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CLINICAL REPORT

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Severe SOPH syndrome due to a novel *NBAS* mutation in a 27-year-old woman—Review of this pleiotropic, autosomal recessive disorder: Mystery solved after two decades

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Abstract

Autosomal recessive SOPH syndrome was first described in the Yakuts population of Asia by Maksimova et al. in 2010. It arises from biallelic pathogenic variants in the *NBAS* gene and is characterized by severe postnatal growth retardation, senile facial appearance, small hands and feet, optic atrophy with loss of visual acuity and color vision, and normal intelligence (OMIM #614800). The presence of Pelger-Hüet anomaly in this disorder led to its name as an acronym for Short stature, Optic nerve atrophy, and Pelger-Hüet anomaly. Recent publications have further contributed to the characterization of this syndrome through additional phenotype–genotype correlations. We review the clinical features described in these publications and report on a 27-year-old woman with dwarfism with osteolysis and multiple skeletal problems, minor anomalies, immunodeficiency, diabetes mellitus, and multiple secondary medical problems. Her condition was considered an unknown autosomal recessive disorder for many years until exome sequencing provided the diagnosis by revealing a founder disease-causing variant that was compound heterozygous with a novel pathogenic variant in *NBAS*. Based on the major clinical features of this individual and others reported earlier, a revision of the acronym is warranted to facilitate clinical recognition.

KEYWORDS

combined immunodeficiency, diabetes mellitus, dwarfism and osteolysis, long survival, novel *NBAS* variant, SOPH syndrome

1 | INTRODUCTION

In 2010, Maksimova et al. identified a novel short stature syndrome in the isolated Yakuts population living in northeastern Siberia

This article is devoted to the memory of Professor Robert "Bob" Gorlin, DDS, PhD (January 11, 1923 - August 29, 2006), University of Minnesota Regents' Professor Emeritus of Oral Pathology, who had the opportunity to meet and discuss this patient during his visit to New Orleans in 2005.

(Maksimova et al., 2010). This autosomal recessive (AR) syndrome was characterized by postnatal growth retardation with short stature, minor facial anomalies with senile appearance, small hands and feet, optic atrophy with loss of visual acuity and color vision, and normal intelligence. Leukocytes showed the Pelger-Hüet anomaly. The authors named this condition SOPH syndrome, as an acronym for Short stature, Optic nerve atrophy and Pelger-Hüet anomaly (OMIM # 614800). Using genome-wide homozygosity mapping, the authors demonstrated that the cause for this syndrome was due to a missense variant in the *NBAS* gene. This gene, located on chromosome 2p24.3, encodes a protein originally identified in neuroblastoma cells. *NBAS* encodes a component protein of the syntaxin 18 complex and is involved in Golgi-to-endoplasmic reticulum (ER) retrograde transport of vesicles, allowing the distribution of proteins necessary for balanced intracellular trafficking of molecules from the ER to the Golgi compartments (Aoki et al., 2009).

