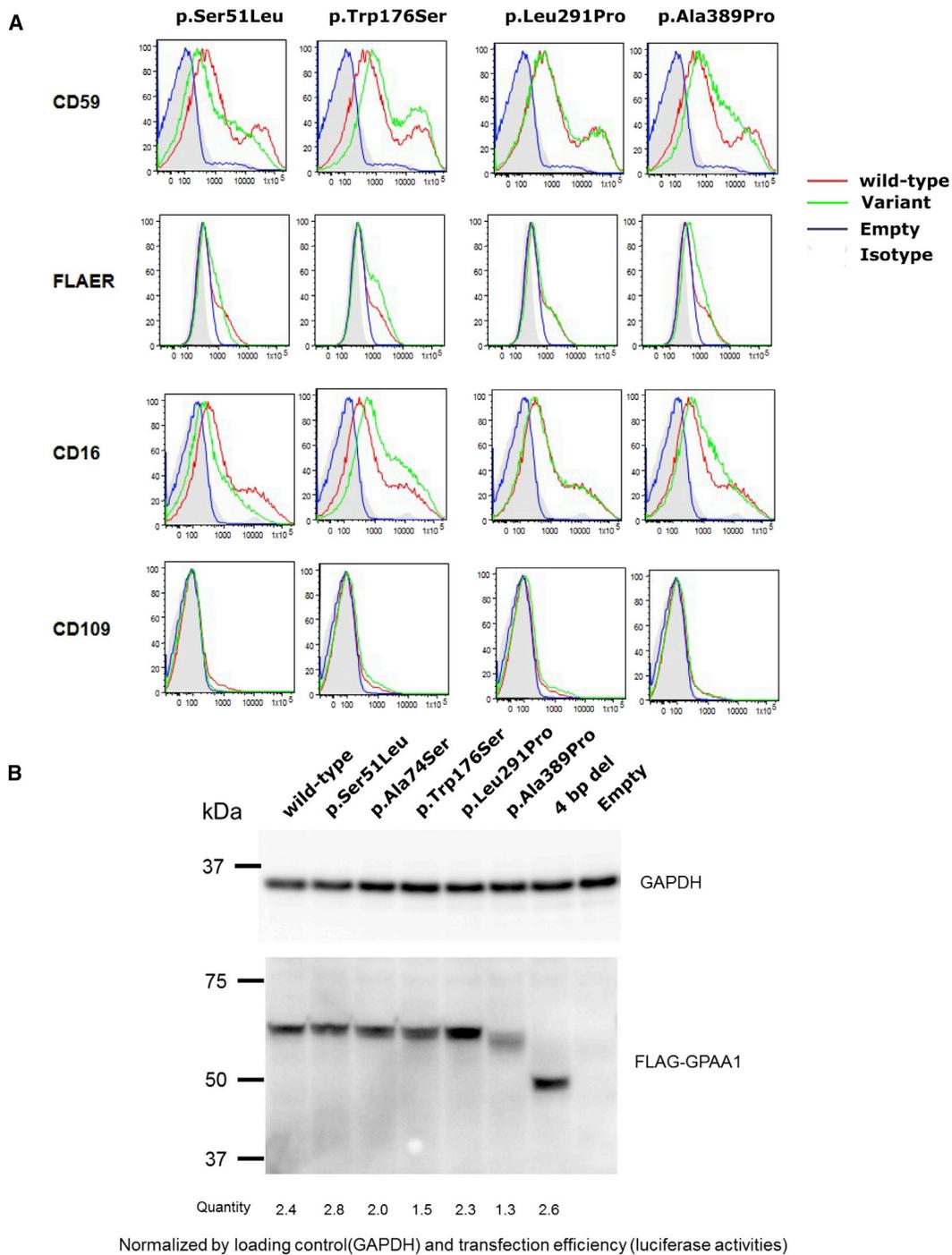
Figure 4. Activity in *GPAA1*-Knockout Cells

(A) Rescue of *GPAA1*-knockout cells. *GPAA1*-knockout cells were transiently transfected with a plasmid encoding wild-type or variant GPAA1 under the control of a weak promoter (pTA plasmid) by lipofection. Transfection efficiency was monitored by luciferase assay, and flow-cytometry analysis was performed 2 days after transfection. These results show slightly decreased labeling only for the p.Ser51-Leu and p.Ala389Pro variants (fewer cells with a strong signal), possibly because the residual activity of the other variants was sufficient to provide a rescue in this experiment.

