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Case Report

X-linked intellectual developmental disorder with onset of neonatal heart failure: A case report and literature review

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ABSTRACT

X-linked intellectual developmental disorder is a rare X-linked genetic disease, manifested as heart disease, intellectual impairment, and developmental disorders.

We report a male infant who presented with dyspnea after birth. Physical examination on admission revealed poor responsiveness, deep eye sockets, a small mandible, abnormalities of the outer ears, and reduced limb muscle tone. The child was moaning with shortness of breath and a positive three-concave sign without pulmonary rales. The heart sounds were weak with a grade 2/6 diastolic heart murmur. Echocardiography showed an enlarged heart with increased trabeculae in the left ventricular muscle wall. X-linked mental retardation syndrome type 34(MRXS34, OMIM# 300967) was diagnosed after exome sequencing showed a c.1131G > A hemizygous variant in the *NONO* gene. After timely therapy including respiratory support, cardiac glycosides, and diuresis, the child's condition improved and he was discharged at one month of age.

A literature review showed that, to date, 22 live births with X-linked mental retardation have been reported. The *NONO*-related phenotype can be summarized as a neurological and cardiac developmental disorder, which may be accompanied by multisystem malformations. The present case enriches the knowledge of X-linked intellectual developmental syndromes.

MRXS34 is characterized by intellectual disability, motor delay, poor language skills, dysmorphic facial features, cardiomyopathy, and mild abnormalities in brain structure. It is associated with mutations in the *NONO* gene, encoding the non-POU domain-containing octamer-binding protein. Due to the paucity of reports on the disorder, the clinical characteristics and pathological spectrum of *NONO*-related diseases are poorly understood. Here, we report a case of MRXS34 that was admitted to our hospital. Moreover, we review the literature and summarize the clinical characteristics and genotypes of reported patients with MRXS34 to promote an increased understanding of the disease and provide a basis for genetic diagnosis and genetic counseling.

1. Case presentation

A male infant with a gestational age of 37 weeks was admitted to the hospital 10 h after birth due to difficulty in breathing. His weight was3000 g (50th centile), with a length of 48 cm (50th centile), and a head circumference of 31 cm (8th centile).Electrocardiogram monitoring showed that his heart rate was 140 beats/min, the respiration rate was 66 beats/min, and the oxygen saturation was less than 90%. Physical examination on admission showed poor responsiveness, a wide forehead, sunken eye sockets, and malformation of the external auricles. He was moaning with irregular breathing and showed a positive three-concave sign without rales in both lungs. The heart sounds were low in intensity, with a grade 2/6 diastolic heart murmur. The liver was not enlarged. His left foot was swollen and the original nervous reflex could not be elicited (Fig. 1).The parents were healthy and non-consanguinous mating. The mother had 10 pregnancies, of which only two survived, one of which was the patient and the other a healthy 10-year-old boy. The other pregnancies resulted in induced abortions due to unexplained fetal demise.

After admission, the laboratory findings included a B-type natriuretic peptide (BNP) level of 4635.82 pg/mL and a creatine kinase (CK) level of 703 ng/mL. Chest X-ray showed a significantly increased cardiothoracic

Abbreviations: MRXS34, X linked mental retardation type 34 syndrome; BNP, B-type brain natriuretic peptide;; CK, Creatine kinase;; LVNC, Left Ventricular Non Compaction.

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proportion (0.7). Echocardiography showed heart enlargement, with significantly increased trabeculae in the left ventricular muscle wall and abnormality in the motion of the left ventricular wall (EF56%) (Fig. 2). The main findings on the electrocardiogram were ST-T changes (Fig. 3). No obvious abnormalities were found on brain MRI.

After informed consent from the parents, the child underwent exome sequencing which showed that the child had a hemizygous variant c.1131G > A (p.Ala377=) in the *NONO* gene. Sanger sequencing was used to verify variants in the gene in the child and the parents. The mother's X chromosome was found to carry the pathogenic variant (Fig. 4). Based on the child's medical history and relevant laboratory test results, the diagnosis was MRXS34.