Several recent publications, most describing the identification of *NBAS* variants through whole exome sequencing (WES), have broadened our understanding of the clinical phenotype of SOPH syndrome, have described its occurrence in different racial and ethnic groups, and have provided more insight into phenotypic-genotypic correlations. In 2015, Haack et al. reported 11 patients with pathogenic variants in *NBAS* and a history of recurrent acute liver failure (RALF) triggered by febrile infections in early childhood. A few patients had other concomitant clinical findings such as acute renal failure and epilepsy, celiac disease, Crohn's disease, erythema nodosum or cardiomyopathy. Soon after, Segarra et al. (2015), using WES, reported on two previously undiagnosed patients with a disorder of recurrent liver failure, short stature, loose skin, a skeletal dysplasia with fractures and cervical instability, immunodeficiency, optic atrophy and retinal dystrophy, and minor anomalies. Capo-Chichi et al. (2015) reported on three Lebanese sibs born to consanguineous parents who exhibited RALF with very early onset, osteoporosis and developmental delay, and a history of neonatal fractures and dysmorphic features. The two older siblings in this family had been previously reported (Megarbane et al., 2008), raising the possibility of a new metabolic syndrome. Kortum et al. (2017) reported on an almost 5-year-old girl with characteristic SOPH syndrome who also experienced acute liver failure. This report suggested that individuals with the *NBAS* founder variant p.Arg1914His, originally reported in the Yakuts population, were less susceptible to RALF. Park et al., 2017 reported on a brother and sister with short stature, progeroid face, normal intelligence, and Pelger-Hüet anomaly but also frequent upper respiratory infections, elevated serum liver enzymes levels and optic atrophy with foveal hypoplasia not previously reported. Several recent reports have emphasized the occurrence in individuals diagnosed with SOPH syndrome of: RALF (Calvo et al., 2017; Cardenas, DiPaola, Adams, Holtz, & Ahmad, 2017; Lenz et al., 2019; Ono et al., 2019; Regateiro et al., 2017; Rius et al., 2018; Staufner et al., 2015; Wang et al., 2018), ocular manifestations (Nucci et al., 2019), growth hormone deficiency (Li et al., 2018), short stature or severe skeletal involvement (Balasubramanian et al., 2017; Kim et al., 2017; Palagano et al., 2018), and early onset of recurrent or severe infections due to abnormalities in both antibody and cell-mediated immunity documenting a combined immunodeficiency (Balasubramanian et al., 2017; Capo-Chichi et al., 2015; Li et al., 2018; Regateiro et al., 2017; Segarra et al., 2015). These individuals required frequent antibiotic treatments, and a few were successfully treated with long-term IgG replacement therapy (Kim et al., 2017). At least three reports recently described individuals with extremely severe or complex presentations of SOPH syndrome (Carli et al., 2019; Fischer-Zirnsak et al., 2019; Sunwoo, Kim, Kim, Oh, & Lee, 2018).

Here, we describe a 27-year-old Hispanic woman with dwarfism of intrauterine origin, along with severe skeletal manifestations and progressive osteolysis, striking dysmorphic features, Pelger-Hüet anomaly, combined humoral-cellular immunodeficiency, and diabetes mellitus type 1 with onset at age 12. Since infancy she has had multiple medical problems that delayed her development. However, her intelligence was normal. Multiple syndromes and skeletal disorders were considered among possible diagnoses but ultimately excluded. Her last genetic evaluation was performed before SOPH was first reported in 2010. Recently, WES established the molecular diagnosis for the severe disorder in this individual. Our patient represents a severe case of SOPH syndrome with survival into the third decade of life. This report provides additional insight into the clinical variability of SOPH syndrome, further expands on its natural history and suggests expansion of the acronym to improve clinical recognition of this syndrome.

2 | CLINICAL REPORT

The proposita was born to a 36-year-old father and a 30-year-old mother, both healthy and non-consanguineous. She was the product of their second pregnancy. The first pregnancy produced a normal girl who is currently 28 years old. Their third pregnancy produced dizygotic twins, a male and a female, who were evaluated at 6–7 months of gestation. Intrauterine growth restriction (IUGR) was observed in the female twin. They were born pre-term via Cesarean section. The male twin had a birth weight of 1,940 g. and is currently 22 years old and normal. The female twin had a birth weight of 1,600 g, was born with club feet and fracture of both femurs, had severe failure to thrive that required a G-tube, never gained more than 2.5 kg, and had tracheomalacia, multiple colds, bronchitis, and pneumonia. She was in the PICU until her death at age 9 months. According to the provided clinical description, this girl presented exactly the same phenotype as the proposita in this report but no genetic study or autopsy was performed.

