



A newborn with a pathogenic variant in ASXL2 expanding the phenotype of SHAPNS: a case report and literature review

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Background: Shashi-Pena syndrome (SHAPNS) is a developmental disorder caused by mutations in additional sex combs-like Protein 2 (*ASXL2*). Since 2016, only 12 cases from 10 families have been reported. However, neonatal period characteristics remain largely unknown. Herein, we report a case with a pathogenic variant in *ASXL2* in a newborn.

Case Description: A newborn was diagnosed with a previously unreported *de novo* truncating mutation in *ASXL2* (NM_018263.6) at 21 days and the clinical characteristics of all probands with *ASXL2*-related SHAPNS was reported in the literature. He had persistent hypoglycemia caused by inappropriate insulin levels and achieved stable glucose levels after octreotide treatment. Magnetic resonance imaging (MRI) revealed a small cerebellum, and fundoscopy showed bilateral retinal paving-stone-like white lesions. The results of trio-based whole exome sequencing (WES) were returned on the 21st day of life, and a heterozygous *de novo* truncating pathogenic c.1792C>T (p.Gln598*) variant in exon 11 of the *ASXL2* gene was identified. The clinical features of our patient and another 10 probands with *ASXL2*-related SHAPNS reported in the literature were included in this review. More than half shared recognizable clinical features, including hypertelorism (11/11), broad nasal tip (10/11), arched eyebrows (9/11), a large V-shaped glabellar nevus flammeus on the forehead (9/11), low-set ears (8/11), posteriorly rotated ears (7/11), proptosis (6/11) and deep palm creases (6/11). Major clinical issues included feeding difficulties (10/11), developmental delay (10/11), skeletal and/or extremity abnormalities (8/11), progressive macrocephaly (8/11), hypotonia (8/11), hypoglycemia (6/11) and seizures (6/11). Neurodevelopmental regression was possible in patients (2/11) with normal MRI findings who later developed nonfebrile seizures.

Conclusions: We present a newborn diagnosing the SHAPNS by trio-WES, which is the earliest age of diagnosis. The application of octreotide for hypoglycemia, the small cerebellum and bilateral paving-

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stone-like white lesions of the retinas are described for the first time in an individual with *ASXL2*-related SHAPNS. Additional clinical reports of neonates with damaging *ASXL2* variants are necessary to verify the mechanism and optimal treatment of *ASXL2*-related hypoglycemia, neurological damage and optic impairment. Neurological, endocrinological, ophthalmological, and rehabilitative follow-ups of these patients are necessary and important.

Keywords: China Neonatal Genomes Project (CNGP); neonate; *ASXL2*; Shashi-Pena syndrome (SHAPNS); case report

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Introduction

ASXL2-related Shashi-Pena syndrome (SHAPNS, OMIM #617190) was originally described in 2016 in six unrelated individuals who had *de novo* truncating variants in *ASXL2*

(NM_018263.6) and shared a recognizable clinical phenotype (1). SHAPNS is a rare autosomal dominant disorder characterized by hypoglycemia, neonatal feeding difficulties, minor congenital heart disease, hypotonia, seizures, cerebral atrophy, developmental disabilities, macrocephaly and a typical facial appearance consisting of a glabellar nevus flammeus, hypertelorism, arched eyebrows and prominent eyes (1).

The incidence of *ASXL2*-related SHAPNS is unknown. To date, only 12 individuals with *ASXL2*-related SHAPNS have been reported in the literature (1-5), three of whom came from one family (3). Clinical information for the early neonatal period was limited in all the case reports. Reports of individuals with damaging *ASXL2* variants (NM_018263.6) and related clinical features are essential to reveal the full phenotype of this syndrome from birth to adulthood (1,3) and assist physicians in optimal clinical management, family consultation, and strategy determination for follow-ups.

Undoubtedly, in neonates admitted to the intensive care unit with nonspecific clinical features, a rapid genetic diagnosis is vital for prompt targeted treatments and improved clinical outcomes (6). However, early and timely diagnosis of rare congenital disease remains challenging in the neonatal period. In 2016, we launched the China Neonatal Genomes Project (CNGP), which led to the discovery of a number of new gene variants underlying congenital disorders, and a significant number of diagnosed neonatal patients have benefited from more focused medical management and long-term care (7).

In this study, we describe the clinical data of a neonate with a previously unreported *ASXL2* variant (NM_018263.6) that was detected via trio exome sequencing carried out by the CNGP. In addition, we focus on the neonatal-onset manifestations, management and short-term prognosis of

Highlight box

Key findings

- We presented a newborn diagnosing the Shashi-Pena syndrome (SHAPNS) by trio-WES, which is the earliest age of diagnosis.
- The application of octreotide for hypoglycemia, the small cerebellum and bilateral paving-stone-like white lesions of the retinas are described for the first time in an individual with *ASXL2*-related SHAPNS.

What is known and what is new?

- SHAPNS is a developmental disorder caused by mutations in additional sex combs-like protein 2 (*ASXL2*) and characterized by hypoglycemia, neonatal feeding difficulties, minor congenital heart disease, hypotonia, seizures, cerebral atrophy, developmental disabilities, macrocephaly and a typical facial appearance consisting of a glabellar nevus flammeus, hypertelorism, arched eyebrows and prominent eyes. Since 2016, only 12 cases from 10 families have been reported and the majority of related patients were discovered and diagnosed at an older age.
- This is the first time that octreotide was administered in patients with persistent hypoglycemia secondary to SHAPNS and successfully helped our patient achieve euglycemia without hypoglycemic brain injury. Unusual funduscopy results of paving-stone like white-lesion and small cerebellum on the MRI were identified in patients with SHAPNS for the first time.

What is the implication, and what should change now?

- Further clinical reports of more neonatal individuals with damaging *ASXL2* variants are necessary to verify the mechanism and optimal treatment of *ASXL2*-related hypoglycemia, neurological damage and optic impairment.
- Neurological, endocrinological, ophthalmological, and rehabilitative follow-ups of these patients are necessary and important.



Figure 1 Images of the neonate with *ASXL2* pathogenic variant at six days of age. (A) Deep palmar creases. (B) Overlapping toes. (C) Hirsutism on the back.

SHAPNS. Moreover, to assist physicians in optimal clinical management, family consultation and strategy determination for follow-ups, we summarize important information on the clinical genotype, phenotype, major clinical issues and prognosis of this syndrome found in a literature review, building on the data for *ASXL2*-related SHAPNS previously reported by Shashi *et al.* (1), Cuddapah *et al.* (2), Wang *et al.* (3), Alqaisi *et al.* (4) and Jiao *et al.* (5). We present the following case in accordance with the CARE reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-22-220-/rc>).

