The Liberfarb syndrome, a multisystem disorder affecting eye, ear, bone, and brain development, is caused by a founder pathogenic variant in the PISD gene

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INTRODUCTION

The enzyme phosphatidylserine decarboxylase (PISD) is responsible for the conversion of phosphatidylserine (PS) to phosphatidylethanolamine (PE), a process that is essential in all living organisms. PE is an abundant phospholipid in cellular membranes and is particularly enriched in mitochondrial membranes. PISD is located in the inner mitochondrial membrane of eukaryotic cells and it was shown to be essential for the production of PE in situ. Experiments in mice have shown that complete inactivation of PISD causes lethality during embryonic development, with no embryos surviving further than embryonic day 12, and histologic images revealed abnormally shaped and fragmented mitochondria. Although this enzyme has been studied extensively in model organisms due to its essential function in eukaryotes, little is known about the role of PISD in relationship to human health and disease.

Keywords: PISD; Liberfarb syndrome; skeletal dysplasia; retinal degeneration; phospholipid metabolism
Here, we report the identification of a genetic and likely hypomorph variant in PISD, found in homozygosity in five individuals from three families sharing a severe multisystem disorder involving brain, eye, ear, bone, and connective tissue.

MATERIALS AND METHODS

Patients and families
This study was performed according to the tenets of the Declaration of Helsinki, following the signature of written informed consent forms (including the use of images, if applicable) by the patients and their family members and the approval by the institutional review boards of our respective institutions.

Next-generation sequencing
Genomic DNA was extracted from peripheral blood leukocytes according to standard procedures, and then exome libraries (Agilent SureSelectXT Reagent Kit; Agilent Technologies) were sequenced on an Illumina HiSeq 2500 at the Genomic Technologies Facility in Lausanne, Switzerland. Bioinformatic analyses were performed as described previously. Briefly, raw reads were mapped to the human reference genome (hg19/GRCh37) using the Novoalign software (V3.08.00, Novocraft Technologies). Next, Picard (version 2.14.0-SNAPSHOT) was used to remove duplicate reads and Genome Analysis Toolkit (GATK) (version 3.8) was used to perform base quality score recalibration on both single-nucleotide variants and insertion–deletions. A VCF file with the variants was generated by HaplotypeCaller. Then, DNA variants were filtered based on quality, frequency in ExAC, gnomAD, 1000 Genomes, ESP (NHBLI Exome Variant Server, http://evs.gs.washington.edu/EVS), GME (GME Variome http://igm.ucsd.edu/gme/index.php), and ABraOM, and on predicted impact on protein sequence and messenger RNA (mRNA) splicing. Finally, they were annotated according to a specific in-house pipeline.

Homoyzogosity mapping and haplotype analysis
Large segments of homozygosity (>1 Mb) were computed from exome sequencing data with a tool developed in-house, AutoMap (unpublished), enabling the detection of shared regions of homozygosity in multiple probands. Then, sequences were visualized to detect shared haplotypes.

Sanger sequencing
To confirm the PISD variant identified by next-generation sequencing (NGS), polymerase chain reaction (PCR) amplification and Sanger sequencing were performed using standard reagents and conditions. The sequences of the primers used in these experiments are 5′-gagttgactccaaacactgt-3′ (forward) and 5′-gaattgcagctctctctgt-3′ (reverse).

In silico analysis of the variant
Annotation of chr22:32015826-32015835del was verified by VariantValidator and its predicted effect on splicing was assessed with MaxEntScan, HumanSpliceFinder, SplicePort, NNsplice, and SpliceAI.

Minigene splicing assay
The genomic sequences of the PISD gene of one patient and a control individual spanning exon 8–intron 8–exon 9 and containing the putative splicing variant were amplified by PCR with oligos carrying the recombinant sites attB1 and attB2 (forward 5′-ggggcacaagtttggaaaaagacgccgtctgatgtcagtgaac-3′ and reverse 5′-ggggcacaagtttggaaaaagacgccgtctgatgccagttc-3′). This minigene was then cloned into a pDEST26 vector (Gateway cloning system, Thermo Scientific). All plasmids were sequenced to verify the correct insertion of mutated and wild-type DNA fragments. The splicing assay was performed by transiently transfecting HEK293T cells with each minigene plasmid using FuGENE HD (Promega). At 24 hours post-transfection, cells were harvested and total RNA was extracted. This was subsequently reverse-transcribed with GoScript (Promega), using oligo-dT probes. The complementary DNAs (cDNAs) of both plasmids were then amplified with sequence-specific primers (5′-gtcataaaaaagacccatg-3′ and 5′-gtcattggagagcct-3′). PCR products were separated by agarose gel electrophoresis and fragments were analyzed by Sanger sequencing.

