

Case Report

Marshall-Smith Syndrome in a Chinese Boy

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Abstract

Marshall-Smith syndrome (MSS) is a malformation disorder that is characterised by accelerated bone maturation, developmental delay and facial deformation. The current medical literature describes more than 50 patients as having MSS, involving the nervous system, musculoskeletal system, respiratory system, connective tissues, eyes, and ears. Here, we report a new patient diagnosed with MSS with an additional finding – a perianal wart and a large scrotum.

Key words

Marshall-Smith syndrome

Introduction

Marshall-Smith syndrome (MSS), initially reported by Marshall in 1971, is a malformation disorder characterised by accelerated bone maturation, developmental delay and facial deformation.¹ Six years ago, researchers reported that de novo mutations in the gene encoding transcription factor nuclear factor 1X (NFIX) was the cause of MSS.² Upper airway obstruction is possibly due to craniofacial and laryngeal anomalies, and aspiration pneumonia results from epiglottitis dysplasia and pharyngeal incoordination. The above two respiratory complications lead to the high mortality of the disease. In recent years, airway support and other supportive treatments have ensured a longer life in these patients. Here, we present a novel phenotype of MSS in a Chinese boy, including a perianal wart and a large scrotum.

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Case Report

A 3.05-kg male infant was born at 39 weeks of gestational age to a 30-year-old G6P2 mother. She had a long history of cigarette smoking, including approximately 7-8 cigarettes per day on average during pregnancy, and turbid amniotic fluid at the time of delivery. The infant was delivered by selective cesarean section. At 18 days of age, the boy was admitted to the neonatal intensive care unit due to progressive dyspnoea. On admission, his weight was 2600 g (5-10th percentile), his length was 50 cm (50-90th percentile), and his head circumference was 31.5 cm (3rd percentile). He had reduced subcutaneous fat and suffered from malnutrition. Continuous positive airway pressure was performed due to inspiratory stridor and retraction. The typical appearance of malformations was as follows: a small anterior fontanel (0.3×0.2 cm), overlapping cranial sutures on his forehead, a low hairline, protruding eyes, blue sclera, megalocornea, corneal clouding (Figure 1A), a normal anterior chamber depth, a right intraocular pressure of 21 mmHg, a left intraocular pressure of 29 mmHg, normal eye movement, a flat midface, an upturned nose, a soft subcutaneous mass on the right side of the nose (Figure 1B), glossoptosis, deep palatine arches (Figure 1C), thin fingers and toes (Figures 1D and 1E), poor muscle tone and reflexes, a perianal wart and a large scrotum (Figure 1F). His complete blood cell count, arterial blood gas, and liver, thyroid and renal function test results were within normal ranges. Echocardiography indicated a patent foramen

ovale. Chest X-ray revealed increased pulmonary vascular markings and cardiomegaly. The patient did not pass the newborn hearing screening. Ultrasound of the eyes revealed deep cupping of the optic discs and horizontal corneal diameters of approximately 16.0 mm. No abnormalities were noted on head magnetic resonance imaging. Laryngoscopy indicated a thickening of the subglottic soft tissue, hypertrophy of the bilateral inferior nasal concha and rhinostenosis.

A molecular analysis was performed by Hangzhou Hi-tech Incubation Park consisting of whole-exome

sequencing of the infant and his parents. No genetic anomalies were found in the parents. A frame shift mutation (c.1156_1160del:p.Q386fs) in exon 8 of the patient's *NFIX* gene was found. However, his parents did not carry this mutation, which indicated a novel mutation in the patient.

Discussion

MSS is a malformation disorder characterised by accelerated bone maturation, growth retardation and facial



Figure 1 Typical appearance of malformations: (A) protruding eyes, blue sclera, megalocornea, and corneal clouding; (B) a flat midface, upturned nose, and a soft subcutaneous mass on the right side of the nose; (C) glossotropism and deep palatine arches; (D) and (E) thin fingers and toes; (F) a perianal wart and a large scrotum.

Table 1 Pathogenicity of gene mutations

Gene	NM_ID ^a	Exon	cDNA	Protein	Heterozygosity	Mutation type	Mutation frequency	Pathogenicity
<i>NFIX</i>	NM_001271043	8	c.1156_1160del	p.Q386fs	Heterozygous	Frameshift	0	Pathogenic

^aThe mRNA serial number from the NCBI serialisation library

malformation. Currently, more than 50 patients have been described as having MSS in the medical literature, with involvement of the nervous system, musculoskeletal system, respiratory system, connective tissues, eyes, and ears. Facial features include low-set ears, a high forehead, an upturned nose, a low nose bridge, a flat midface, eclabium, gingival hypertrophy, irregular tooth locations, an outstretched tongue, and a micromandible. Typical ophthalmic abnormalities consist of shallow orbits, bilateral proptosis, blue sclera, high myopia, glaucoma, visual hypoplasia, and keratohelcosis. Severe dyspnoea results from a combination of aspiration pneumonia and upper respiratory tract obstruction (due to nasal stenosis, atretorrhinia, laryngomalacia, laryngeal stenosis, and a narrow glottis). Several patients have external ear malformations and sensorineural or conductive hearing loss. Regarding bone and connective tissue, we found dysosteogenesis, accelerated bone maturation, a short stature, scoliosis, non-traumatic fractures, osteopenia, and overlapping cranial sutures in the patient described herein. His proximal and middle fingers (toes) were wide, and his terminal fingers (toes) were short and narrow. Abnormal physical growth and behaviors are common in MSS and