Case presentation

A 2-day-old male neonate with feeding difficulty, recurrent hypoglycemia and specific facial features was admitted to the Department of Neonatology of Children's Hospital of Fudan University. Trio-based WES was performed for this neonate and his parents according to the protocol of the CNGP (8). Clinical information was prospectively collected. Informed consent was acquired.

This male neonate was born to a 29-year-old woman (gravida 1, para 1) via spontaneous vaginal delivery on September 9th, 2021. No resuscitation was needed. He was born at 40⁺² weeks' gestational age with a birth weight of 3,030 g (10th–50th percentile), length of 48 cm (10th–50th percentile) and head circumference of 36 cm (90th percentile). The Apgar scores were 8, 10 and 10, respectively. At the age of two days (September 10th, 2021), he was transferred to the Department of Neonatology of Children's Hospital of Fudan University due to three episodes of hypoglycemia (1.6–1.8 mmol/L) and two

episodes of cyanosis while orally feeding.

Both mother and father were in good medical conditions. Antenatal care was unremarkable. There was no family history of inheritable disorders.

Upon admission, his physical examination revealed a large V-shaped glabellar nevus flammeus, proptosis, hypertelorism, a broad nasal tip, a broad forehead, low-set and posteriorly rotated ears, thick ear lobes, arched eyebrows, retrognathia, deep palmar creases (*Figure 1A*), overlapping second and fourth toes (*Figure 1B*), small nails and hirsutism on the back (*Figure 1C*).

After admission, his feeding status was designated nil per os, and he received continuous intravenous parental nutrition. He required a maximum glucose infusion rate of 9 mg/kg/min to maintain normal glucose level. A series of investigations was performed to clarify the underlying cause of cyanosis. Echocardiography showed a patent ductus arteriosus (3.7 mm) and an atrial septum defect (6.2 mm), both with left to right shunt. Barium radiography of the upper digestive tract showed evidence of gastroesophageal reflux disease (GERD). Laryngoscopy showed that he had laryngomalacia. On magnetic resonance imaging (MRI), the size of cerebellum was relatively small, with a diameter of 45.7 mm (*Figure 2A*). Fundoscopy showed bilateral paving-stone-like white lesions in the retinas (*Figure 2B,2C*) and no significant change at follow-ups when he was at the age of 6 weeks. The small cerebellum and bilateral paving-stone-like white lesions of the retinas were identified for the first time in an individual with *ASXL2*-related SHAPNS.

He underwent diagnostic fasting and glucagon tests, which indicated unreasonably high levels of insulin. When his plasma glucose level decreased to 2.1 mmol/L, the levels

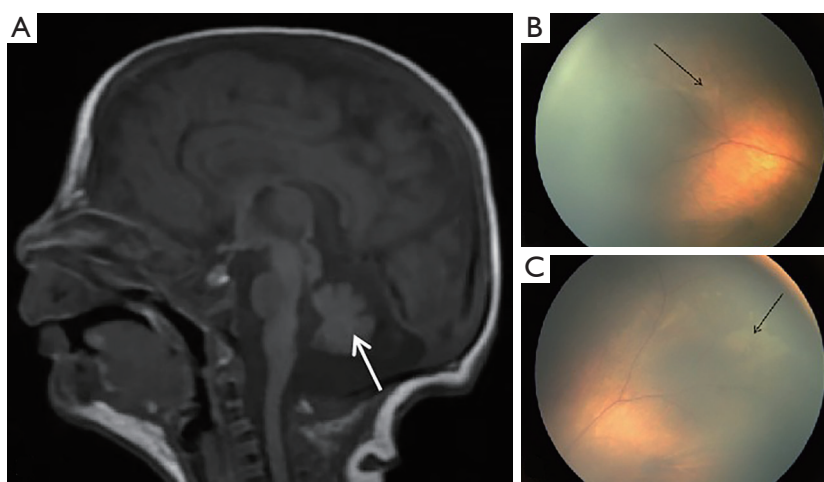


Figure 2 MRI and funduscopy findings of the neonate with *ASXL2* pathogenic variant at six days of age. (A) A small cerebellum with a diameter of 45.7 mm on MRI (indicated by white arrow). Funduscopy of the right eye (B) and left eye (C). The black arrows indicated bilateral paving-stone-like white lesions in the retinas. MRI, magnetic resonance imaging.

of insulin, low free fatty acids and beta hydroxybutyrate were 2.1 $\mu\text{U/mL}$, 0.34 and 0.06 mmol/L, respectively. Thirty minutes after glucagon administration, his plasma glucose level increased to 2.3 mmol/L.

He tolerated full enteral feeding orally without cyanosis at the age of 10 days. However, at the age of 19 days (September 27th, 2021) the volume of enteral feeding was decreased, and he required continuous intravenous infusion of dextrose at 9 mg/kg/min because of recurrent hypoglycemia. He was treated with glucagon at 12 $\mu\text{g/kg/hour}$ (September 27th, 2021) which was gradually weaned off and switched to octreotide injection subcutaneously (started at 0.006 mg every 8 hours) at the age of 35 days (October 13th, 2021). Since then, he maintained euglycemia ranging from 3.0 to 5.8 mmol/L and was successfully weaned off intravenous dextrose when he was 41 days old (October 19th, 2021). At the age of 45 days (October 23rd, 2021), he was discharged home on full enteral feeding with additional 2.5 gram of enzymatic rice flour in every 70 mL of breast milk per 3 hour and subcutaneous octreotide injection (0.004 mg/kg every 8 hours). *Figure 3* depicted a detailed timeline of the treatment for hypoglycemia.

He was followed-up in outpatient clinics and had no neurodevelopmental delay at the age of 4 months. The detailed clinical characteristics are summarized in *Table S1*. Based on the above history, we performed a genetic test.

All procedures performed in this study were in accordance with the ethical standards of the Research Ethics Committee of the Children's Hospital of Fudan

University (CHFudanU_NNICU11) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Molecular studies

DNA samples were sequenced to identify the casual gene with whole-exome sequencing (WES). Genomic DNA samples were extracted from whole blood using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). DNA fragments were enriched for exome sequences using the Agilent SureSelectXT Human All Exon 50-Mb kit. Sequencing was performed on an Illumina HiSeq 2000/2500 platform. The average on-target sequencing depth was 200x. Clean reads were aligned to the reference human genome (UCSC hg19) by the Burrows-Wheeler Aligner (BWA; v.0.5.9-r16). For variant calling, GATK best practice (V.3.2) was employed for single-nucleotide variants (SNVs)/small indels. Variants were confirmed in the proband and the parents, if available, using Sanger sequencing (*Figure 4*). Primers were designed for polymerase chain reaction amplification using Primer Premier 5.0 software. Sequence analysis was performed with Mutation Surveyor (Soft Genetics, State College, PA).