After admission, he was given invasive ventilator-assisted ventilation, together with anti-infection, cardiotonic, and diuretic treatments to improve his cardiac function. The child's breathing and heart function gradually improved. On day 33 of hospitalization, he was successfully discharged. He continued to take hydrochlorothiazide, spironolactone, and digoxin at home. The child is now 4.5 months of age, with a weight of 6800 g (35thcentile), a length of 63 cm (40th centile) and a head circumference of 41 cm(15thcentile). The muscle tone of the limbs remains low. Although he can turn over, he is unable to hold his head steady. Echocardiographic reexamination showed increased trabeculae in the ventricular muscle wall and the left ventricular ejection fraction had improved to 61%.

2. Discussionand conclusions

2.1. Literature review

The PubMed, Embase, HGMD, Chinese National Knowledge Infrastructure, and WanFang databases were searched from inception to August 2023 using the following keywords: “X-linked intellectual developmental disorder”, “*NONO* gene”, “congenital heart disease” or “X-linked”, “Intellectual development disorder”, and “congenital heart disease”. This resulted in the extraction of 12 articles written in English, reporting 22 cases of MRXS34 caused by pathogenic variants in the NONO gene [1–12]. Thus, including the present case, 23 cases were reviewed (Table 1). There were 7 cases of fetuses that died in utero or were aborted. The clinical characteristics of the patients are described below.

All patients were male. The age at diagnosis ranged from infant to adult, with two patients diagnosed at birth, most in infancy, and the latest diagnosis was at 29 years old [8].Two patients of severe ventricular dysfunction at 78 days [8] and 3 months respectively [12], while one died of unknown causes at the age of 17 [11]. The remainders are alive.

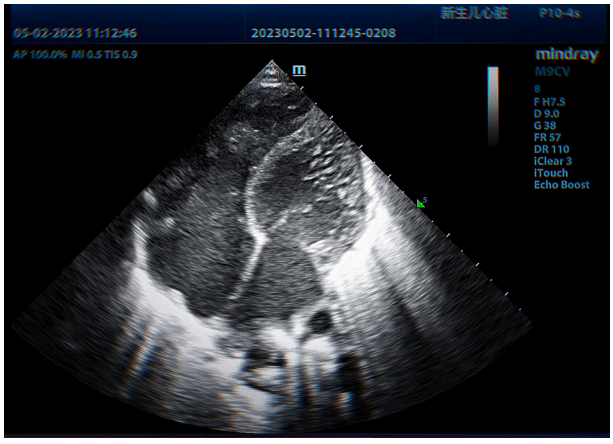

Fig. 2. The enlarged heart and Left ventricular parietal muscle trabeculae increased.

All the surviving patients had developmental delays and 20 patients showed intellectual disability. Twenty patients had large head ratios and 17 had congenital structural and functional abnormalities of the heart, with 16 showing myocardial trabeculae,8 having ventricular septal defects,6 having atrial septal defects, and 4 having patent ductus arteriosus. The remaining abnormalities were Ebstein anomaly, dilated cardiomyopathy, and abnormalities of the aortic arch. 14 patients showed abnormal development of the corpus callosum, and 2 had cerebellar structural abnormalities, while 16 patients had hypotonia and 12 had feeding difficulties or dysphagia. The remaining symptoms included epilepsy, abnormal behavior, skeletal deformities, sunken eyes, deformities of the external ear, hearing impairment, strabismus, and visual impairment (Table 1).

Twenty-one variants in the *NONO* gene associated with the disorder have been identified retrieved (Table 2). Seven of the cases in the literature died in utero or miscarried, all with heart disease. As well as spontaneous abortions, there were also voluntary abortions as the families could not accept the poor prognosis.

