WES Reveals Novel Heterozygous NBAS Gene Mutations Associated with Fanconi Syndrome in a Patient with SOPH Syndrome: Case Report

Jia Yean Thong^{1#}, Zifeng Li^{2#}, Alice Halim^{1#}, Xiaochuan Wang³, Michael Halim^{4*}, Xiaowen Zhai^{2*}

¹Zhongshan Hospital, Shanghai Medical College of Fudan University, Shanghai, China

²Department of Hematology and Oncology, Children's Hospital of Fudan University, China

³Department of Immunology, Children's Hospital of Fudan University, China

⁴University of Salford, MSc Biomedical Science, Greater Manchester, United Kingdom

Corresponding Author(s): **Michael Halim*** and **Xiaowen Zhai****

Address: *University of Salford, MSc Biomedical Science, Greater Manchester, United Kingdom. **Department of Hematology and Oncology, Children's Hospital of Fudan University, No. 399 Wanyuan Rd, Minhang District, Shanghai 201102, China.

Received date: 11 January 2021; **Accepted date:** 12 February 2021; **Published date:** 20 February 2021

Citation: Thong JY, Li Z, Halim A, Wang X, Halim M, Zhai X. WES Reveals Novel Heterozygous NBAS Gene Mutations Associated with Fanconi Syndrome in a Patient with SOPH Syndrome: Case Report. *Asp J Pediatrics Child Health*. 2021 Feb 20;3(1):1-10.

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Abstract

Variations in the NBAS gene is known to cause a spectrum of phenotypes ranging from isolated recurrent acute liver failure (RALF) to a multisystemic presentation known as SOPH syndrome. Patients with SOPH present with optic atrophy, acute liver failure, short stature, and Pelger-Huet anomaly. We report the presence of a novel pair of biallelic heterozygous mutations c.5139-5T>G and c.2203-2A>G in the NBAS gene of a patient with SOPH syndrome. A 9-year-old patient was clinically diagnosed with SOPH following clinical laboratory analyses. Current interventions for managing the disease encompass IVIG, methylprednisolone, calcium, and vitamin D administration. Whole-exome sequencing (WES) results showed two mutations: c.2203-2A>G and c.5139-5T>G, in the NBAS gene, which had not been previously reported. Notably, we hypothesize that NBAS mutations could potentially contribute to the development of Fanconi syndrome, a clinical diagnosis reported in our patient. Our study also supports the renaming of SOPH to SOPHIA to allow early detection and effective treatment.

Keywords

Short Stature, Optic Atrophy, Pelger-Huet Anomaly, Neuroblastoma Amplified Sequence, Mutation, Whole-Genome Sequencing, Myopia, Case Report, Acute Liver Failure, Fanconi Syndrome

Introduction

Autosomal recessive short stature with optic atrophy and Pelger-Huet anomaly (SOPH) syndrome arises from biallelic pathogenic variants in the NBAS (neuroblastoma amplified sequence) gene. SOPH syndrome is characterized by small hands, postnatal retardation, optic atrophy, loss of color vision, senile

facial appearance, and loss of normal intelligence [1]. Moreover, SOPH is characterized by key clinical indicators such as optic atrophy, Pelger-Huet anomaly, and short stature [2]. Patients with SOPH syndrome exhibit recurrent episodes triggered by fever with dehydration, elevated transaminases, and vomiting [3]. Haack et al. [4] reported the presence of biallelic

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mutations in the NBAS gene, which revealed heterozygous mutations and reduced NBAS proteins. Recurrent acute liver failure (RALF) is a complication associated with SOPH syndrome [5-7]. Maksimova, Nogovicina, Kutanov, and Alekseeva [8] identified the c.G57G41>A mutation in the NBAS gene as the primary cause of the underlying defects in SOPH syndrome. We present a case of a 9-year-old Chinese female with SOPH syndrome following an analysis of the mutations on the NBAS gene by whole-exome sequencing (WES).