The variants with low quality and out of capture regions were initially filtered out. Then ANNOVAR (9) and

- September 9th, 2021 Born with feeding difficulty, recurrent hypoglycemia and cyanosis
- September 10th, 2021 Admission and parental nutrition
- September 11th, 2021 Partial enteral feeding together with intravenous dextrose
- September 18th, 2021 Full enteral feeding without cyanosis but with recurrent hypoglycemia
- September 19th, 2021 Enteral feeding together with intravenous dextrose
- September 27th, 2021 Continuous glucagon infusion (12 ug/kg.h)
- October 3rd, 2021 Continuous glucagon infusion (10 ug/kg.h)
- October 4th, 2021 Continuous glucagon infusion (9.6 ug/kg.h)
- October 5th, 2021 Continuous glucagon infusion (8.4 ug/kg.h)
- October 6th–12th, 2021 Continuous glucagon infusion (7.2 ug/kg.h)
- October 13th, 2021 Subcutaneous octreotide injection (0.006 mg every 8 hours)
- October 15th, 2021 Subcutaneous octreotide injection (0.01 mg every 8 hours)
- October 17th, 2021 Subcutaneous octreotide injection (0.013 mg every 8 hours)
- October 21st, 2021 Discharge with full enteral feeding (2.5 g enzymatic rice flour in every 70 mL of breast milk per 3 hour) and subcutaneous octreotide injection (0.013 mg every 8 hours)

Figure 3 Timeline of the relevant events and specific treatment.

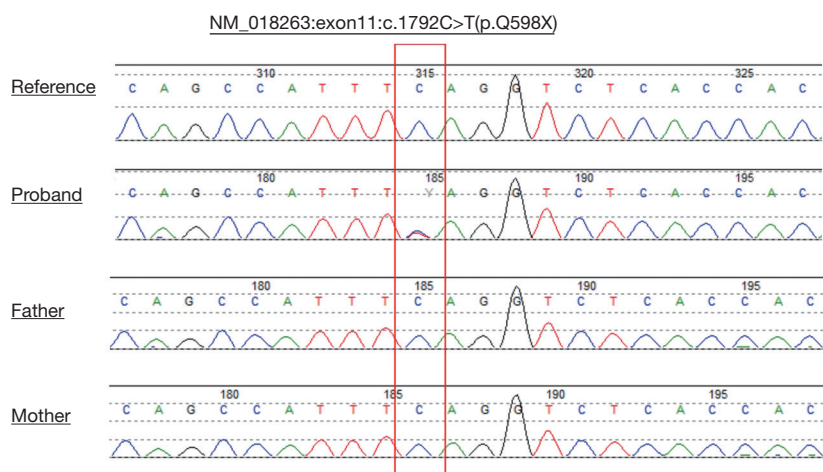


Figure 4 Analysis and results of sanger sequencing of the family.

VEP (10) software were applied to annotate the remain variants with gene information, variant impacts (splicing region, loss of function), scores of missense variant (SIFT, PolyPhen-2, and MutationTaster), population frequencies (our internal database, ExAc, 1000 Genomes and gnomAD) and the classification of the variant in public database (ClinVar and HGMD). After annotation, a second variant filtering, except the variants recorded as pathogenic in our internal list or ClinVar or HGMD, was carried out based on the following criteria: (I) with allele frequency greater than or equal to 2% or with homozygous variant counts greater than or equal to 5 in our internal database, ExAC, 1000 Genome or gnomAD); (II) not predicted as detrimental by

any prediction tools; (III) variants in our black list genes; (IV) do not follow the inheritance mode of the disease gene. Up to this point, a few dozen candidate variants for each sample need further clinical review. Finally, the pathogenicity of the candidate variants was analyzed according to the standards and guidelines recommended by the American College of Medical Genetics and Genomics (ACMG) (11-13). Based on the above strategy, after the first filtering, there were 21 candidate variants left in this patient that need further manual review (Table S2). After the analysis of the pathogenicity of the candidate variants based on ACMG guidelines, only one variant was discovered pathogenic and could be responsible for the phenotypes of the patient. This

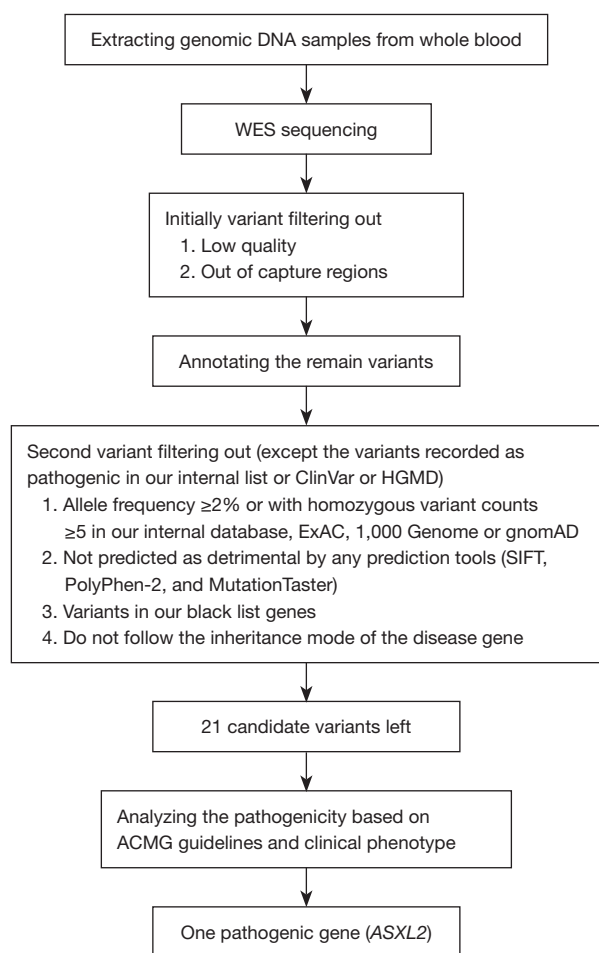


Figure 5 Filtering strategy of variant. WES, whole-exome sequencing; ACMG, American College of Medical Genetics and Genomics.

variant in *ASXL2* is absent in ExAc, 1000 Genomes and gnomAD. A flow chart to illustrate the filtering strategy of variants is given below (Figure 5).