Quantitative real-time PCR assay (qPCR)
The expression levels of the wild-type (WT) construct and the one bearing the deletion (del) were assessed using the SYBR green technology (FastStart Universal SYBR Green, Roche) in a QuantStudio 12K Flex real-time PCR system (Applied Biosystems). RPLPO and GAPDH were used as endogenous reference genes to normalize the results. A specific primer pair was used for the amplification of the correctly spliced transcript (forward 5′-ccatcctccacactacactc-3′ and reverse 5′-ggtgggctggtgtggtgt-3′). The size of the amplified products was verified by the presence of a single melting peak at the appropriate temperature and their relative expression level was assessed by the ddCt method and by taking into account efficiency of each primer pair. Significance of the difference between two groups was calculated with unpaired Student’s t-test, assuming equal variance.

Targeted variant sequencing of DNA from paraffin-embedded tissue
DNA was extracted from paraffin sections of tiny esophageal biopsies using Nucleospin DNA FFPE (Macherey-Nagel) following manufacturer guidelines. The high-quality DNA was then PCR amplified and sequenced by capillary electrophoresis using the following primers: forward 5′-ggtgaggttaagctcagta-3′ and reverse 5′-gagttgaccaacctgtactgt-3′.

Estimation of the degree of consanguinity between affected individuals 1 to 4
In general, an individual having parents who are siblings is expected to have 100/4 = 25% of autozygous regions across
their entire genome, and $100/16 = 6.25\%$ if the parents are first cousins. This can be generalized to $100/2^n$ for parents distant by $n$ degrees of relationship (meioses). In this report, affected individuals 1, 2, and 3 shared a common autozygous haplotype of 3.36 Mb, corresponding to approximately 0.1% of the human genome. We calculated that this haplotype's size corresponds to 9.92 estimated meioses, suggesting that the Portuguese and Brazilian patients had a common ancestor approximately five generations ago. Of note, these data do not allow us to estimate the age of the variant itself, which might be significantly older.

RESULTS

Clinical evaluation

Family 1: patients 1 and 2

Patient 1 is a currently 22-year-old man of Portuguese origin, the first child of a healthy couple where parents are second cousins once removed; the maternal grandfather and the paternal great-grandmother were siblings (Fig. 1a). He was referred to genetics at age 2 years 10 months for short stature, generalized joint laxity, and suspicion of skeletal dysplasia. He was born at 38 weeks after an uneventful pregnancy by Cesarean section for pelvic presentation. At birth, weight was 3.4 kg (0 SD), length 47 cm (P5, −1.7 SD), and
occipital–frontal circumference (OFC) 37 cm (+1.5 SD). He was admitted to the neonatal unit for 2 days because of respiratory difficulties, with a favorable clinical evolution. Investigation at this point consisted of a karyotype (46,XY), transfontanellar and abdominal ultrasound with normal results, hemogram and thyroid function with normal results, and skeletal survey. Postnatal growth was below −2 SD for length/stature with bilateral hip dislocation as well as severe kyphoscoliosis developing during childhood. Kyphoscoliosis was surgically corrected at age 7 years. Bilateral hip dislocation was treated by traction followed by surgical repositioning with subsequent relapse requiring an additional intervention with osteotomy. Elbow joint dislocation became more pronounced. Height at 11 years was 98.5 cm (P ≪ 3, −7.54 SD); current adult height is 130 cm (P ≪ 3, −7.55 SD). Notably, the cranial circumference growth curve also drifted toward the 5th percentile.

Developmental milestones were delayed (head control at 3 months; sitting alone at 8/9 months; first words after 2 years; walking alone at around 4 years), possibly in part secondary to orthopedic findings. Learning difficulties were noted at preschool and a developmental evaluation at 5 years 1 month revealed a global IQ of 50.1; at 7 years 6 months IQ was 68.8 and at the age of 16 years a WISC-III testing revealed a moderate intellectual deficit with a verbal IQ of 46; attention deficit was also reported.