Case Description

A 9-year-old patient was referred to Fudan University Children's Hospital, Shanghai, China for persistent abdominal distension. The patient was born to healthy, non-consanguineous parents. At 6-years old, she was referred to Fudan University Children's Hospital due to short stature, immunodeficiency, pneumonia, and low white blood cells counts. The patient also presented with thin body habitus, prominent nasolabial folds, small hands, and large protruding eyes (Fig-1).

Fig-1:

A 9-year-old patient diagnosed with SOPH. A; Facial dysmorphism was evident as a result of the patient's progeroid features; B. Ventral view the of the patients' palms showed brachydactyly; C. The dorsal view of the patient showed wrinkled skin at the proximal interphalangeal joints of the fingers; D. Pelger-Huet anomaly.

Complete Blood Count (CBC) revealed low levels of WBC counts ($1.41 \times 10^9/L$ [normal $4 - 10 \times 10^9/L$]), low

neutrophil counts ($0.10 \times 10^9/L$ [normal $2-7 \times 10^9/L$]), low RBC count ($3.01 \times 10^{12}/L$ [normal $3.5- 5.5 \times 10^{12}$]) and eosinophilia: EO% (24.8% [normal, 0.5-5%]). Immunology studies revealed low levels of CD3+ (37.01% [normal, 64%-73%]), low CD4+ (18.50% [normal, 29%-36%]), low CD4+/CD8+ ratio (0.94 [normal, >1.0), low CD8+ (19.69% [normal, 24%-34%]) and low NK (CD56+) cells [6.69 [normal, 11%-23%]). The levels of B lymphocytes were however elevated (52.76% [normal, 14%-21%]). Bone marrow aspiration revealed Pelger-Huet anomaly of the neutrophil granulocytes, myeloid hyperplasia (erythrocyte lineage: 21.60%; granulocyte lineage: 61.20%), and scarce platelets.

Results of her fundus and visual evoked potential exams revealed no visual acuity changes, which ruled out optic atrophy. Her height, weight and BMI details at age 7 years old were as follows: Height: 107.10 cm [< -3 SDs]; Weight: 15.80 kg [< -3 SDs]; BMI: 13.77 kg/m^2 [< -1 SDs] (Fig-2). Moreover, her most recent bone scans revealed that she did not have osteoporosis.

Fig-2: Evaluation of the patient's growth and development.

The patient's records presented by her parents indicated frequent episodes of upper respiratory tract infections and hives. Moreover, the pregnancy, birth, and postnatal period were uneventful. At 3 years old,

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the patient was hospitalized for ascites, acute bronchitis, and pleural effusion. She also presented with recurrent fevers over a period of one month. Abdominal distension, chronic cough, and occasional abdominal pain were also evident upon admission. Serum chemistry profile revealed hypophosphatemia, mildly elevated CK and AST levels. However, the levels of ALT were within normal range and her coagulation studies were normal. Abdominal ultrasound revealed presence of fluid in the pleural and pelvic cavities, enlarged liver and spleen, and a thickened Glisson capsule. The patient also exhibited relatively low levels of IgA, IgM, low complement C3c and CD4+/CD8+ levels, suggesting weakened immunity. Upon her discharge from the hospital, her symptoms improved following antibiotic therapy. During her outpatient follow up, her CBC revealed markedly low levels of WBCs, RBCs, neutrophil counts and anaemia with low haemoglobin which prompted another hospitalisation.

During the course of her hospitalisation, her haemoglobin levels further decreased for reasons unknown which warranted blood transfusion of washed blood when it reached 53 g/L [normal, 110-160 g/L]. The patient was also diagnosed with Hashimoto's

thyroiditis upon thyroid function examination which revealed markedly elevated thyroglobulin and anti-TPO antibodies. As such, she received levothyroxine treatment and follow-ups.

At age 5, she was hospitalised with acute exudative tonsillitis and an EBV infection. The serum chemistry profile revealed elevated levels of ALT, AST, LDH while albumin, globulin, retinol-binding protein, phosphorus and BUN levels were very low, suggesting a damaged liver.