Results

The patient's karyotyping result was normal. The results of trio-WES were returned at the age of 21 days and a heterozygous *de novo* truncating pathogenic c.1792C>T (p.Gln598*) variant in exon 11 of the *ASXL2* gene was identified. This variant was classified as likely pathogenic based on the following evidence: PVS1 Strong [Clinical validity classification of gene is definitive and 13 pathogenic null variants were reported in ClinVar for this gene, across

2 different exons, of which 5 variants in this exon; and this nonsense variant predicted to undergo nonsense-mediated decay and exon is present in biologically-relevant transcript] + PS2_Moderate (*de novo* with confirmed parental relationships in a patient with phenotype consistent with gene but not highly specific) + PM2_Supporting (absent from gnomAD, 1000 Genomes and ExAC population databases) (12,13). Genetic counseling was performed, and he was diagnosed with *ASXL2*-related SHAPNS based on his phenotype and sequencing results.

Literature review and summary of 11 cases

A review of the literature in PubMed was performed using the following terms: “*ASXL2*” and “Shashi-Pena Syndrome”. For patients from one family, the medical records of the other patients from the proband's family were incomplete, thus only the proband of this family was included in this review. The results were checked by two independent authors to exclude duplicate papers and to select those to read in extenso. Every author contributed to writing parts of the manuscript related to her or his specialty. Since 2016, only 12 cases from 10 families have been reported. Ten probands of the families were included in the review.

Demographic birth data of 11 patients with *ASXL2*-related SHAPNS

Among 8 male and 3 female patients, the median age at diagnosis of *ASXL2*-related SHAPNS was 4.6 years, ranging from the age of 21 days to 31 years. *ASXL2* variants (NM_018263.6) are listed as follow: c.1792C>T, p.Gln598* (this paper); c.1225_1228delCCAA, p.Pro409Asnfs*13; c.1288G>T, p.Glu430*; c.2081dupG, p.Gly696Argfs*11; c.2424delC, p.Thr809Profs*32; c.2485C>T, p.Gln829*; c.2472delC, p.Ser825Valfs*16; c.2971_2974delGGAG, p.Gly991Argfs*3; c.4228T>G, p.Cys1410Gly; c.1217dup, p.Glu407* and t(2;11)(p23;q23). The majority of the patients (8/11) had *de novo* truncating mutations. Overall, the median (range) gestational age, birth weight, occipitofrontal circumference and length in this group were 39 weeks (32–42 weeks), 3,000 grams (2,071–4,860 grams), 35.5 cm (34–37 cm) and 49.3 cm (42–59.5 cm), respectively. The majority of the individuals were born at term, with birth parameters appropriate for gestational age. Only 2 patients had macrocephaly at birth. The detailed information is described in Table S1.

Table 1 Clinical synopsis of 11 patients with *ASXL2*-related SHAPNS

Classification	Number (percentage)
Facial and skin features	
Hypertelorism	11 (100.0)
Broad nasal tip	10 (90.9)
Arched eyebrows	9 (81.8)
V-shaped glabellar nevus flammeus on the forehead	9 (81.8)
Low-set ears	8 (72.7)
Posteriorly rotated ears	7 (63.6)
Proptosis	6 (54.5)
Broad forehead	5 (45.5)
Hirsutism	5 (45.5)
Retrognathia	4 (36.4)
Ptosis	4 (36.4)
Capillary malformations	3 (27.3)
Long face	3 (27.3)
Flat face	1 (9.1)
Other abnormal eye findings	4 (36.3)
Skeletal and/or extremity manifestations	
Deep palmar creases	6 (54.5)
Overlapping toes	3 (27.3)
Brain MRI findings	
Normal	2 (18.2)
Enlarged extra-axial spaces	2 (18.2)
White matter volume loss	2 (18.2)
Ventriculomegaly	2 (18.2)
Small cerebellum	1 (9.1)
Choroid plexus papilloma	1 (9.1)
Cardiovascular findings	
Normal	1 (9.1)
Atrial septal defect	4 (36.4)
Patent foramen ovale	3 (27.3)
Patent ductus arteriosus*	1 (9.1)
Mitral and tricuspid regurgitation	1 (9.1)
Tricuspid insufficiency*	1 (9.1)
Pericardial effusion*	1 (9.1)
Ventricular ectopy bradycardia	1 (9.1)

*, one patient had evidence of patent ductus arteriosus, patent foramen ovale, mild tricuspid insufficiency, mild pericardial effusion and pulmonary hypertension at 2 months of age and died of heart disease at 16 months of age. SHAPNS, Shashi-Pena syndrome; MRI, magnetic resonance imaging.

Clinical synopsis of 11 patients with *ASXL2*-related SHAPNS

Table 1 shows the common clinical features in 11 individuals with *ASXL2*-related SHAPNS. More than half of the patients shared recognizable facial features, including hypertelorism (11/11), broad nasal tip (10/11), arched eyebrows (9/11), a large V-shaped glabellar nevus flammeus on the forehead (9/11), low-set ears (8/11), posteriorly rotated ears (7/11), proptosis (6/11), and deep palmar creases (6/11). Less than half of them had a broad forehead (5/11), hirsutism (5/11), retrognathia (4/11), ptosis (4/11), capillary malformations (3/11), long faces (3/11) and overlapping toes (3/11).

Four patients had remarkable eye findings, including retinal paving-stone-like white lesions since birth (1/11), pigmentary retinal dystrophy (1/11), mild left optic atrophy recognized at the age of 7 years, ovoid-shaped corneas (1/11) and bilateral presenile cataracts recognized at the age of 24 years (1/11).

Two patients (2/11) had normal MRI findings. The others had MRI findings of enlarged extra-axial spaces (2/11), white matter volume loss (2/11), ventriculomegaly (2/11), a small cerebellum (1/11), and choroid plexus papilloma (1/11).

Unremarkable cardiovascular findings were recorded for only 10 patients. The other had non-life-threatening heart problems, including an atrial septal defect (4/11), a patent foramen ovale (3/11), mild mitral and tricuspid regurgitation (1/11) and ventricular ectopy bradycardia (1/11). One patient had evidence of patent ductus arteriosus, patent foramen ovale, mild tricuspid insufficiency, mild pericardial effusion and pulmonary hypertension at the age of 2 months and died of heart disease at the age of 16 months. The detailed clinical characteristics are summarized in *Table S1*.

Major clinical issues and prognoses of 11 patients with *ASXL2*-related SHAPNS

Table 2 illustrates the major clinical issues and prognosis of the patients at the median follow-up age of 4.1 years, ranging from the age of 4 months to 31 years, one of whom died of heart disease at the age of 16 months.