The pregnancy of our proposita was complicated by bleeding during the first trimester and IUGR in the second trimester, prompting a Cesarean section at 35 weeks of gestation. Birth weight was 1,640 g. (−2.47 *SD*) and birth length 40 cm. (SGA). From birth, the child had failure to thrive and growth retardation. In early childhood, hypertonia, wide fontanelle, relative macrocephaly, big eyes, blue sclerae, a high palate, small hands, delayed developmental milestones (did not hold head up at 9 months), excessive sweating, and hyperextension of

knees were reported. From the age of 21 months, she presented several fractures of the femurs, and was able to walk only at 30 months. In her 31st month, visual problems were detected and optic nerve atrophy was diagnosed. Her impaired central vision was associated with achromatopsia (saw only black and white), photophobia, and myopia. At the age of 3 years, her voice was a high-pitched voice, and two episodes of herpes zoster were diagnosed. At the age of 4 years, an MRI scan showed a thin optic chiasma, small hypophysis, and a thin corpus callosum, leading to consideration of partial septo-optic dysplasia. At the age of 6 years, because of dwarfism, growth hormone therapy was prescribed but it was discontinued after 6 months because of no effect on growth. At the age of 7 years, because of recurrent respiratory infections, a combined humoral and cellular immunodeficiency was diagnosed and treatment with IVIG (Sandoglobulin) was initiated. At the age of 11 years, she presented with diabetes mellitus type 1, which has been well-controlled (HbA1c 7%) on therapy. At the age of 12 years, she presented with torticollis and difficulties walking. Radiological studies showed severe cervical scoliosis and kyphosis, leading to her referral to New Orleans for further evaluation and surgery due to dynamic compression of C-spine.

At the age of 13 years, her height was 89 cm (−9.25 *SD*) and the occipitofrontal circumference (OFC) was 46 cm (−1.4 *SD*) Major findings included dwarfism with small head circumference, anterior fontanelle measuring 1 cm, triangular face, prominent eyes, blue sclerae, prominent nose and chin, high pitched voice, some lost teeth, pubic hair, severe C-kyphosis, short thorax, Tanner level II-III maturation, stiffness of knees, cold feet with broad halluces, brachydactyly with wide distal phalanges along with increased number of big whorls (7) in the finger patterns, transitional single palmar flexion creases, and presence of hypothenar patterns. A skeletal survey showed an open fontanelle, wormian bones in the lambdoid suture, large sella turcica, thin ribs, severe C-kyphosis, developmental dysplasia of vertebrae, osteolysis, small pelvis, shortness of long bones, widening halluces.

The orthopedic concerns centered on the cervical spine: bone loss of both the anterior and posterior arches caused collapse, lordosis, scoliotic deformity, and eventual dislocation of C4 on C5. Spinal cord compression was prevented by bone loss causing spinal canal widening. Occipito-cervical fixation was performed. Rods were surgically placed from the occiput to the third thoracic vertebra in an attempt to provide mechanical support to the cervical spine. Bone loss was also prominent in the clavicles, scapulae and distal phalanges of the fingers. The patient had a relatively good recovery after spinal surgery. However she continued having intermittent fevers due to bronchiectasis.

At the age of 16 years, due to progressive pain, decreased neck mobility, spine instability due to osteolysis and cervical fracture, the patient was re-evaluated and spinal support was extended into the thoracic spine. At this time, the patient required tracheostomy and gastrostomy. Her height was 90 cm (<−11 *SD*), her IGF-1 was 72 ng/ml (NV 180–501) and IGF-BP3 0.9 mg/L (NV 2.68–6.47) both low for age (Esoterix, Endocrinology Services, Calabasas Hills, California). The stimulated IGF-1 (after 3 doses of rGH 0.033 mg/kg) was still low for age (152 ng/ml). Pathogenic variants in the *IGF1*, *IGF1R*, and mandibuloacral dysplasia-associated *LMNA* (OMIM #248370) genes were ruled out.