To further investigate the cause of her clinical findings, WES was performed. Two important mutations were revealed upon sequencing the NBAS gene. The patient's genotypic data revealed two heterozygous splice-site mutations in the NBAS gene (**Table-1**).

The data for this WES is obtained from the genetics department of the Children's Hospital, Fudan University, Shanghai, China, and is successfully registered in the Genome Sequence Archive in BIG Data Center, Beijing Institute of Genomics (BIG, <http://gsa.big.ac.cn>), Chinese Academy of Sciences, with Project Accession No. **HRA000627**.

Table-1: The patient's data showing genotypic information

Gene	Chr	GM information	Zygosity	Disease name	Inheritance	ExAC Het/Hom	HGMD classification	Source variation
NBAS	chr2:15417230	NM_015909:exon43: c.5139-5T>G	Het	Infantile liver failure syndrome 2, [MIM:616483]; Short stature, optic nerve atrophy, and Pelger-Huet anomaly, [MIM:614800]	Autosomal Recessive	o o	-	Paternal
NBAS	chr2:15601463	NM_015909:exon21: c.2203-2A>G	Het	Infantile liver failure syndrome 2, [MIM:616483]; Short stature, optic nerve atrophy, and Pelger-Huet anomaly, [MIM:614800]	Autosomal Recessive	o o	-	Maternal

Key: Chr - Chromosome; Hom - Homozygous; Het - Heterozygous; GM - Gene Mutation

At the age of 7 years, the patient presented with mucosal bleeding and hepatosplenomegaly. Lab evaluations revealed severe thrombocytopenia (platelet: $11 \times 10^9/L$) and Fanconi syndrome with proximal renal tubular acidosis (RTA). The patient also had low 25-hydroxy vitamin D (9.56 mg/mL) with normal PTH levels. Nonetheless, her renal ultrasound was unremarkable. She received washed blood

transfusion due to thrombocytopenia and low hemoglobin levels.

Between ages 4 and 8, she had 18 episodes of recurrent infections requiring the administration of IVIG due to her immunodeficiency. The patient was subjected to antipyretic therapy for fever reduction following IVIG therapy, enlarged liver, and to prevent

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acute liver failure. Over the past year, she was also given steroids, vitamin C and calcium to manage her condition.

Discussion

Hereditary short stature syndrome is a genetically heterogeneous condition that has been prevalent among Yakuts in Asia [9]. Even though most of the patients with SOPH syndrome have been known to present with short stature, Pelger-Huet anomaly, optic atrophy and liver failure due to mutations in the NBAS gene [10,11], several other mutations in the NBAS gene can also result in abnormal liver functions [12]. The aetiology of these mutations is attributed to recurrent episodes of liver failure, short stature, Pelger-Huet anomaly, and optic atrophy [7,13-15].

We hypothesised that the novel NBAS mutations in our patient can potentially explain her abnormal liver function, which was evident by elevated levels of AST, ALT, LDH and markedly low levels of albumin, BUN, retinol-binding proteins, and globulin. Additionally, our patient developed Fanconi syndrome, with hypophosphatemia since an early age being one of the

main clinical indicators [16], unravelling the potential association of NBAS mutations with Fanconi syndrome. Keefe and Nokhari [17] previously reported genetic changes that contributed to the development of Fanconi syndrome; the absence of the NBAS gene in the report supports the possibility of NBAS mutations having important implications to Fanconi syndrome. (WES) of our patient revealed a paternal mutation c.5139-5T>G, which was an intron variant identified as a splice site mutation located 5 nucleotides upstream exon 43. At this position, this variant interacts with the R1NT1 and ZW10 regions of the C terminal, which are involved in cellular transport between the Golgi apparatus and endoplasmic reticulum [18]. The maternal mutation c.2203-2A>G was identified as a splice site mutation in the intron, 2 nucleotides upstream exon 21, where the mRNA region translates to proteins that play a role in the secretory pathway Sec39 domain and the interaction with p31 protein (Fig-3) [18]. Our study showed that these two mutations play important roles in the severity and aetiology of SOPH, as well as liver dysfunction and immunological suppression.