Feeding difficulties were common in 10 patients after birth, the majority of which were transient (8/10), one of which caused by GERD, one of which caused by intestinal obstruction treated with Meckel's diverticulectomy, six of which with unknown reasons, and only one patient required persistent total parental nutrition and life-long gastrojejun

Table 2 Prognosis of 11 patients with *ASXL2*-related SHAPNS at follow-up

Prognosis	Number (percentage)
Feeding difficulties	10 (90.9)
Developmental delay	10 (90.9)
Macrocephaly at follow-ups	8 (72.7)
Skeletal and/or extremity manifestations	8 (72.7)
Hypotonia	8 (72.7)
Seizure activities	6 (54.5)
Hypoglycemia	6 (54.5)
Appendicular hypertonia	2 (18.2)
Growth retardation	2 (18.2)

SHAPNS, Shashi-Pena syndrome.

feeding due to severe GERD.

Hypoglycemia was another major issue in 6 patients after birth. One patient with chromosomal balanced translocation had transient hypoglycemia after birth, which resolved quickly with 10% dextrose supplementation. The other neonatal patient of onset transient hypoglycemia with a heterozygous variant had episodic early morning hypoglycemia starting at the age of 2.5 years of unknown causes with inappropriate insulin level, treated with regular feeding to avoid fasting periods. The other four patients, including our patient, all had persistent hypoglycemia.

The underlying causes and therapies for persistent hypoglycemia included an inappropriate insulin level (2/4) treated with octreotide or continuous gastric tube feedings, ketotic hypoglycemia and central adrenal insufficiency (1/4) between the age of 12 months and 24 months treated with gastrojejunal feeding and glucocorticoid replacement, and an unknown etiology (1/4), where the patient received regular feeding to avoid fasting periods.

Only 2 patients had macrocephaly at birth, and this number increased to 8 at follow-ups. Axial hypotonia and appendicular hypertonia occurred in 8 and 2 patients in this group, respectively. Skeletal and/or extremity issues were common in this group, found in 8 patients, and included overlapping toes (3/11), osteoporosis (3/11), kyphosis (2/11), advanced bone age (2/11), fractures (2/11), scoliosis (1/11) and torticollis (1/11) with the youngest age of 4 months old.

Both febrile and nonfebrile seizure activity was recognized in 6 patients, with the earliest age at onset being 1.2 years. Among which 2 male had febrile seizure at 1.2 years and 8.5 years, 3 (2 male and 1 female) had non-

febrile seizure activity at 4, 13 and 23 years and 1 female had both febrile and non-febrile seizure activity at 4 years. One patient had suspected seizure activity but not confirmed by EEG was not included. A total of 90.9% (10/11) of the patients had developmental delay at follow-ups, with the earliest age being 4 months. Two patients who had early normal MRI findings but developed nonfebrile seizures at the age of 13 years and 23 years also had development delay, which indicated the possibility of neurodevelopmental regression in this group.

Discussion

This study also expands the detailed neonatal phenotype spectrum of *ASXL2*-related SHAPNS, provides further confirmation of the previously described phenotypes attributed to pathogenic variants in *ASXL2* and outlines treatments for persistent hypoglycemia. Through the literature review, we identified an additional 10 individuals from 10 different families who had pathogenic variants in this gene, providing a clearer picture of the spectrum of clinical features and prognoses and a better understanding of *ASXL2*-related SHAPNS.

ASXL2 is one of the human homologs of the *Drosophila* additional sex combs (*ASX*) gene, which is an enhancer of the trithorax and polycomb (ETP) gene and is likely to act as a histone methyltransferase in complexes with other proteins (14). *ASXL2* is located on chromosome 2p23 and is associated with lipogenesis, heart morphogenesis, skeletal destruction, glucose homeostasis and leukemia (15-19).

As depicted in *Table 1*, individuals with pathogenic variants in *ASXL2* share several features, including hypoglycemia, neonatal feeding difficulties, skeletal and/or extremity manifestations, minor congenital heart disease, axial hypotonia, febrile and nonfebrile seizure activity, developmental delay as early as the age of four months, macrocephaly and a typical facial appearance consisting of arched eyebrows, hypertelorism, a broad nasal tip, a large V-shaped glabellar nevus flammeus on the forehead, low-set ears, posteriorly rotated ears and proptosis. The clinical features of the individuals from one family with a complex chromosomal balanced translocation affecting the *ASXL2* gene were not significant, and the mental developmental prognosis was better than that of individuals with classic de novo truncating mutations in *ASXL2*.

Special attention should be given to *ASXL2*-related persistent hypoglycemia. Neonatal recurrent or prolonged hypoglycemia can lead to cerebral injury and poor

neurodevelopmental outcomes (20). In an animal study, *ASXL2*-deficient mice were found to be insulin resistant and glucose intolerant, indicating that *ASXL2* is a master regulator of glucose homeostasis (18). Thus, tight control of glucose levels is of utmost importance in high-risk neonates, including those with *ASXL2*-related SHAPNS. In previous studies, the etiology of hypoglycemia was not clear. Inappropriate insulin levels, ketotic hypoglycemia and central adrenal insufficiency might be the causes.

Our patient underwent diagnostic fasting and glucagon tests, which indicated inappropriately high levels of insulin. *ASXL2* acts as an epigenetic regulator and regulates gene networks in various types of cancers, such as breast cancer, hepatocellular carcinoma and acute myeloid leukemia (14,19,21,22). To date, no patients with SHAPNS have been reported to develop cancer at follow-ups. Octreotide is a long-acting somatostatin analog and is usually prescribed in patients with hypoglycemia due to inappropriate insulin levels (23). Our patient quickly achieved stable glucose levels after octreotide therapy and was successfully weaned off intravenous dextrose. Further studies and close follow-ups to verify the efficacy and advantages of octreotide in the treatment of persistent hypoglycemia are needed.

Patients with *ASXL2* mutations might have optic impairment. In previously reported cases, the patients were diagnosed with *ASXL2*-related SHAPNS beyond the neonatal period; thus, little is known about eye-related manifestations in early life. Only three previously reported cases included descriptions of eye examinations. A 7-year-old male patient who experienced persistent hypoglycemia was noticed to have pigmentary retinal dystrophy and mild left optic atrophy (2). An 8-year-old male child had ovoid-shaped corneas, and another female patient had bilateral presenile cataracts diagnosed at 24 years old, both of whom had transient hypoglycemia (1). Our patient had prolonged hypoglycemia, underwent several funduscopy investigations and was noticed to have persistent bilateral paving-stone-like white lesions of the retinas.