An ophthalmologic evaluation at age 7 revealed best corrected visual acuity (BCVA) of 20/800 for distance and 20/250 for near, with no significant refractive error. A horizontal/torsional manifest nystagmus was detected after age 5 years, which dampened in convergence and in lateroverversion. After age 9 years, it became obvious that the proband was mostly using an eccentric point of fixation. Fundus examination disclosed optic disc pallor, generalized mottling of the retinal pigment epithelium (RPE) with areas of atrophy interspersed with pigmentary changes. Bone spicules were identified in the midperiphery and vascular caliber was reduced, rapidly evolving to peripheral avascular areas with remaining ghost vessels (Fig. 2d). These findings, in association with a nonrecordable electroretinogram (ERG) at age 8 years, are compatible with a diagnosis of severe early-onset retinal degeneration (EORD). At age 7 years, suspicion

Fig. 2 Clinical synopsis. (a–c) Patient 4 at the age of 9 years. There is a marked spinal deformity with forward tilting of the pelvis (because of bilateral hip joint dislocation), exaggerated lumbar lordosis, and dorsal kyphosis with scoliosis. Features are identical to those of patient 5 (Fig. 2 in Liberfarb et al., 1986).17 (d) Ocular fundus examination of patient 1 at age 9 years showing optic disc pallor, generalized mottling of the retinal pigment epithelium (RPE) with areas of atrophy interspersed with pigmentary changes, and “bone spicules” identified in the macula and the midperiphery. Vascular caliber was reduced, with peripheral areas being avascular with remaining ghost vessels. (e) Fundus of patient 2 at age 6 years showing atrophy of the optic disc, extremely thin vessels, atrophic central macular area with pigment clumping. (f–k) Skeletal features including bilateral hip dislocation with femoral head dysplasia (patient 3, age 7 years), dislocation of ulna and radial head at the elbow (patient 5, age 15 years), severe epiphyseal dysplasia with striations of metaphyses (patient 3, age 7 years), delay in carpal and phalangeal ossification but no marked dysplasia (patient 3, age 2 years), platyspondyly but no spinal deformity at age 2 months, and extremely severe spinal deformity at adult age (patient 5).
of hypacusis was substantiated with an audiogram revealing an auditory threshold at 60 dB bilaterally. Subsequently, evoked acoustic potentials confirmed bilateral sensorineural hearing loss with electrophysiological thresholds at 50 and 60 dB respectively in the right and left ears, and hearing aids were prescribed. More recently, symptoms of nasal obstruction have appeared due to hypertrophy of conchae. No other health problems were noted. Neurological examination was unremarkable. Dentition was normal.

Patient 2 is the younger brother of patient 1. Pregnancy was normal including third trimester ultrasound. He was born at 38 weeks by Cesarean section with weight 3.2 kg (P25), length 47 cm (P < 5; −1.7 SD), OFC 36.5 (P50–75, approximately +1 SD), and Apgar 10/10, and was admitted to the neonatal unit for hypotonia for 7 days with a good evolution. He was referred to genetics at age 4 months because of short stature and short limbs. At age 9 months he had short limbs, short thorax, short neck, and joint laxity with limitation of elbow extension. While global development was normal at 9 months, later language development was delayed. A global developmental evaluation at 4 years revealed an IQ of 66; at 7 years his IQ was 52, with attention deficit also reported; at 11 years his global IQ was 41. Sensorineural hearing loss was diagnosed at the age of 3 years. Ophthalmological examinations revealed a similar, yet more severe, ocular phenotype as his older sibling, since a sensory horizontal nystagmus was noted at age 2 years. At his last examination at age 6 years, he presented a BCVA of 20/400 for distance and 20/200 for near. Fundus examination disclosed findings compatible with severe EORD, revealing bilateral optic atrophy, areas of RPE atrophy and hyperpigmentation in the macula, peripheral bone spicules, and thin retinal vessels (Fig. 2e). At 6 years, seizures with fever occurred and he was admitted to hospital for encephalitis. Orthopedic complications included knee dislocation with valgus left knee, bilateral necrosis of femoral head and pes planus, with surgery performed on left knee and feet, and mild scoliosis. Current weight (age: 12 years) is 27 kg (P < 5; −3 SD), current height is 121 cm (P ≪ 5; −4.32 SD).