Menarche occurred at 20 years with subsequent oligomenorrhea. At that age, she required Nissen fundoplication and pylorotomy. Due to severe osteopenia with hypercalciuria, bisphosphonates were prescribed. Despite therapy, she presented with recurrent fractures of the ribs, left scapula and right femur after minimal trauma. At age 21, after a fracture of the hip, she became unable to walk. At age 22, the bisphosphonates therapy was discontinued and subsequently she had no more fractures. She currently takes only calcium and vitamin D along with her permanent treatments for diabetes, immunodeficiency, and chronic bronchiectasis. At the ages of 21 and 22 years, she was admitted to the ICU due to severe respiratory syncytial virus infections. However, with preventive therapy with palivizumab (Synagis), she has not required new admissions. Although infections diminished significantly since the start of IgG replacement therapy (first by intravenous, then by subcutaneous injections), the patient still requires frequent antibiotics treatment due to different recurrent infections (cotrimoxazol every 72 hr). On IgG replacement, her IgG concentrations are within the normal range and IgM and IgA remain very low. In addition, she has a T cell and Natural Killer cell lymphopenia. Alkaline phosphatase has always been slightly elevated (from 111 to 174 U/L; NV: 35–105 U/L), with occasional elevated LDH (up to 762 U/L; NV: 240–480 U/L), a slight elevation of AST (up to 170 U/L; NV: 5–32 U/L), ALT (up to 186 U/L; NV: 5–33 U/L) and GGT (up to 206 U/L; NV: 3–40 U/L) were observed during a prolonged hospitalization for post-viral bacterial pneumonia. At age 26, glaucoma was diagnosed. Because of oligomenorrhea, a recent ultrasound study revealed an apparent accessory, hypoplastic, unicorn uterus; only one ovary was visualized. In addition, she showed very high levels of FSH/LH, with very low levels of E2 and AMH, which was indicative of premature ovarian failure. The patient also has a neurogenic bladder. At the age of 27 years, her height was 96 cm (−10 *SD*) and weight 12 kg. (−39 *SD*). Figure 1 shows major findings in this patient at different ages.

After many years without an etiological diagnosis for this severe, undetermined autosomal recessive syndrome, WES was performed to identify the molecular cause.

3 | WHOLE EXOME SEQUENCING

Clinical whole exome sequencing was performed at Invitae. Briefly, genomic DNA samples obtained from the patient and her parents were fragmented and subjected to hybridization capture of targeted exonic regions. Next-generation sequencing was performed using Illumina HiSeq to an average of 150× depth of coverage. Targeted regions included approximately 95% of the mappable exome, and 10 base pairs of flanking intronic regions. Single nucleotide variants, indels, and exonic deletions and duplications were called using an in-house bioinformatics method as previously described (Kurian et al., 2014). Provided phenotype information was used to narrow the