Fig-3: Gene and protein structures of the NBAS and their mutations.

The functional domains and the NBAS proteins are represented in this diagram. These domains encompass the secretory and N proteins, the neuroblastoma-amplified sequence at the N terminal, and the sec 39 domain. Boxes numbered 1 to 52 represent the exons while the lines between the exons are introns. Mutations of the NBAS gene in our current study are shown in red, while NBAS mutations from previous studies are indicated in black.

Several mutations have been previously reported, such as the missense mutations in the NBAS genes, which constitute c.2674G>T, c.1018G>C, and the c.5741G>A mutations [19-26]. These mutations affect

the evolutionarily conserved amino acids and can be very damaging thus resulting in liver dysfunction and Pelger-Huet anomaly [18]. The current study, however, showed that two additional mutations

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c.5139-5T>G and c.2203-2A>G, which both occurred at introns of the NBAS gene, contributed substantially to the severity of SOPH syndrome by causing abnormal liver function due to changes in liver enzyme levels and immune cells. These changes also revealed the manifestation of Fanconi syndrome in SOPH patients carrying these mutations.

Previous studies employed several other techniques such as genome-wide homozygosity mapping, in silico analysis, Sanger direct sequencing, and western blot analysis for the analysis of these mutations [25-28]. WES was employed in the identification of the generic variants in our study, which had not been previously reported. Nonetheless, we did not follow up the WES results with Sanger sequencing [14], which is considered the gold standard for DNA sequencing. However, Strom et. al. [29] published a study that assessed the accuracy of confirmatory testing by

Sanger sequencing in 144 exome sequences and concluded that their laboratory would discontinue routine Sanger confirmation of exome sequences that meet quality thresholds. They proposed that the slight probability of a genetic variant identified by WES being a false positive is only a minor consideration compared to the uncertainty of genotype-phenotype relationship [29].

Other authors showed how the aetiology of biallelic mutations in the NBAS gene resulted in recurrent episodes of acute liver failure, as shown in our study [4,6,27,28,30,31]. Nonetheless, these two mutations were not identified in any of these studies, thus indicating their significance in causing abnormal liver function and Fanconi syndrome in SOPH patients. A comparison of the SOPH mutations in our current study and other studies is shown in **Table-2**.

Table-2: A comparison between the SOPH mutations in the current study and those reported in the literature

Study	NBAS mutation	Notable clinical features	Notable Investigations	Management / Treatment	Outcome / Prognosis
Our study	Heterozygous P: c.5139-5T>G M: c.2203-2A>G	Facial dysmorphism; short stature; senile skin; hepatosplenomegaly; developmental delay	Elevated LFTs with episodes of pyrexia and recurrent infections; pancytopenia; Pelger-Huet anomaly; reduced T lymphocytes and NK cells; renal function abnormalities (Fanconi syndrome with proximal renal tubular acidosis); bone marrow aspiration shows myeloid hyperplasia	Antipyretic therapy; IVIG & IM Human thrombopoietin for thrombocytopenia; steroids are given over the past year	Improved outcome following administration of methylprednisolone, vitamin D and calcium.
Maksimova et al. [2]	Homozygous c.5741G>A	Facial dysmorphism; short stature; senile skin; bone dysplasia; hepatomegaly; fractures	Pelger-Huet anomaly of granulocytes; optic nerve atrophy; achromatopsia	Undefined	Enhanced growth upon hormonal therapy for correcting short stature.
Segarra et al. [3]	Heterozygous P: ex. 35-47 del. M: c.5741G>A	Facial dysmorphism; short stature; senile skin; developmental delay; skeletal dysplasia; bone fractures; muscular hypotonia	Elevated LFTs with episodes of pyrexia and recurrent infections; hypogammaglobulinemia; low T-cells; low B-cells; osteoporosis; optic nerve atrophy; Pelger-Huet anomaly	Regular IVIG Immunoglobulin replacement therapy; Bisphosphonates given to manage osteoporosis, physical therapy & orthopaedic recommendations	Improved immunological functions following immunoglobulin replacement therapy and bisphosphonates. Overall, there is a subsequent improvement in life expectancy.