ASXL2 is highly expressed in eyes and plays an important role in genetic pathways that regulate optic development (24,25). A complex phenotype with bilateral chorioretinal, iris colobomas and neurological structural changes was found to be associated with a fused protein partially encoded by the *ASXL2* gene (26), indicating that *ASXL2* might be associated with some optic developmental disorder. Moreover, patients with persistent hypoglycemia were found to have visual impairment (20,27,28). Therefore, long-term follow-ups of the eyes and further clinical reports of individuals regarding

eye investigations are necessary and important.

ASXL2 mutations play an important role in neurological damage. A few patients had MRI findings of enlarged extra-axial spaces (2/11), white matter volume loss (2/11) and ventriculomegaly (2/11). In our patient, MRI at the age of six days revealed a small cerebellum. Additional clinical reports of individuals regarding the structure of the cerebellum are helpful. Here, we found that in addition to these core features, patients with *ASXL2* pathogenic variants tended to have a higher likelihood of having progressive macrocephaly (2/11 at birth and 8/11 at follow-ups) and a possibility of neurodevelopmental regression in patients (2/11) with normal early MRI findings but later development of nonfebrile seizures. These findings suggested that early and regular follow-ups in the neurology and rehabilitation department might be necessary.

Strengths and limitations

This is a rare disease that the numbers of the patients were limited, and the majority of related patients were discovered and diagnosed at an older age. Our patient had the diagnosis at the age of 21 days, leading to the timeliest interventions and treatment for relevant early onset medical issues. This is the first time that octreotide was administered in patients with persistent hypoglycemia secondary to SHAPNS and successfully helped our patient achieve euglycemia without hypoglycemic brain injury. So far, the long-term prognosis of this patient was lacked. Unusual funduscopy results of paving-stone like white-lesion and small cerebellum on the MRI were identified for the first time which required future follow-ups.

Conclusions

Further clinical reports of more neonatal individuals with damaging *ASXL2* variants are necessary to verify the mechanism and optimal treatment of *ASXL2*-related hypoglycemia, neurological damage and optic impairment. With the advent of advanced genomic screening, such as CNGP, we are likely to identify younger patients. Neurological, endocrinological, ophthalmological, and rehabilitative long-term follow-ups of these patients is necessary and important.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tp.amegroups.com/article/view/10.21037/tp-22-220/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the Research Ethics Committee of the Children's Hospital of Fudan University (CHFudanU_NNICU11) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Table S1 Detailed clinical characteristics of 11 patients with ASXL2-related Shashi-Pena Syndrome

Characteristics	Summary	Individual 1 (this paper)	Individual 2 (5) ^a	Individual 3 (1)	Individual 4 (4)	Individual 5 (1)	Individual 6 (1)	Individual 7 (3) ^a	Individual 8 (2)	Individual 9 (1)	Individual 10 (1)	Individual 11 (1)
Demographic data												
Age at diagnosis	4.6 years (21 day-31 years)*	21 days	6 months	10 months	3 years	4 years 1 month	4 years 7 months	6 years	7 years	8 years	10 years	31 years
ASXL2 variants	8 had de novo truncating mutations	c.1792C>T, p.Gln598*	c.2485C>T, p.Gln829*	c.2081dupG, p.Gly696Argfs*11	c.1217dup, p.Glu407*	c.2472delC, p.Ser825Valfs*16	c.1225_1228delCCAA, p.Pro409Asnfs*13	t(2;11)(p23;q23)	c.4228T>G, p.Cys1410Gly	c.2424delC, p.Thr809Profs*32	c.2971_2974delGGAG, p.Gly991Argfs*3	c.1288G>T, p.Glu430*
Sex	Male 72.7% (8/11)**	Male	Male	Male	Male	Male	Female	Female	Male	Male	Male	Female
Gestational age	39 weeks (32 - 42)*	40 ⁺² weeks	34 weeks	39 weeks	Term	33 ⁺⁶ weeks	40 ⁺² weeks	39 ⁺⁵ weeks	32 weeks	35 weeks	37 weeks	42 weeks
Birth weight	3,000 g (2,071-4,860)*	3,030 g	2,100 g	4,860 g	N/A	2,071 g	3,300 g	2,715 g	N/A	3,900 g	2,140 g	3,000 g
Birth length	49.3 cm (42-59.5)*	48 cm	42 cm	59.5 cm	N/A	N/A	53 cm	49cm	N/A	52.1 cm	48 cm	49.6 cm
OFC	35.5 cm (34-37)*	36 cm	N/A	37 cm	N/A	N/A	35.5 cm	N/A	N/A	34 cm	N/A	34.5 cm
Macrocephaly at birth	18.2% (2/11)**	Yes	N/A	Yes	N/A	No	No	No	No	No	No	No
Clinical manifestations after birth												
Feeding difficulties	90.9% (10/11)**	Yes, transient	Yes, at 2 months of age	Yes, transient	Yes, transient	Yes, transient	Yes, transient	Yes, transient	Yes, persistent	Yes, transient	Yes, transient	N/A
Causes for feeding difficulties		GERD	N/A	N/A	Intestinal obstruction treated with Meckel's diverticulectomy	N/A	N/A	N/A	GERD	N/A	N/A	N/A
Hypoglycemia	54.5% (6/11)**	Yes, persistent	No	Yes, persistent	Yes, transient	N/A	Yes, transient neonatal hypoglycemia and episodic early morning hypoglycemia starting at 2.5 years	No	Yes, persistent between 12-24 months of age	N/A	N/A	Yes, transient
Potential cause hypoglycemia	2 inappropriate insulin level, 1 ketotic hypoglycemia and central adrenal insufficiency	Inappropriate insulin level	N/A	Unknown cause	Unknown cause	N/A	Inappropriate insulin level, low free fatty acids and ketones	N/A	Ketotic hypoglycemia, central adrenal insufficiency at 9 years of age	N/A	N/A	Unknown cause
Therapy for hypoglycemia	1 octreotide intracutaneously, 1 10% dextrose intravenously, 1 continuous feeding via gastric tube, 1 gastro-jejunal feeding with glucocorticoid replacement 1 regular feeding to avoid fasting periods	Octreotide	N/A	Continuous feedings via gastric tube	N/A	N/A	Eating regularly and avoiding long fasting periods.	N/A	Total TPN supplementation since 6 months and gastro-jejunal tube decompression as needed; Glucocorticoid replacement.	N/A	N/A	10% dextrose
Prognosis at follow-up												
Age at follow-up	4.1 years (4 months - 31 years)*	4 months	16 months	4 months	4 years	4 years 1 month	4 years	6 years	13 years	8.5 years	7 years 10 months	31 years
Developmental delay	90.9% (10/11)**	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Macrocephaly at follow-up	72.7% (8/11)**	No	N/A	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes
Hypotonia	72.7% (8/11)**	No	Yes	Yes	Yes	Yes	Yes, axial	No	Yes, axial	Yes	Yes	No
Seizure activities (SA) in infancy	54.5% (6/11)**; 2 male had febrile SA at 1.2 years and 8.5 years, 2 (male and female) had non-febrile SA at 13 years and 23 years, 1 female had both febrile and non-febrile SA at 4 years	No SA at 4 months	No	No SA at 4 months	Yes, treated with sodium valproate.	Yes, febrile SA at 14 months of age	Yes, febrile and non-febrile at 4 years, treated with sulthiame	No	Yes, non-febrile SA at 13 years, treated with lacosamide and phenobarbital	Yes, febrile seizure at 8.5 years	No, suspected SA not confirmed with EEGs at 7.5 years	Yes, epilepsy at 23 years
Hypertonia	18.2% (2/11)**	No	No	No	No	No	Yes, appendicular	No	Yes, appendicular	No	No	No
Growth retardation	18.2% (2/11)**	No	Yes	No	N/A	No	No	Yes	No	No	No	No
Clinical synopsis												
Facial features												
Hypertelorism	100.0% (11/11)**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Broad nasal tip	90.9% (10/11)**	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Arched eyebrows	81.8% (9/11)**	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
V-shaped glabellar nevus flammeus	81.8% (9/11)**	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Low-set ears	72.7% (8/11)**	Yes	N/A	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Posteriorly rotated ears	63.6% (7/11)**	Yes	N/A	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes

Table S1 (continued)

Table S1 (continued)

Characteristics	Summary	Individual 1 (this paper)	Individual 2 (5) [#]	Individual 3 (1)	Individual 4 (4)	Individual 5 (1)	Individual 6 (1)	Individual 7 (3) [§]	Individual 8 (2)	Individual 9 (1)	Individual 10 (1)	Individual 11 (1)
Proptosis	54.5% (6/11)**	Yes	No	Yes	No	Yes	No	No	Yes	Yes	Yes	No
Deep palmar creases	54.5% (6/11)**	Yes	No	Yes	Yes	No	Yes	No	No	Yes	N/A	Yes
Broad forehead	45.5% (5/11)**	Yes	No	Yes	No	Yes	Yes	No	Yes	No	No	No
Hirsutism	45.5% (5/11)**	Yes	Yes	No	Yes	No	Yes	No	No	No	No	Yes
Retrognathia	36.4% (4/11)**	Yes	No	Yes	No	Yes	Yes	No	No	No	No	No
Ptosis	36.4% (4/11)**	No	No	No	Yes	No	Yes	No	No	Yes	No	Yes
Capillary malformations	27.3% (3/11)**	No	No	Yes	No	No	Yes	No	No	Yes	No	No
Long face	27.3% (3/11)**	No	No	No	No	Yes	No	No	Yes	Yes	No	No
Flat face	9.1% (1/11)**	No	No	No	No	No	Yes	No	No	No	No	No
Other abnormal eye findings	36.4% (4/11)**	Yes, paving stone like white lesions since birth	N/A	N/A	N/A	N/A	N/A	N/A	Yes, pigmentary retinal dystrophy, mild left optic atrophy at 7 years	ovoid shaped corneas	N/A	Bilateral presenile cataracts at 24 years old
Skeletal and/or extremity manifestations												
Overlapping toes	27.3% (3/11)**	Yes, toe 2 overlapping 3; toe 4 overlapping 5	No	No	No	Yes, toe 2 overlapping 4	No	No	Yes, toe 2 overlapping 3	No	N/A	No
Osteoporosis	27.3% (3/11)**	No	No	No	No	Yes	No	Yes	No	No	N/A	Yes
Kyphosis	18.2% (2/11)**	No	No	Yes	No	No	No	No	Yes	No	N/A	No
Advanced bone age	18.2% (2/11)**	No	No	No	No	No	No	No	No	Yes	N/A	Yes
Fractures	18.2% (2/11)**	No	No	No	No	Yes, at 39 months	No	No	Yes	No	N/A	No
Scoliosis	9.1% (1/11)**	No	No	No	No	No	Yes	No	No	No	N/A	No
Torticollis	9.1% (1/11)**	No	No	No	No	Yes	No	No	No	No	N/A	No
Cardiovascular findings												
Normal	9.1% (1/11)**	No	No	No	N/A	N/A	No	No	No	No	N/A	Yes
Atrial septal defect	36.4% (4/11)**	Yes	No	Yes	N/A	N/A	Yes	No	No	Yes	N/A	No
Patent Foramen Ovalle	27.3% (3/11)**	Yes	Yes	No	N/A	N/A	No	No	No	Yes	N/A	No
Other cardiovascular problems	27.3% (3/11)**	No	Yes, patent ductus arteriosus, mild tricuspid insufficiency, pulmonary hypertension, small pericardial effusion	No	N/A	N/A	No	Yes, mild mitral and tricuspid regurgitation	Yes, bradycardia, ventricular ectopy	No	N/A	No
Brain MRI findings												
Normal	18.2% (2/11)**	No	N/A	No	N/A	No	N/A	No	Yes	No	No	Yes
Enlarged extra-axial spaces	18.2% (2/11)**	No	N/A	Yes	N/A	Yes	N/A	No	No	No	No	No
White matter volume loss	18.2% (2/11)**	No	N/A	No	N/A	No	N/A	No	No	Yes	Yes	No
Ventriculomegaly	18.2% (2/11)**	No	N/A	No	N/A	No	N/A	Yes	No	No	Yes	No
Small cerebellum	9.1% (1/11)**	Yes	N/A	No	N/A	No	N/A	No	No	No	No	No
Choroid plexus papilloma	9.1% (1/11)**	No	N/A	Yes	N/A	No	N/A	No	No	No	No	No

[#], This patient was reported to have minor ear abnormalities and congenital foot deformity but without details. He died of heart disease at 16 months of age. [§], Only the female proband of the family was included in the review. *, median (range). **, percentage (case/total number of patients). OFC, occipitofrontal circumference; N/A, not available; GERD, gastro-esophageal reflux disease.