3. Discussion

MRXS34 is an X-chromosome disorder that affects multiple systems. It is caused by pathogenic variants in the *NONO* gene. The gene is located at Xq13.1 and consists of 13 exons. *NONO* encodes the non-POU domain-containing octamer-binding protein *NONO*, also known as

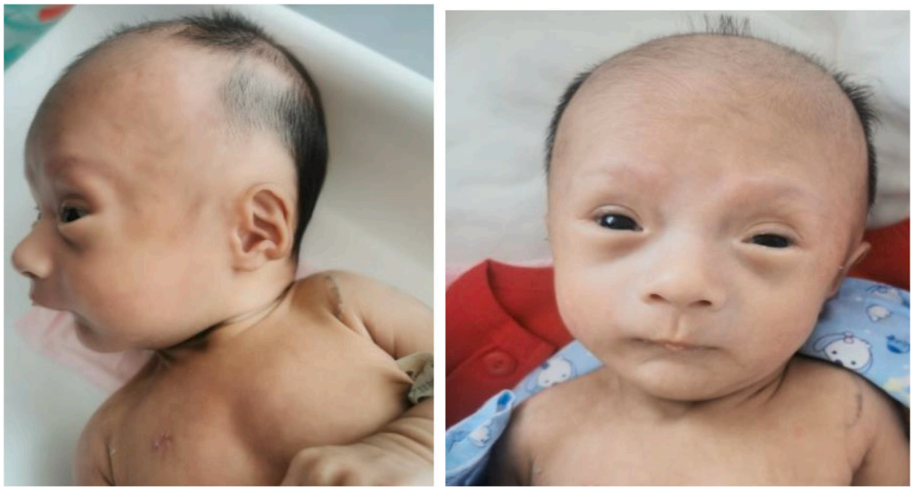

Fig. 1. The patient had wide forehead, sunken eye sockets and abnormality of the helix at 1 month.

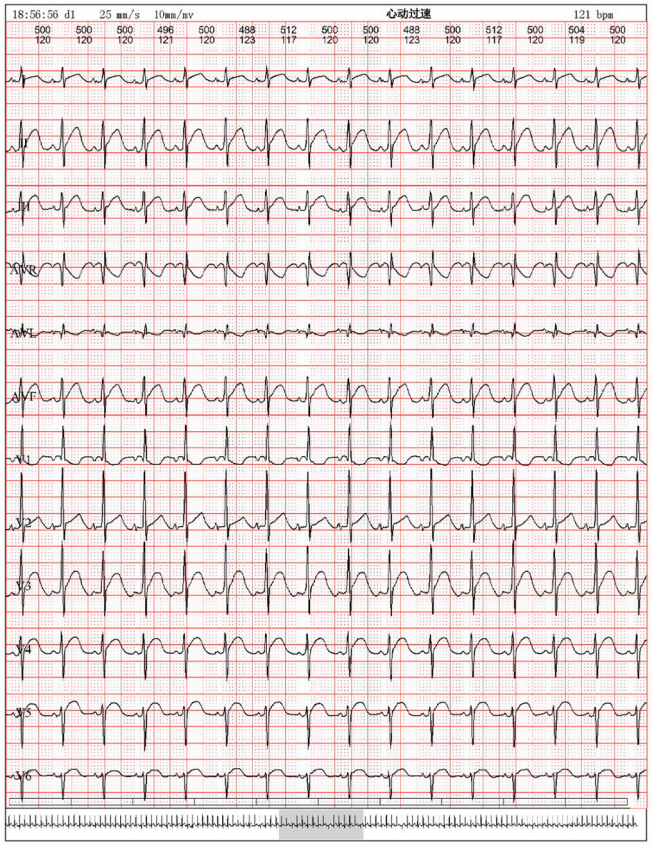

Fig. 3. : ECG showed ST-T changes.

p54NRB, a DNA-binding protein that belongs to a highly conserved family associated with behavior in Drosophila and nucleotide splicing in humans. *NONO* genes encode RNA and DNA-binding proteins and are involved in RNA synthesis, transcriptional regulation, and DNA repair. *NONO* X-linked syndrome is caused by hemizygous loss-of-function variants in the *NONO* gene. Functional studies have shown that the loss of *NONO* protein in cells can lead to both mental retardation and MRXS34 in male patients [8,13,14].