**Family 2: patients 3 and 4**

These two affected brothers were born to healthy Brazilian parents who were first cousins (Fig. 1b). Patient 3 was born at term, after an uneventful pregnancy. At birth, weight was 2.8 kg (P10; −1.5 SD), length 44 cm (P < 3; −2.2 SD), and OFC 36 cm (P75; +1 SD). Motor development was retarded: sitting and walking without support were possible at the ages of 1 year 6 months and 4 years respectively. Scoliosis was noted by the parents “very early.” Clinical examination at the age of 14 years 6 months revealed the following values: height 91.5 cm (P ≪ 2; approximately −8 SD), weight 12.4 kg (P ≪ 2; approximately −9 SD), and OFC 49.5 cm (P ≪ 2; −4 SD). He had severe scoliosis, lumbar lordosis, thoracic kyphosis, bilateral hip dislocation, and bilateral impairment of elbow extension. Language was rudimentary.

Patient 4 was born after an unremarkable full-term pregnancy. Primary adaptation was good. At birth, weight was 3.0 kg (P25; −1 SD), length 44 cm (P < 3; −2.2 SD), and OFC 36 cm (P75). He sat and walked without support at the ages of 1 year 3 months and 3 years, respectively. Scoliosis was observed by the parents since the first year of life. Clinical examination at the age of 11 years 9 months revealed height 100.5 cm (P ≪ 2; approximately −6 SD), weight 15.5 kg (P ≪ 2; approximately −5 SD), and OFC 48 cm (P ≪ 2; approximately −5 SD). He had scoliosis, lumbar lordosis, and bilateral impairment of elbow extension (Fig. 2a–c). There was developmental delay (not formally measured) and very poor language development.

In both patients 3 and 4, brainstem auditory potentials were normal. There was a concern for bilateral cataracts in patient 3, but a formal ophthalmological evaluation could not be performed. However, brain magnetic resonance image (MRI) showed, in both sibs, bilateral optic nerve atrophy and cerebellar atrophy affecting the upper portion of the vermis and the hemispheres. Neurological examination including electromyography (EMG) and neural conduction studies ruled out myopathy and peripheral neuropathy. Patient 4 had onset of seizures at the age of 11 years and has been on anticonvulsant medication since.

**Family 3: patient 5**

Detailed clinical features of this patient as a girl were published in 1986.17 The patient continued to be followed after initial publication until her death at age 35 years. Briefly, the girl was born to consanguineous parents who had immigrated to the United States from the Azores islands (Portugal). She had first been hospitalized in Portugal at age 17 months for failure to thrive; short stature was noted with marked delay of bone age. Repeat hospitalization at 3 years 8 months of age noted short stature (P < 5), early retinal changes, 25° thoracic scoliosis, lordosis, and hyperextensible joints including marked genu valgum and dislocatable hips. At time of her first hospitalization in Boston (Boston Children’s Hospital), at age 7 years 6 months, examination continued to show short stature as well as respiratory difficulty with subglottic tracheal stenosis, tapetoretinal degeneration, sensorineural hearing loss, and developmental delay. Musculoskeletal problems included thoracic scoliosis increased to 90°, bilateral genu valgum passively positioned to 60°, and bilateral dislocated patellae, dislocated hips, and elbow deformities with dislocated radial heads. Initial surgical management included tracheostomy, bilateral Roux–Goldthwait procedures for patellar dislocation and posterior spinal fusion. In summary, the main observations in this patient were short stature, severe scoliosis, joint laxity, skeletal dysplasia, pigmentary degeneration of the retina, severe sensorineural hearing loss, and moderate developmental delay. No additional orthopedic procedures were performed after spinal fusion as described in the original report. Orthotic support continued over several years with bilateral knee–ankle–foot orthoses and spinal support thoracic–lumbar–sacral orthoses. The patient died at age 35 years following cardiac arrest and anoxic encephalopathy.
The five patients shared a similar clinical pattern. One component was a progressive disease of bone and connective tissue. At birth, there was no scoliosis and no overt joint dislocations. During childhood, the combination of epiphyseal dysplasia and joint laxity resulted in luxation of the femoral head and even more significantly in progressive, severe spinal deformation with lumbar hyperlordosis, thoracic kyphosis, and variable degree of scoliosis (Fig. 2). Joint laxity at the knee joint resulted in severe genua valga. Luxation of the radial head also developed in the first decade. Essential radiographic features were delayed vertebral ossification (but no platyspondyly); markedly delayed ossification of all epiphyses, contributing to joint instability and retarded bone age; and fine metaphyseal striations observed in childhood x-rays, especially at the knees (Fig. 2f-k). The formal classification is that of a spondyloepimetaphyseal dysplasia with predominantly epiphyseal involvement; however, as confirmed by the follow-up of patient 5, severe joint instability with joint dislocations and progressive severe spinal deformation were clinically more significant than the skeletal dysplasia. The second cardinal feature in affected individuals was retinal degeneration. This became clinically apparent in childhood. Detailed ophthalmological evaluation was available for patients 1, 2, and 5 (the findings in patient 5 were published in 1986).17 Patients 3 and 4 had optic atrophy on MRI. The fundus findings were pale optic disks, RPE mottling, severely reduced caliber of the retinal vessels, and areas of bone spicule pigment deposition (Fig. 2d,e). ERG was nonrecordable in patient 1 at age 8 years. These findings are compatible with EORD.