Table S2 Candidate variants of the neonate in this paper

Gene	Location	Mutation	Zygosity	Disease	Inheritance	ExAC (AC Hom)	HGMD	Source
<i>ACADSB</i>	chr10:124810704	NM_001609:exon9:c.1128+3_1128+7del	Heterozygous	2-methylbutyrylglycinuria, [MIM:610006]	AR	0 0	DM?-related	De novo
<i>ADGRV1</i>	chr5:89989749	NM_032119:exon33:c.7176C>T(p.S2392S)	Heterozygous	Usher syndrome, type 2C, [MIM:605472]; Usher syndrome, type 2C, GPR98/PDZD7 digenic, [MIM:605472]	AD/AR/DD/Digenic	402 0	DM	Paternal
<i>ASXL2</i>	chr2:25972633	NM_018263:exon11:c.1792C>T(p.Q598X)	Heterozygous	Shashi-Pena syndrome, [MIM:617190]	AD	0 0		De novo
<i>BRCA2</i>	chr13:32971119	NM_000059:exon26:c.9586A>G(p.K3196E)	Heterozygous	Fanconi anemia, complementation group D1, [MIM:605724]	AD/AR	12 0	DM?	Maternal
<i>COL4A3</i>	chr2:228177642	NM_000091:exon52:c.*1057_*1058del	Heterozygous	Hematuria, benign familial, [MIM:141200]; Alport syndrome 3, autosomal dominant, [MIM:104200]; Alport syndrome 2, autosomal recessive, [MIM:203780]	AD/AR	0 0		De novo
<i>KLHL10</i>	chr17:39998122	NM_152467:exon2:c.242A>T(p.N81I)	Heterozygous	Spermatogenic failure 11, [MIM:615081]	AD	68 0	DM?	Maternal
<i>LPIN2</i>	chr18:2937867	NM_014646:exon7:c.991G>T(p.A331S)	Heterozygous	Majeed syndrome, [MIM:609628]	AR	138 0	DM?	Maternal
<i>NKX2-5</i>	chr5:172659738	NM_004387:exon2:c.809G>A(p.C270Y)	Heterozygous	Hypoplastic left heart syndrome 2, [MIM:614435]; Tetralogy of Fallot, [MIM:187500]; Hypothyroidism, congenital nongoitrous, 5, [MIM:225250]; Conotruncal heart malformations, variable, [MIM:217095]; Ventricular septal defect 3, [MIM:614432]; Atrial septal defect 7, with or without AV conduction defects, [MIM:108900]	AD	7 0	DM	Paternal
<i>PROS1</i>	chr3:93624903	NM_000313:exon5:c.431C>A(p.T144N)	Heterozygous	Thrombophilia due to protein S deficiency, autosomal dominant, [MIM:612336]; Thrombophilia due to protein S deficiency, autosomal recessive, [MIM:614514]	AD/AR	92 2	DM	Maternal
<i>PSEN1</i>	chr14:73602899	.	Heterozygous	Pick disease, [MIM:172700]; Alzheimer disease, type 3, with spastic paraparesis and apraxia, [MIM:607822]; Dementia, frontotemporal, [MIM:600274]; Cardiomyopathy, dilated, 1U, [MIM:613694]; Alzheimer disease, type 3, with spastic paraparesis and unusual plaques, [MIM:607822]; Alzheimer disease, type 3, [MIM:607822]	AD	0 0	DM?	Paternal
<i>SCAPER</i>	chr15:76866620	NM_020843:exon23:c.2717A>G(p.Q906R)	Heterozygous	Intellectual developmental disorder and retinitis pigmentosa, [MIM:618195]	AR	4 0	.	Paternal
<i>SCAPER</i>	chr15:76696901	NM_020843:exon27:c.3431A>G(p.H1144R)	Heterozygous	Intellectual developmental disorder and retinitis pigmentosa, [MIM:618195]	AR	19 0	.	Maternal
<i>SYT1</i>	chr12:79842893	NM_005639:exon11:c.1258G>A(p.V420I)	Heterozygous	Baker-Gordon syndrome, [MIM:618218]	AD	278 1	DM?	Maternal
<i>TNFRSF13B</i>	chr17:16852187	NM_012452:exon3:c.310T>C(p.C104R)	Heterozygous	Immunodeficiency, common variable, 2, [MIM:240500]; Immunoglobulin A deficiency 2, [MIM:609529]	AD/AR	390 1	DM	Maternal
<i>TSPEAR</i>	chr21:46086421	NM_144991:exon1:c.82+44927C>A	Heterozygous	Ectodermal dysplasia 14, hair/tooth type with or without hypohidrosis, [MIM:618180]	AR	1 0	.	Maternal
<i>TSPEAR</i>	chr21:46011414	NM_144991:exon2:c.83-23525G>A	Heterozygous	Ectodermal dysplasia 14, hair/tooth type with or without hypohidrosis, [MIM:618180]	AR	150 1	.	Paternal
<i>TTN</i>	chr2:179519476	NM_001267550:exon191:c.38198_38202delinsT (p.P12733Lfs*213)	Heterozygous	Muscular dystrophy, limb-girdle, autosomal recessive 10, [MIM:608807]; Cardiomyopathy, familial hypertrophic, 9, [MIM:613765]; Tibial muscular dystrophy, tardive, [MIM:600334]; Salih myopathy, [MIM:611705]; Cardiomyopathy, dilated, 1G, [MIM:604145]; Myopathy, myofibrillar, 9, with early respiratory failure, [MIM:603689]	AD/AR	0 0	DM?-related	De novo
<i>TTN</i>	chr2:179441038	NM_001267550:exon326:c.69821G>A(p.G23274D)	Heterozygous	Muscular dystrophy, limb-girdle, autosomal recessive 10, [MIM:608807]; Cardiomyopathy, familial hypertrophic, 9, [MIM:613765]; Tibial muscular dystrophy, tardive, [MIM:600334]; Salih myopathy, [MIM:611705]; Cardiomyopathy, dilated, 1G, [MIM:604145]; Myopathy, myofibrillar, 9, with early respiratory failure, [MIM:603689]	AD/AR	119 0	DM	Maternal
<i>WNT10A</i>	chr2:219757893	NM_025216:exon4:c.1154G>C(p.R385P)	Heterozygous	Schopf-Schulz-Passarge syndrome, [MIM:224750]; Tooth agenesis, selective, 4, [MIM:150400]; Odontoonychodermal dysplasia, [MIM:257980]	AD/AR	0 0	.	Maternal
<i>WNT10A</i>	chr2:219747116	NM_025216:exon2:c.347T>C(p.I116T)	Heterozygous	Schopf-Schulz-Passarge syndrome, [MIM:224750]; Tooth agenesis, selective, 4, [MIM:150400]; Odontoonychodermal dysplasia, [MIM:257980]	AD/AR	20 0	DM	Maternal
<i>WNT10A</i>	chr2:219746977	NM_025216:exon2:c.208C>T(p.R70W)	Heterozygous	Schopf-Schulz-Passarge syndrome, [MIM:224750]; Tooth agenesis, selective, 4, [MIM:150400]; Odontoonychodermal dysplasia, [MIM:257980]	AD/AR	240 2	DM	Paternal