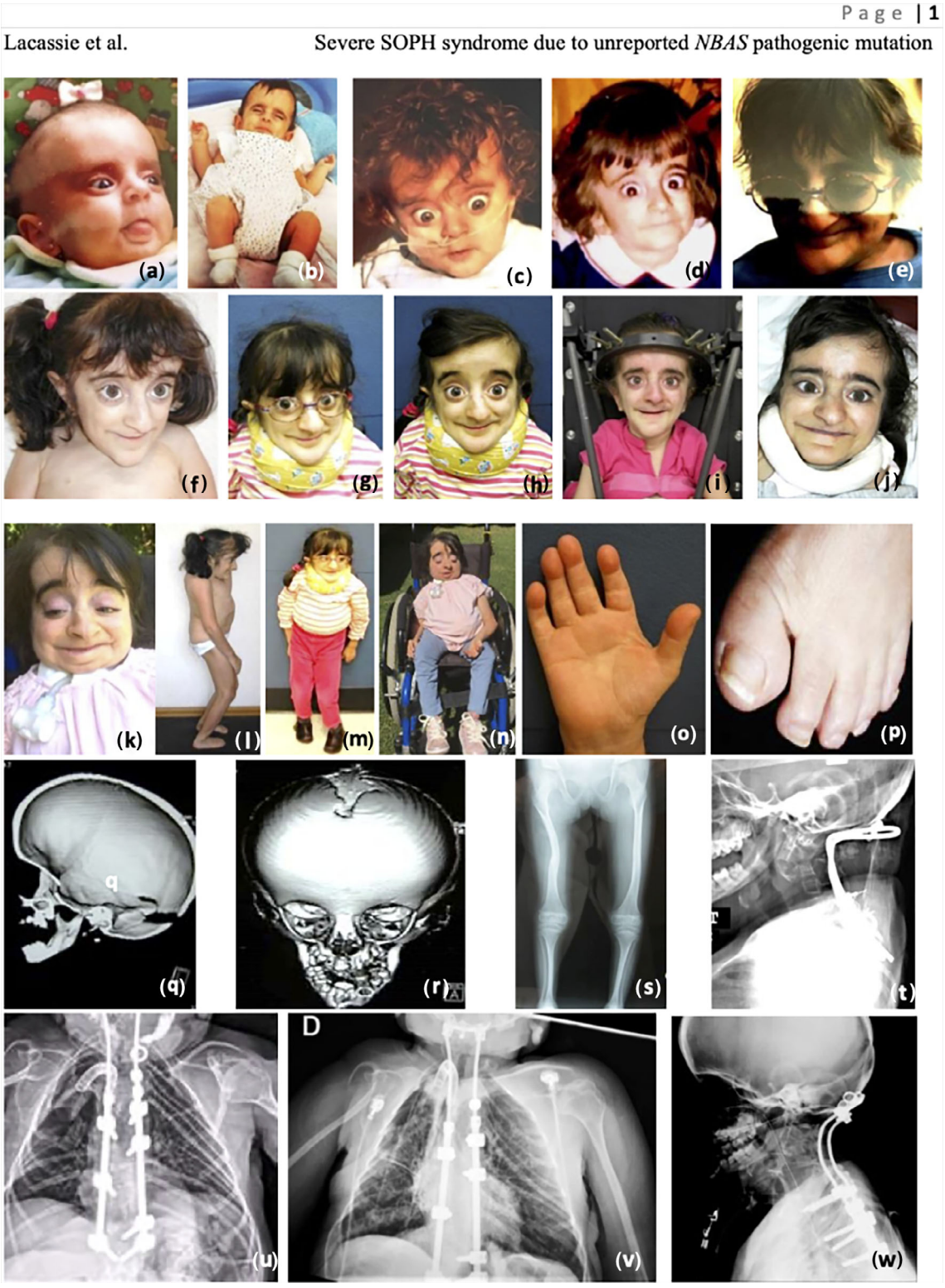

FIGURE 1 Legend on next page.

list of genes to analyze and variants within those were evaluated using Sherloc, a refinement of the ACMG guidelines-based evidence system (Nykamp et al., 2017). Clinically relevant variants potentially related to the proband's phenotype were described in the clinical report.

We identified two compound heterozygous pathogenic variants in *NBAS* (NM 015909.3) in this patient using WES: a paternally inherited c.17C>A (p.Ser6*) variant and a maternally inherited c.5741G>A (p.Arg1914His) variant. The first one has not been

FIGURE 1 Proposita and X-rays at different ages showing major features: (a–j) facies at ages 1 month (a), 3 months (b), 6 months (c), 3 years 9 months (d), 5 years 10 months (e), 7 years (f), 13 years (g–i), 16 years (j), 26 years (k). Most remarkable facial features being triangular shape with prominent eyes, bushy eyebrows, big prominent nose and chin; (l–n) whole body at ages 12, 13 (height 89 cm), and 26 (height 96 cm); (o) right palm showing brachydactyly with prominent finger pads and transitional single transverse palmar flexion crease. There are also hypothenar patterns (not pointed out); (p) left foot showing a wider foot and big hallux; (q–r) radiographs in infancy showing relative macrocephaly, triangular face with prominent forehead, wide open fontanelle, wormian bones in lambdoid suture and large sella turcica; (s) radiograph of lower extremities showing slender long bones with stenotic diaphyseal shafts and flared metaphysis. The capital femoral epiphyses are mildly flattened; (t) lateral radiograph of the cervical spine showing that the initial occipito-cervical fixation at age 13 is no longer adequate due to further bone loss, collapse, and anterior displacement of C3 on C4. There was no neurologic loss due to widening of the spinal canal from osteolysis of the cervical laminae. Note also the osteolysis of the mandible; (u–v) radiographies showing skeletal dysplasia with progressive developmental dysplasia of vertebrae, C4 small, triangular, unstable with intermittent compression of spinal cord with myelomalacia and osteolysis. Also pencil thin ribs, absent right clavicle and dysplastic left, abnormal head of humerus along diaphyseal narrowing with metaphyseal flaring; (w) lateral radiograph of the cervical spine after revision occipito-cervical fusion with extension of spinal instrumentation to the thoracic spine [Color figure can be viewed at wileyonlinelibrary.com]