Similarly, microcephaly was not present at birth but was present in all patients at school age, when it also became clear that developmental delay was significant. The data about hypoacusis are unfortunately not very detailed but are compatible with moderate to severe early-onset loss of hearing, rather than with congenital deafness. Thus, the Liberfarb syndrome appears to be a progressive disorder involving connective tissue, bone, retina, ear, and brain.

**Genetic and molecular findings**

**Next-generation sequencing**

Because of the association of spondyloepimetaphyseal dysplasia and severe joint laxity, and in spite of the pedigree suggestive of recessive inheritance, individuals 1 to 4 were originally evaluated for the presence of monoallelic KIF22 variants associated with spondyloepimetaphyseal dysplasia with joint dislocations, leptodactylic type (SEMDJL; MIM 603546); no such variants were detected. Subsequently, exome sequencing was performed on three affected children, two from the Portuguese family (patients 1 and 2, Fig. 1a) and one from the Brazilian family (patient 3, Fig. 1b). As parental consanguinity had been reported in both families, we searched for large segments of homozgyosity and found two regions that were homozgyous in these three subjects (all positions refers to genome build hg19): chr1:66,067,109-84,880,380 (18.8 Mb) and chr22:28,389,453-34,022,284 (5.63 Mb). No rare (allele frequency <1% in available databases and in-house exomes) coding variants were detected in these regions. Through sequence comparison, we found that a part of the region on chromosome 22 was not only fully homozygous in all three individuals, but also shared the same haplotype in the three children (chr22:29,456,733-32,811,952, 3.36 Mb). The investigation for noncoding rare variants identified only one homozygous variant: chr22:g.32015826_32015835del; NM_014338.3:c.904-12_904-3delCTATCACCCAC, p.(?). This 10-bp deletion, located in intron 8 of the PISD gene at positions from −3 to −12 before the splice acceptor site of the last exon of the gene (exon 9), was predicted to moderately impair the correct splicing of intron 8 by five different splicing predictors (Supplementary Table 1). Familial analysis confirmed that the variant cosegregated with the disease in both pedigrees, according to a recessive pattern of inheritance (Fig. 1). The exome sequence data was reanalyzed for other putatively pathogenic variants in the shared haplotype region, and none was identified. Targeted Sanger sequencing of the DNA of individual 5 (Fig. 1c), extracted from a paraffin-embedded surgical biopsy of the esophagus, confirmed the presence of the same 10-bp deletion identified in the other affected individuals (Fig. 1d).

**Splicing alterations resulting from the variant in PISD**

To functionally test the putative consequences of the deletion and in absence of suitable patient-derived material, we performed minigene-based splicing experiments. We designed a minigene plasmid bearing the last two exons of PISD, with and without the microdeletion identified in the patients, for the purpose of expression in a mammalian cell line (Fig. 3a). After plasmid transfection and incubation in HEK293T cells, we examined transcripts originating from plasmids bearing the pathogenic variant versus their wild-type counterpart. We found that the deletion prevented the proper recognition of the natural acceptor splice site of intervening sequence 8 and led to production of both correctly spliced mRNA and transcripts bearing the full retention of intron 8 (Fig. 3b,c; Supplementary Fig. 1). In turn, this latter event resulted in the creation of a premature stop codon within this intron, and possibly to nonsense-mediated decay (NMD)–triggered degradation. If, for any reason, these aberrant transcripts were to escape NMD mechanisms,18 their further translation into a protein is predicted to produce a truncated protein lacking the last 74 amino acids, including its portion containing the decarboxylase alpha chain and the cleavage site for autocatalysis, as predicted by UniProt.19

Quantitative PCR analyses in this in vitro model indicated that the proportion of correctly spliced mRNA transcripts from plasmids bearing the deletion was only 5.7% compared with transcripts from plasmids carrying the wild-type minigene (Fig. 3d).