These variants are not included in the gnomAD database [19],and were manually re-classified as likely pathogenic (5/21; 24%) or pathogenic (16/21; 76%) according to criteria of the American College of Medical Genetics (ACMG) criteria [20]. The variant spectrum comprised null variants (13/21; 62.9%), frame shifting variants (5/13; 38.5%), nonsense variants(5/13; 38.5%),missense variants(2/13 ; 15.4%),and one deletion of the first six exons including three non-coding exons. In addition, there were 8 splice site variants (8/21; 38.1%).

The information from all published reports was collated. Twenty-five families have been described, including 23 live births and 7 prenatal cases. All patients were male. Cases that had been prenatally diagnosed and aborted all had heart disease as the major symptom. The mother of our patient had also experienced one intrauterine fetal death and had a history of seven spontaneous abortions, indicating that fetuses with the condition are prone to miscarriage [5]. Nearly half of the patients showed prenatal abnormalities (11/23), with five cases of left Ventricular Non-Compaction (LVNC)in the prenatal period [6] and five cases in which this occurred in the neonatal period [4,5]. The incidence of cardiomyopathy in LVNC patients caused by *NONO* pathogenic variants is significantly higher than the incidence in overall LVNC patients, indicating that LVNC is an early diagnostic clue for the presence of MRXS34 [15,16]. *NONO* pathogenic variants may make males more susceptible to LVNC and CHD. Other cardiac lesions are also frequent in patients with *NONO* pathogenic variants, including ventricular and atrial septal defects and interventricular septum. Further work is expected to elucidate the pathophysiological mechanisms underlying *NONO* and LVNC dysfunction.

The severity of cardiac symptoms in these patients varied, with clinical presentations ranging from asymptomatic to congestive heart failure, atrial and ventricular arrhythmias, thromboembolic events, and sudden cardiac death. Those who developed early disease or had