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Haack et al. [4]	Heterozygous: c.409C>T c.1186T>A (undefined inheritance)	Facial dysmorphism; short stature; senile skin; bone dysplasia; hepatomegaly; fractures	Elevated LFT with episodes of pyrexia and recurrent infections; RALF early infancy; coagulopathy; hypogammaglobulinemia; leukopenia; osteoporosis; small C1-C2 vertebrae causing cervical instability	Stabilization surgery to relieve compression of cervical spinal cord	Improved life expectancy upon relief of pain
Capo-Chichi et al. [5]	Heterozygous: c.284C>T c.850A>T (undefined inheritance)	Facial dysmorphism; short stature; senile skin; bone dysplasia; hepatomegaly	Elevated LFT with episodes of pyrexia and recurrent infections; RALF early infancy; hypogammaglobulinemia; reduced NK cells; osteoporosis; small C1-C2 vertebrae causing cervical instability and myelopathy; optic atrophy; Pelger-Huet anomaly	Supportive management (Glucose infusion for hypoglycaemia during pyrexia and liver crises); Mefenamic acid as antipyretic; weekly IVIG Immunoglobulin replacement therapy starting 11 years old; Stabilization surgery to relieve compression of cervical spinal cord	Reduced immunological complications and disease that arise from immunological defects.
Kortüm et al. [6]	c.5741G>A (undefined zygosity)	Facial dysmorphism; short stature; senile skin; bone dystrophy; hypotonia	Elevated LFTs with episodes of pyrexia; optic atrophy; complete achromatopsia	Undefined	Corrected vision upon optic atrophy surgery.
Fischer-Zirnsak et al. [7]	Heterozygous P: c.5714G>A M: c.2827G>T	Facial dysmorphism; short stature; senile skin; small hands and feet (micromelia and brachydactyly); bone dystrophy; muscular hypotonia	Elevated LFTs with episodes of pyrexia; hypogammaglobulinemia; reduced B lymphocytes; optic atrophy; Pelger-Huet anomaly	Regular IVIG Immunoglobulin replacement therapy	Improved quality of life following immunological treatment, where the patient stopped having recurrent candida tonsilitis and HSV infections
Maksimova et al. [8]	Heterozygous P: c.6496-6497insA M: c.5741G>A	Facial dysmorphism; short stature; senile skin; developmental delay; skeletal anomalies; hepatosplenomegaly	Elevated LFTs with episodes of pyrexia and recurrent infections; hypogammaglobulinemia; elevated CD19 B cells; bone marrow smear showed hypoplasia in erythroid cells; osteoporosis; optic atrophy; Pelger-Huet anomaly	Antipyretic treatment to minimize liver damage; prophylactic antibiotic; Regular IVIG Immunoglobulin replacement therapy; extensive follow up in specialized departments; bisphosphonates to manage osteoporosis	Improved life expectancy due to antipyretic liver treatment