reported previously and the second was reported in the original publication describing SOPH syndrome (Maksimova et al., 2010). The c.17C>A sequence change in exon 1 creates a premature translational stop signal (p.Ser6*) and is predicted to result in an absent or disrupted protein product. This variant is absent in the gnomAD database containing genome sequence data from the general population. The p.Arg1941His variant in exon 45 is present in gnomAD with a frequency of 0.02% and has been previously reported in several individuals with SOPH syndrome (Balasubramanian et al., 2017; Maksimova et al., 2010; Kortum et al., 2017; Kim et al., 2017; Park et al., 2017). This patient harbored variants in other genes besides *NBAS*, but none were judged to be related to this individual's phenotype based on the clinical data.

4 | DISCUSSION

The clinical features and genotype–phenotype correlations in SOPH syndrome were recently reviewed (Carli et al., 2019). Findings in our proposita further add insight into the clinical variability of this disorder. A comparison of the main clinical features of SOPH syndrome among the Yakuts (Maksimova et al., 2010) and that of our patient is shown in the Appendix. Existing publications on SOPH syndrome suggest that the major phenotypic features are variable intrauterine and postnatal growth retardation, ranging from mild short stature to severe dwarfism, skeletal findings with fractures often at birth, progressive osteolysis and neurological involvement, progressive progeroid facial features, optic atrophy with loss of visual acuity and color vision, a peculiar high-pitched voice, recurrent infections and immunodeficiency (allergic reactions in some individuals), diabetes mellitus, recurrent febrile episodes with acute liver failure early in life and, depending on the pathogenic variant present in NBAS, involvement of other organs or systems leading to congenital heart disease, renal, and uterine anomalies or other clinical outcomes. It is notable that insulin dependent diabetes mellitus (IDDM) and hypoplasia of the uterus were mentioned in the first descriptions of SOPH syndrome in 2010 (see Table S1). Most patients present with Pelger-Hüet anomaly that may not be detected during initial clinical evaluation. Most patients with this syndrome do not have intellectual disability despite some developmental delay due to skeletal, nutritional, or medical problems associated with or secondary to this condition. The history of infections and low antibody and cell-mediated immunity in our patient further establishes that individuals with SOPH syndrome suffer from a combined immunodeficiency that has to be quickly diagnosed and treated. Chronic IgG replacement and aggressive antibiotic treatment significantly improved our patient's quality of life reducing recurrent infections and avoiding severe infections.

The NBAS protein is a subunit of the syntaxin-18 complex, a SNARE protein that is important for ER membrane fusion (Aoki et al., 2009). It has been implicated in nonsense-mediated decay and Golgi-to-Endoplasmic Reticulum retrograde traffic. Knock down of *NBAS* in zebrafish using morpholino injection at high doses results in severe embryonic developmental defects including brain malformations and aberrant somite (Anastasaki, Longman, Capper, Patton, & Cáceres, 2011), while injections of lower doses show less severe deficits in chondrocranium development (Palagano et al., 2014). The *NBAS* gene is expressed in a wide range of tissues and during skeletal morphogenesis and development of cell lineages in the brain are among its key roles (Palagano et al., 2018). As a result, one main feature of SOPH syndrome is progressive osteolysis that mainly involves three areas: (a) the cervical spine, where progressive osteolysis causes cervical instability and collapse and eventual spinal cord compression, (b) the pelvis, where progressive osteolysis causes dissolution of hip sockets and loss of ability to walk, and (c) the mandible, where progressive osteolysis causes tooth loss and impairs oral feeding. Stabilization of the cervical spine is of utmost importance in surviving patients with a severe form, as in the case of our proposita and previously reported cases (Segarra et al., 2015). The distinctive presence of widened halluces, and brachydactyly with widened distal phalanx, which in general is associated with bigger finger patterns, might contribute to its clinical recognition. The mechanism by which pathogenic variants in *NBAS* lead to other aspects of the clinical phenotype requires further investigation.