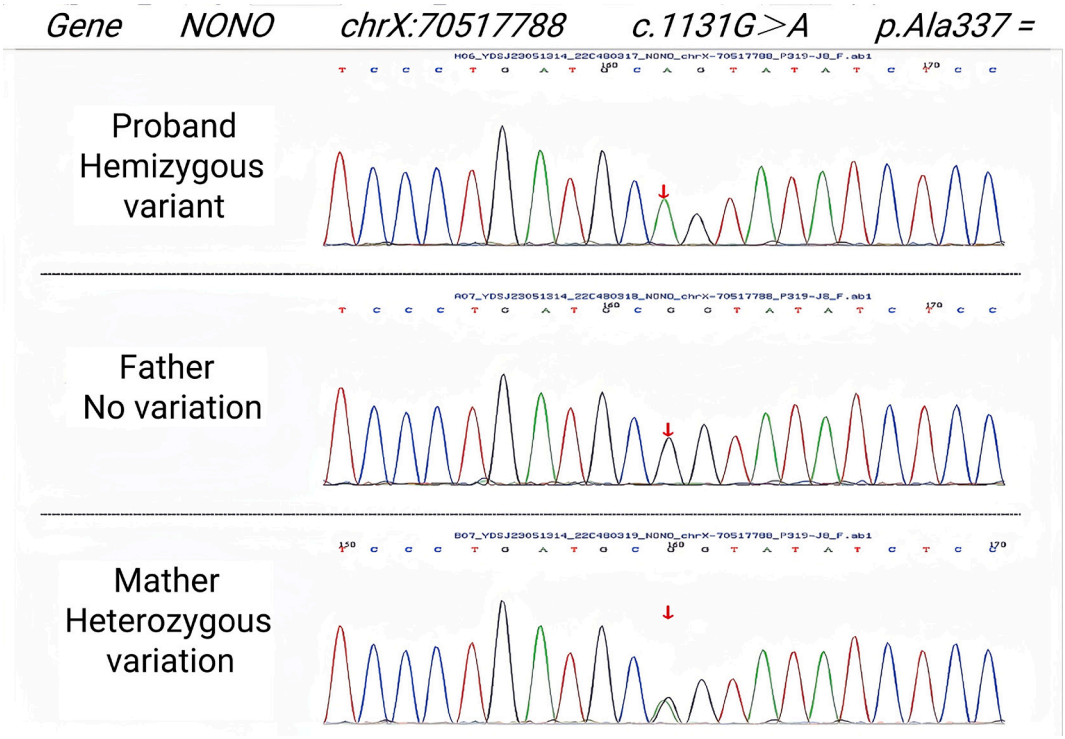

Fig. 4. Genetic studies revealing a point pathogenic variant on *NONO* and the mother carrying the gene.

Table 1
Characteristics and proportions of all reported cases.

Human Phenotype Ontology (HPO)	Live-born individuals	Prenatal case
Abnormality of the cardiovascular system	17/19(89.4%)	7/7(100%)
NCC/cardiac hypertrabeculation	16/19(84.2%)	5/7(71.4%)
VSD	8/19(42.1%)	4/7(57.1%)
ASD	6/19(31.5%)	1/7(14.2%)
PDA	4/19(21.0%)	–
Ebstein anomaly/ dysplastic tricuspid valve	4/19(21.0%)	3/7(42.8%)
idiopathic dilated cardiomyopathy	1/19(5.2%)	
Right aortic arch	2/19(10.4%)	1/7(14.2%)
pulmonic stenosis	0	5/7(71.4%)
Abnormality of the nervous system		
Corpus callosum anomaly	14/19(73.6%)	
Ventriculomegaly	4/19(21.0%)	
Seizures	6/23(26.1%)	
Cerebellar anomaly	2/19(10.5%)	
Global developmental delay	23/23(100%)	
Intellectual disability	20/20(100%)	
Behavioral abnormality	9/23(39.1%)	
Abnormality of the musculoskeletal system		
Muscular hypotonia	16/22(72.7%)	
Skeletal malformation	8/23(34.7%)	
Scoliosis	5/23(21.7%)	
Abnormality of head or neck		
Relative macrocephaly	20/23(86.9%)	
Prominent forehead	12/23(52.1%)	
Abnormality of the nasal tip	9/23(39.1%)	
Deep set eyes	7/23(30.4%)	
Abnormality of the ear		
Abnormality of the outer ear	10/21(47.6%)	
Hearing impairment	5/16(31.2%)	
Abnormality of the eye		
Strabismus	8/21(38.1%)	
Visual impairment	6/19(31.6%)	
Abnormality of the integument		
Sparse scalp hair	3/17(17.6%)	
Hypertrichosis	2/17(11.7%)	
Abnormality of the limbs		
Abnormal foot morphology	9/23(39.1%)	
Abnormal hand morphology	7/23(30.4%)	
Abnormality of the digestive system		
Failure to thrive	12/22(54.5%)	
Gastroesophageal reflux	4/22(18.2%)	
Other abnormalities		
Cryptorchidism	8/21(38.1%)	
Recurrent infections	5/20(40.0%)	
Non-ossifying fibroma	1	
urinary tract malformation	1	
thrombocytopenia	4	

For characteristics visible by clinical examination, 23 was chosen as the common denominator. For features that could only be detected by imaging, individuals who had undergone the relevant examinations were used as the denominator. These values were then used to calculate the ratio of symptom frequencies.

obvious heart disease were more likely to experience rapid disease progression and even death. Of these, two reported cases were relatively serious, with extensive myocardial insufficiency, requiring intensive care, and died within the first three months of life [8,12]. Our patient developed respiratory failure and heart failure after birth and required ventilator support and cardiotonic diuresis to survive. These findings suggest that the phenotype and severity of the disease, as well as the prognosis, varies, with isolated LVNC considered relatively benign, while hypertrophic and dilated LVNC are associated with an increased risk of death [17].