(B) The p.Ala389Pro variant leads to protein instability. HEK293 cells were transiently transfected with various GPAA1 cDNAs, and proteins were analyzed by western blotting with an anti-FLAG antibody (Sigma). Intensities of the bands were normalized with the loading control (GAPDH), and luciferase activity was used for evaluating transfection efficiencies. The western blot of the tagged protein indicates that p.Ala389Pro, in the second transmembrane domain, leads to protein instability.

barrier and because pyridoxine passes through the blood-brain barrier and is converted to pyridoxal-phosphate, which is important for GABA synthesis, pyridoxine supple-mentation sometimes helps control seizures in individuals with GPI-biosynthesis defects, including some individuals with *PIGO* and *PIGV* mutations.[39,40] This potential
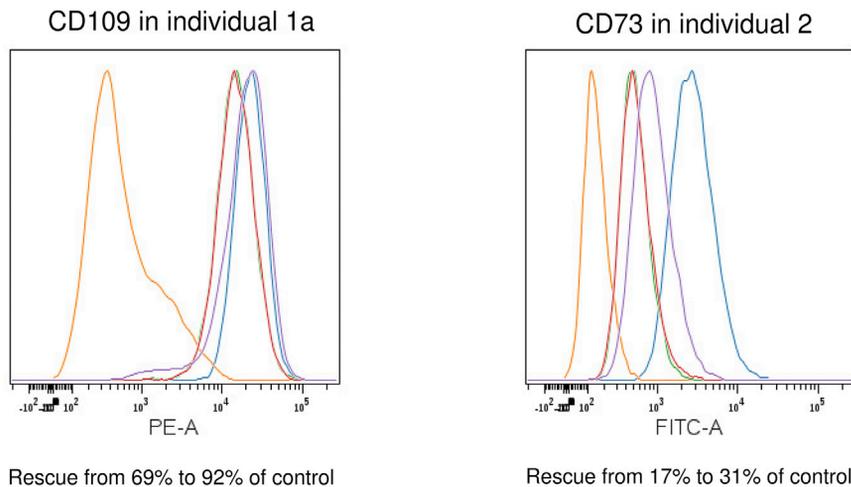
CD109 in individual 1a

Rescue from 69% to 92% of control

CD73 in individual 2

Rescue from 17% to 31% of control

— Isotype control
— Affected individual cells - untransduced
— Affected individual cells - transduced with empty vector
— Affected individual cells - transduced with GPAA1 vector
— Unaffected individual cells

Figure 5. Lentiviral Rescue Assays in Fibroblasts from Individuals 1a and 2
Skin fibroblasts derived from individuals 1a and 2 were transduced with GPAA1-expressing Lv105 lentivirus or empty-vector lentivirus and then transduced, and non-transduced cells were stained with CD109 and CD73 for 1 hr at room temperature. The non-specific binding was washed before analysis of the cell-surface abundance of GPI-APs by the BD FACScanto II system. Shown are representative results from experiments done in triplicate.

treatment has not yet been tested in our cohort. Future studies on *GPAA1* deficiency, such as in mouse models, could allow further pathophysiological studies to explore the cerebellar and bone manifestations and explore therapeutic avenues.

In summary, we have reported bi-allelic mutations in *GPAA1* in ten individuals presenting with global developmental delay, hypotonia, early-onset seizures, cerebellar atrophy, and osteopenia. Moreover, our functional studies demonstrated that these individuals have low cell-surface amounts of GPI-AP and thus that these mutations cause a defect in the biosynthesis of GPI-APs. Therefore, our work expands the group of GPI-biosynthesis disorders and contributes to the understanding of the role of the GPI transamidase complex in health and development.

Supplemental Data

Supplemental Data include eight figures and one table and can be found with this article online at https://doi.org/10.1016/j.ajhg.2017.09.020.

Conflicts of Interest

The Department of Molecular and Human Genetics at Baylor College of Medicine receives revenue from clinical genetic testing done at Baylor Genetics Laboratory.

Web Resources

ExAC Browser, http://exac.broadinstitute.org/
GenBank, http://www.ncbi.nlm.nih.gov/genbank/
OMIM, http://www.omim.org/
UCSC Genome Browser, https://genome.ucsc.edu/
UniProt, http://www.uniprot.org/uniprot/

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