4.1 | Genotype/phenotype correlations in our patient

The p.Arg1914His variant inherited from the mother is the most commonly observed pathogenic variant associated with SOPH syndrome.

TABLE 1 Features seen in patients with c.5741G>A p.(Arg1914His) and a LOF variant in *NBAS*

	This study	Balasubramanian et al., 2017 (patient 1)	Balasubramanian et al., 2017 (patient 2)	Kortum et al., 2017	Kim et al., 2017 (patient 10A)	Kim et al., 2017 (patient 10A)	Fischer-Zirnsak et al., 2019 (patient 1)	Fischer-Zirnsak et al., 2019 (patient 2)
PMID		27789416	27789416	28031453	28425089	28425089	31015584	31015584
Patient age	27 years	10 years	6 years	4.75 years	7.7 years	4.7 years	2 years 8 months	15 years
Gender	Female	Male	Male	Female	Male	Female	Male	Male
Prenatal clinical features	Intrauterine growth restriction	ND	ND	Intrauterine growth restriction and oligohydramnios	ND	ND	Intrauterine growth restriction	Intrauterine growth restriction
Postnatal growth failure—short stature	Postnatal dwarfism	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Poor weight gain and feeding difficulties	Yes	Yes	Yes, but feeding difficulties not noted	Yes	Yes	Yes	Yes	Yes
Delayed psychomotor difficulties	Yes	ND	ND	Yes	Motor delay in infancy in one sibling	ND	Yes, developmental delay	Yes
Intellectual disability	No	ND	Mild intellectual disability	No	ND	ND	ND	ND
Facial features	Triangular face, bushy eyebrows, small orbits, bilateral proptosis, hypoplastic cheekbones, straight nose with prominent glabella, thin lips, high palate, prominent chin, progeroid appearance	Prominent forehead, proptosis	Progeroid appearance, brachycephaly, broad forehead, proptosis, low set years	Triangular shaped face, prominent forehead, proptosis, convergent strabismus, thick eyebrows, small mouth, thin lips	Triangular shaped face, proptosis, small chin	Triangular shaped face, proptosis, small chin	Triangular shaped face, broad forehead, progeroid, appearance proptosis	Triangular shaped face, broad forehead, microcephaly
Ophthalmology	Bilateral optic nerve atrophy with nonprogressive loss of visual acuity, associated with complete or incomplete	Horizontal nystagmus, bilateral optic atrophy, myopia	Horizontal nystagmus and bilateral optic atrophy, grey sclera	Optic atrophy with progressive loss of visual acuity	Optic atrophy, corneal opacity and nystagmus	Optic atrophy	ND	Optic atrophy, myopia

TABLE 1 (Continued)

	This study	Balasubramanian et al., 2017 (patient 1)	Balasubramanian et al., 2017 (patient 2)	Kortum et al., 2017	Kim et al., 2017 (patient 10A)	Kim et al., 2017 (patient 10A)	Fischer-Zirnsak et al., 2019 (patient 1)	Fischer-Zirnsak et al., 2019 (patient 2)
	achromatopsia (color blindness), blue sclera, glaucoma							
Skull findings	Relative macrocephaly, wide anterior fontanelle, wormian bones	Microcephaly, large anterior fontanelle, wormian bones	Microcephaly, thin skull vault, large anterior fontanelle, no wormian bones	Congenital microcephaly, large fontanels, open sutures, hypoplastic maxilla, wormian bones	Small head size (−1.6 *SD*), wormian bones, widened J shaped sella	Microcephaly, wormian bones, widened J shaped sella	Large fontanels, wormian bones	Large fontanels, wormian bones