include the following: a happy disposition, a gregarious nature, palikinesia, hypophrenia, and linguistic and mental retardation. Some of these patients cannot talk or walk. MSS patients have truncal and peripheral hypertonia, active tendon reflexes, an open mouth caused by oral incoordination, quadriplegia due to cervical stenosis, callosal agenesis, ventricle enlargement, macrogyria, polymicrogyria, septum pellucidum dysplasia, and epilepsy (which is rare). Other prevalent features include hypertrophic pylorostenosis, craniosynostosis, and exomphalos.³

The typical clinical manifestations of MSS in the current patient included hypoevolutism, upper airway obstruction, pneumonia, abnormal appearance, glaucoma, thin fingers and toes, encephalodysplasia, and hearing screening failure. Additionally, we found some novel phenotypes, e.g., a perianal wart and large scrotum. Shaw et al³ reported a case with an anteriorly displaced anus and a case with hypospadias, and Gómez-Santos et al⁴ reported a newly diagnosed MSS patient with additional findings of hypertrophy of the labia minora and the clitoris. With the exception of the above three cases, no cases of facial masses or malformed urethra, genitals, or anus have been reported.

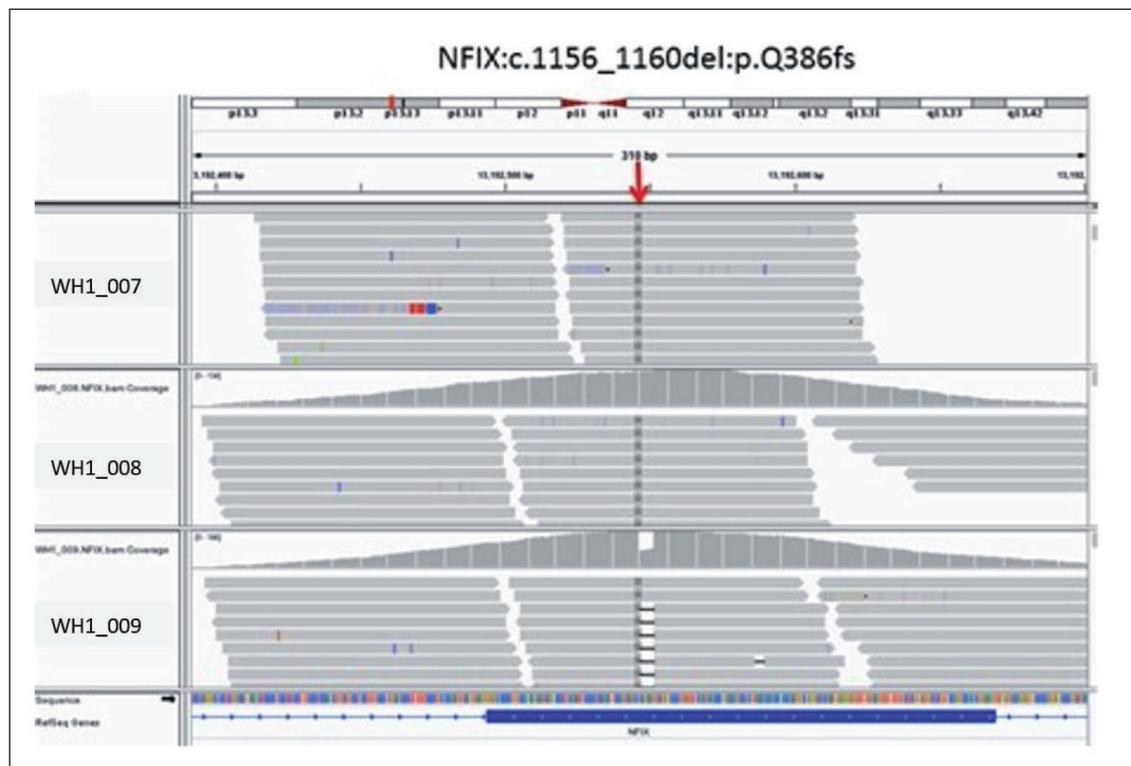


Figure 2 Sequence diagram of the gene mutation sites; WH1_007 father, WH1_009 baby, WH1_008 mother.

According to our survey, this MSS case is the first to be reported in mainland China, demonstrating that Chinese individuals can also suffer from this disorder, i.e., MSS syndrome is a global disease. Moreover, the result revealed a novel mutation (c.1156_1160del) in exon 8 of the *NFIX* gene, which cannot be found in five other SNP databases (dbSNP, ESP, ExAC, HTD and HGVD). However, we did not perform molecular function analysis of this novel mutation ((c.1156_1160del); therefore, the pathogenic significance with this novel mutation in the *NFIX* gene needs to be further studied.

Declaration of Interests

The authors declare that they have no conflicts of interest.

Declaration of Informed Consent

We obtained informed consent to include photographs in this case report.

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