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Maksimova et al. [9]	Heterozygous P: c.500_501delT M: c.5752A>C	Facial dysmorphism; short stature; small hands and feet (micromelia and brachydactyly)	Elevated LFTs with episodes of pyrexia and recurrent infections; hypogammaglobulinemia; optic nerve atrophy; Pelger-Huet anomaly	Regular IVIG Immunoglobulin replacement therapy	Improved quality of life following immunological treatment
Mégarbane et al. [10]	Heterozygous P: c.3158A>G M: c.2950delA	Facial dysmorphism; short stature; senile skin; developmental delay; skeletal anomalies; hepatomegaly	Elevated LFTs with episodes of pyrexia and recurrent infections; hypogammaglobulinemia; optic nerve atrophy; Pelger-Huet anomaly	Standard management for acute respiratory infection	Proper management of acute respiratory infection minimised respiratory depression and related complications
Kunishi et al. [11]	Heterozygous P: c.1018G>C M: c.2674G>T	Short stature; hepatomegaly; developmental delay	Elevated LFTs with episodes of pyrexia and infections (2 ALF episodes); Elevated lymphocytes w/ left shift; Severe coagulopathy (<i>elevated PT, INR, APTT</i>); renal dysfunction (<i>elevated Cre & BUN</i>); cytokine storm (<i>elevated IL-6 & neopterin</i>); bone marrow aspiration shows hypercellularity w/ hemophagocytosis; Pelger-Huet anomaly	Early antipyretic therapy with acetaminophen & glucose infusion Intensive treatment during liver crises: Plasmapheresis, haemodialysis, IV antibiotics, IVIG, glucose infusion	Improved life expectancy due to antipyretic liver treatment
Park and Lee [12]	Homozygous c.1948C>T	Facial dysmorphism; short stature; senile skin; small hands and feet (specifically brachydactyly); hepatosplenomegaly	Elevated LFTs with episodes of pyrexia; absent KREC & normal TREC (<i>crucial in the formation of T- and B-cell receptors</i>); absent CD19+ cells, low CD8+ lymphocytes & NK cells;	Regular IVIG Immunoglobulin replacement therapy & antimicrobial prophylaxis; corticosteroid therapy	Improved functions of the immune system, where there are significant improvements in gastrointestinal and cutaneous manifestations of eczema as well as the reduction of hypereosinophilia
He et al. [13]	Heterozygous c.1628_1629insA c.5741G>A (undefined inheritance)	Facial dysmorphism; skeletal dysplasia; osteoporosis; short stature; developmental delay; senile skin; muscular hypotonia	Elevated LFTs with episodes of pyrexia and recurrent infections; hypogammaglobulinemia; low T-cells; low B-cells; thrombocytopenia; optic nerve atrophy; Pelger-Huet anomaly	Regular IVIG Immunoglobulin replacement therapy & antimicrobial prophylaxis; corticosteroid therapy; gastrostomy to manage of hepatic encephalopathy	Enhanced immunological functions and the ultimate improvement of life quality and life expectancy.

where: P = Paternal; M = Maternal

Conclusion

In conclusion, we report a pair of novel biallelic heterozygous NBAS mutations present in introns that were previously unreported, and the association of Fanconi syndrome with SOPH. As the mutations c.5139-5T>G and c.2203-2A>G were shown to influence disease severity by not only affecting liver function and skeletal muscles but also contributing to immunodeficiencies, our study supports the renaming of SOPH to SOPHIA, an acronym for Skeletal-Ocular-Pelger-Huet-Immunology-Acute liver failure syndrome, as proposed by Lacassie et al. [1]. We strongly believe that this acronym would allow future physicians to detect this syndrome more easily and hence, administer effective treatment, as SOPH encompasses a wide range of expressions oftentimes requiring a multidisciplinary approach; especially the presence of immunodeficiencies, an under-recognized presentation in SOPH, should be recognized early on to improve their patients' prognoses.

Acknowledgements

Jia Yean Thong, Zifeng Li, Alice Halim and Michael Halim contributed equally to the research and writing of this case report.

Consent Letter

We sincerely thank our patient and her parents for their wholehearted support in our research, and we hope that it will not only benefit other patients with similar conditions, but more importantly contribute to the field of medicine.

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Keywords: Short Stature, Optic Atrophy, Pelger-Huet Anomaly, Neuroblastoma Amplified Sequence, Mutation, Whole-Genome Sequencing, Myopia, Case Report, Acute Liver Failure, Fanconi Syndrome

Manuscript no: ASJPCH-3-1-10

Volume: 3 Issue: 1

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Asp J Pediatrics Child Health