First characterized as a homozygous founder variant in the Yakuts population (Maksimova et al., 2010), it has also been seen in other individuals with SOPH syndrome as a homozygous variant or as a compound heterozygous variant with one of several loss-of-function variants. Importantly, as in the case of our proposita, individuals harboring the p.Arg1914His variant did not present with RALF or severe hepatic disease manifestations (Park et al., 2017). In contrast, most *NBAS* truncating variants reported to date have been found in patients affected with early-onset fever-triggered RALF (Calvo et al., 2017; Haack et al., 2015; Li et al., 2017; Regateiro et al., 2017; Sunwoo et al., 2018). The p.Arg1914His variant is located in exon 45 but its effect on the NBAS protein is unclear because it lies within the C-terminal domain of as yet unknown function. The paternally inherited p.Ser6* novel variant in our patient leads to the creation of a premature translational stop codon in exon 1 and is expected to result in an absent or truncated protein product. This variant occurs at a position that is closest to the N-terminal end of the protein relative to those reported previously and is expected to disrupt the quinoprotein aminedehydrogenase, the beta chain-like, and the secretory pathway sec39 domains.

The absence of overt clinical liver involvement in our patient has also been observed in all previously reported individuals with the p.Arg1914His variant as a compound heterozygous allele with other *NBAS* loss-of-function variants (Capo-Chichi et al., 2015; Segarra et al., 2015). However, there was some effect on liver enzymes in our proposita. The phenotype of patients harboring the p.Arg1914His variant in a compound heterozygous state with *NBAS* truncating variants overlaps with clinical features observed in our patient (Table 1) (Balasubramanian et al., 2017; Kim et al., 2017; Kortum et al., 2017).

5 | NAMING THE SYNDROME

There are different approaches to naming syndromes (Cohen, 1982). From the perspective of clinicians, even though the etiopathogenic denomination is appropriate and reflects the current tendency, acronyms allow a much better recognition than the use of eponyms, locations, or other methods. Maksimova et al. (2010) used the acronym SOPH to refer to this new syndrome. Unfortunately, Pelger-Hüet does not help a clinician identify this syndrome and molecular testing has helped establish that SOPH is a more severe and pleiotropic disorder than previously recognized. For these reasons we propose a slightly longer acronym that might help clinicians recognize this condition more effectively. Instead of SOPH, we propose SOPHIA, a longer but easier to remember acronym for Skeletal-Ocular-Pelger-Huet-Immunology-Acute liver failure syndrome. In the Appendix, we present the acronym SOPHIA along different important features to recognize in this disorder.

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CONFLICT OF INTEREST

Britt Johnson, PhD, Rita Quintana, PhD, and Swaroop Aradhya, PhD are employees of Invitae, the genetic testing laboratory that performed the WES. Rest of the authors declare no conflicts of interests.

AUTHOR CONTRIBUTIONS

Yves Lacassie, Conception and design, clinical description, writing original draft, review, and editing the manuscript. Britt Johnson, Laboratory (WES) testing and interpretation, conceptualization table and writing. Guillermo Lay-Son, Data curation, resources, revising the manuscript. Rita Quintana, WES testing. Andrew King, Surgical evaluations and procedures, analysis and interpretation of data. Fanny Cortes, Data curation, resources. Cecilia Alvarez, Data curation, resources, revising the manuscript. Ricardo Gomez, Conceptualization, analysis and interpretation of data, writing. Alfonso Vargas, Data curation, resources, interpretation of data. Stuart Chalew, Data curation, revising the manuscript. Alejandra King, Data curation. Sylvia Guardia, Data curation, writing, and revising manuscript. Ricardo U. Sorensen, Data curation, review, and interpretation of data. Swaroop Aradhya, Conceptualization, data review and interpretation, editing the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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