**DISCUSSION**

The four living individuals we studied shared a complex multisystem phenotype including microcephaly, early-onset...
retinal degeneration, hearing loss, intellectual disability, severe joint laxity, and short stature with skeletal dysplasia. This combination of clinical features is unusual and led us to speculate that they could share a common molecular basis, possibly the same described more than 30 years ago by Liberfarb and coworkers in a single case (individual 5 in this report). We also noted that the three families seemed to share a Portuguese ethnic background (the Azores islands are part of Portugal, and Brazil has a strong Portuguese admixture as a former Portuguese colony). DNA sequencing confirmed that all five patients were homozygous for a single variant in PISD, within a shared haplotype, likely due to the presence of a common ancestor for all of them approximately five generations ago. Importantly, no other rare variant was detected within the parts of autozygous regions covered by exome sequencing, including the one on chromosome 1.

The homogeneity of this rare phenotype (which we propose to call the Liberfarb syndrome) in these independently ascertained patients from three different continents, as well as the genetic data obtained, strongly suggest the causal relationship between the observed PISD variant and the clinical phenotype. The transfection experiments confirm the effect of this intronic deletion on mRNA splicing. However, the pathogenesis of this disorder and its pleiotropism remain unexplained. PISD is a fundamental biosynthetic protein that has been studied extensively in model systems, due to its central role in lipid and membrane biology.1

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Mitochondria

Based on our data from the gnomAD database (32 variants with a cumulative frequency of ~0.05%).

The global phenotype in those two sisters was considered reminiscent of the CODAS and EVEN-PLUS syndromes (in spite of those two conditions having significant skeletal changes), caused by biallelic variants in the two mitochondrial chaperones LONP1 and HSPA9, and experimental evidence was obtained suggesting an impairment in the function of the mitochondrial membranes. Furthermore, incubation of patients’ fibroblasts with lysophosphatidylethanolamine resulted in an improvement of mitochondrial and lysosomal morphology. In summary, the available evidence suggests that recessive PISD variants may be responsible for quite divergent clinical phenotypes, possibly related to the severity of the variants detected, ranging from apparently isolated skeletal dysplasia to multisystemic conditions affecting brain, ear, eye, connective tissue, and bone. Such a clinical spectrum and pleiotropism is unusual and goes beyond what is usually seen in bone dysplasia families. But how can this variability and pleiotropism be explained? Zhao and coworkers have suggested a possible link between the PISD-associated condition they have observed and the CODAS and EVEN-PLUS phenotypes, supporting the concept of “mitochondrial chaperonopathies.” However, we must remark that variants in two other genes involved in the phospholipid synthesis pathway have also been linked to phenotypes combining skeletal dysplasia and sensory disturbances (eye and ear); biallelic PTDS1 (phosphatidylserine synthase 1) variants determine Lenz–Majewski hyperostotic dwarfism (MIM 151050), and biallelic PCYT1A (CTP-phosphocholine cytidylyltransferase) variants are the cause of spondylometaphyseal dysplasia with cone–rod dystrophy (MIM 608940). While both enzymes are also expressed in the mitochondrion, the functional relationship between PISD, PCYT1A, and PTDS1 remains to be clarified. Of note, the precise pathogenesis of either the mitochondrial chaperonopathies or the phospholipid synthesis disorders listed here remains largely unexplained. As a mere hypothesis, we speculate that the PISD protein might have both a metabolic role (in producing PE) and a structural role in the inner mitochondrial membrane, and that different pathogenic variants might have different functional, and thus phenotypic consequences.

In conclusion, in this study we identified the molecular cause of a multiorgan condition, which we suggest calling the Liberfarb syndrome in honor of the ophthalmologist who first described it in 1986. This disorder is caused by a specific variant that appears to have been inherited from an individual
of Portuguese origin, and has subsequently spread to three geographical regions. The pathogenesis remains unclear, but the accumulating evidence, including other rare families segregating pathogenic variants in PISD, points to a pleiotropic and variable phenotypic spectrum possibly related to mitochondrial dysfunction (“mitochondrial chaperonopathies”) and to phospholipid synthesis disorders. Much work remains to be done to elucidate molecular pathogenesis and genotype–phenotype correlations in these two groups of disorders. At the end of this road, exogenous replacement with specific phospholipids might be a welcome therapeutic outcome.

SUPPLEMENTARY INFORMATION

The online version of this article (https://doi.org/10.1038/s41436-019-0595-x) contains supplementary material, which is available to authorized users.

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DISCLOSURE

The authors declare no conflicts of interest.

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