The disease progressed slowly, and the oldest survivor was 29 years old at the time of the last follow-up [8]. All patients showed intellectual and developmental disabilities, along with language and communication disorders. In addition, associations with other neurological diseases or disorders were evident, including epilepsy, autism, anxiety, intentional tremors, and mild ataxia, but there was no obvious developmental regression [3,8,9]. Mircsof suggested that the *NONO* protein regulates synaptic transcription; thus, a pathogenic variant or deletion in the *NONO* gene would likely lead to impaired cognitive function in humans and mice [2]. Damage to the nuclear localization signal (NLS) of proteins can affect subcellular localization and lead to disease [18].A study on subcellular localization in Drosophila showed that variants in *NONO* could destroy its NLS at the C-terminus, resulting in mild hemizygous function loss [9]. However, larger cohorts are needed to confirm the relationship between pathogenic *NONO* variants and neurological symptoms.

Regarding physical appearance, the principal manifestations of patients were facial deformities, with raised forehead, down-sloping palpebral fissures, deep-set eyes, nasal tip, and deformities of the external ear such as small or large low-set ears and ears with spiral misfolding. Macrocephaly is a cardinal feature and becomes more prominent with age. In addition, several reported patients showed developmental malformations of the urinary system, thrombocytopenia, non-ossifying fibroma, and other symptoms, suggesting that the phenotypic spectrum of X-linked intellectual disability syndromes may be wider than currently recognized [11]. Affected children showed feeding difficulties and reflux during their first few years and thus their growth should be carefully monitored. The oldest patient (29 years old) did not show developmental regression [8]. It is recommended that affected children should be evaluated by regular physical examination for growth, development, vision, and audition. Appropriate supportive treatment should be recommended for patients.

The *NONO*-related phenotype can be summarized as a neurological and cardiac developmental disorder, which may be accompanied by multisystem malformations. However the underlying pathogenesis remains unknown, and further clinical data are needed to expand the phenotype and clarify the mechanisms associated with pathogenic *NONO* variants.

Ethics approval and consent to participate

Study approval and ethical clearance was obtained from the the affiliated hospital of Qingdao university. Written consent was obtained from the guardian of the child prior to data collection. All methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication

We obtained the written consent for publication from the guardian of the patient.

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CRediT authorship contribution statement

Hongmin Xi: Project administration, Writing – original draft, Writing – review & editing. **Lili Ma:** Data curation, Investigation. **Xiangyun Yin:** Investigation, Resources. **Ping Yang:** Data curation, Resources. **Xianghong Li:** Methodology, Project administration, Validation. **Liangliang Li:** Project administration.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

The datasets generated and analyzed during the current study are all

Table 2
Types and numbers of genetic variants in the *NONO* gene.

genovariation	site	Number of cases	genovariation	site	Number of cases
c.154 + 5_154 + 6delGT p.Asn52Serfs	exon4	1	c.651-1G > C p.Phe218_Lys249del	exon7	1
c.154 + 9 A > G p.Asn52Serfs*3	exon4	1	c.767G > T p. Arg256lle	exon8	1
c.90_114del p.(Gln30Hisfs*18)	exon4	1	c.1009C > T p.(Arg337*)	exon9	1
c.246_249del p. Pro83Thrfs*7	exon5	3	c.1093C > T p.Arg365*	exon10	2
c.217C > T p.(Arg73*)	exon5	2	c.1131G > A p.Ala377=	Exon10	2
Xq13.1Deletion	first three coding exons	1	c.1171 + 1G > T de novo	exon11	1
c.348 + 2_ 348 + 15del	intron5	1	c.1171 + 1G > A de novo	exon11	1
c.471del p. Gln157Hisfs*18	exon6	2	c1190_1191del p.(Asn397Lysfs *36)	exon12	1
c.457C > T p.Arg153*	exon6	1	c.1394dupC p.Asn466Lysfs*13	exon13	2
c.550C > T p.Arg184*	exon6	1	C.1357c > G. p.(Pro459Ala),	NLS	3
1167_1171 + 9del	exon11	1			

showed the manuscript.

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