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CASE REPORT

Experience of Mowat–Wilson syndrome prenatal diagnosis for a Chinese family

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Key Clinical Message

Mowat–Wilson syndrome (MWS) is a complex developmental disorder. We report the first prenatal diagnosis provided for a family in mainland China after identifying the causal mutation for the proband. Special focus on MWS-related organs during prenatal ultrasound scan is described which is extremely important for genetic counseling of parents.

Keywords

Causal mutation, Mowat–Wilson syndrome, prenatal diagnosis, *ZEB2*

What's already known about this topic?

- Mowat–Wilson syndrome (MWS, MIM #235730) is a complex developmental disorder caused by heterozygous deletions or truncating mutations of the *ZEB2* gene.

What does this study add?

- We describe the first prenatal diagnosis provided for a family in mainland China after identifying the causal mutation for the proband.
- Genetic testing found no mutation in *ZEB2* and prenatal ultrasound examinations revealed normal nuchal translucency, indirect signs of the normal corpus callosum, and normal male genitalia without hypospadias of the proband's sibling.
- A boy was born at full term who passed meconium at 3 h after birth, and the newborn echocardiogram examination found no obvious heart defects.

Introduction

Mowat–Wilson syndrome (MWS, MIM: 235730) is an autosomal-dominant complex developmental disorder first described by Mowat and colleagues in 1998 in six children with distinctive facial appearance, mental retardation, microcephaly, and short stature [1]. Serial investigations thereafter suggest that several other phenotypes are often associated with MWS such as Hirschsprung disease (HSCR), congenital heart defects, delayed motor development, epilepsy, agenesis of the corpus callosum (ACC), and hypospadias. Deletions or heterozygous pathogenic variants in *ZEB2* (zinc finger homeobox 1B) were identified to underlie this syndrome in 2001 [2]. Since then, more than 260 molecularly proven MWS cases with over 100 different *ZEB2* mutations have been reported [3]. Among which, most mutations were considered to be *de novo* whereas only four families with MWS in siblings have been reported to be likely caused by germ line mosaicism [4]. The prevalence of MWS in Europe and USA is estimated to be 1:50,000–1:70,000 live births, while in Japan, the number reaches 1:90,000 and is approximately 1:130,000 in Hong Kong China. Only one patient has been reported in mainland China previously [5] in addition to the proband in our study [6]. No obvious genotype–phenotype correlation in the MWS patients has been observed. Clinical diagnosis of MWS may occasionally prove to be difficult because of remarkable phenotypic variation and the progress of clinical features with age [7]; thus, molecular diagnosis of *ZEB2* mutation is required to confirm the diagnosis of MWS. This is also important for genetic counseling. Here, we report identification of the causal mutation in a Chinese girl with MWS who deceased at the age of 4 month and 10 days due to heart failure. The prenatal diagnosis was performed for her sibling, and the specific ultrasound features, facial appearance, and genetic findings were reviewed and compared between the two children to better depict the possible prenatal and postnatal morphology findings associated with MWS. We hope that this observation will ultimately help clinicians to raise their suspicion of MWS when similar features are encountered clinically and also allow parents to receive proper prenatal diagnostic tests and counseling in China.

Case Report

In December 2013, a newborn girl was referred to our outpatient department because of abdominal distension and failure to pass meconium. The antenatal course was unremarkable. The parents denied consanguineous marriage, and there was no family history of neurologic or neurodevelopmental anomalies, specifically no history of HSCR or other congenital malformations or genetic abnormalities. On primary examination, no specific facial characteristics were found prompting to any known syndromes, except for the profound microcephaly with a head circumference of 31 cm (<1st centile) (Fig. 1A). Trans-anal pull-through operation was carried out at the age of 23 days to treat her long-segment HSCR. The child deceased at the age of 4 month and 10 days due to severe heart failure and related complications. Whole-genome aCGH analysis and the target gene next-generation sequencing (NGS) were conducted to determine the underlying pathology. A nonsense mutation in *ZEB2*, denoted as p.Arg302Stop at the protein level (Fig. 1C), appeared as the strongest candidate. This substitution creates a premature stop codon (CGA>TGA) in exon seven of the *ZEB2* gene (NM_014795.3), and its presence is consistent with the diagnosis of MWS [8, 9]. Both parents were verified to be wild type, and hence, the patient's mutation was *de novo* [6]. Later on, the proband's mother had her fourth pregnancy (she has the obstetrical history of one induced abortion and one spontaneous abortion before giving birth to the proband) in June 2015 and was seen at 13 + 3 weeks of gestation for first trimester combined screening in early September 2015. First-trimester fetal ultrasound scan revealed a normal nuchal translucency (NT, 1.9 mm for a crown-rump length of 67 mm). And then, the routine mid-trimester fetal ultrasound scan at 21 + 4 weeks showed normal fetal head circumference (HC) of 18.7 cm (50th centile). Visible cavum septi pellucidi (CSP) and the symmetric lateral ventricles (0.6 cm) without teardrop sign or ventriculomegaly were indirect

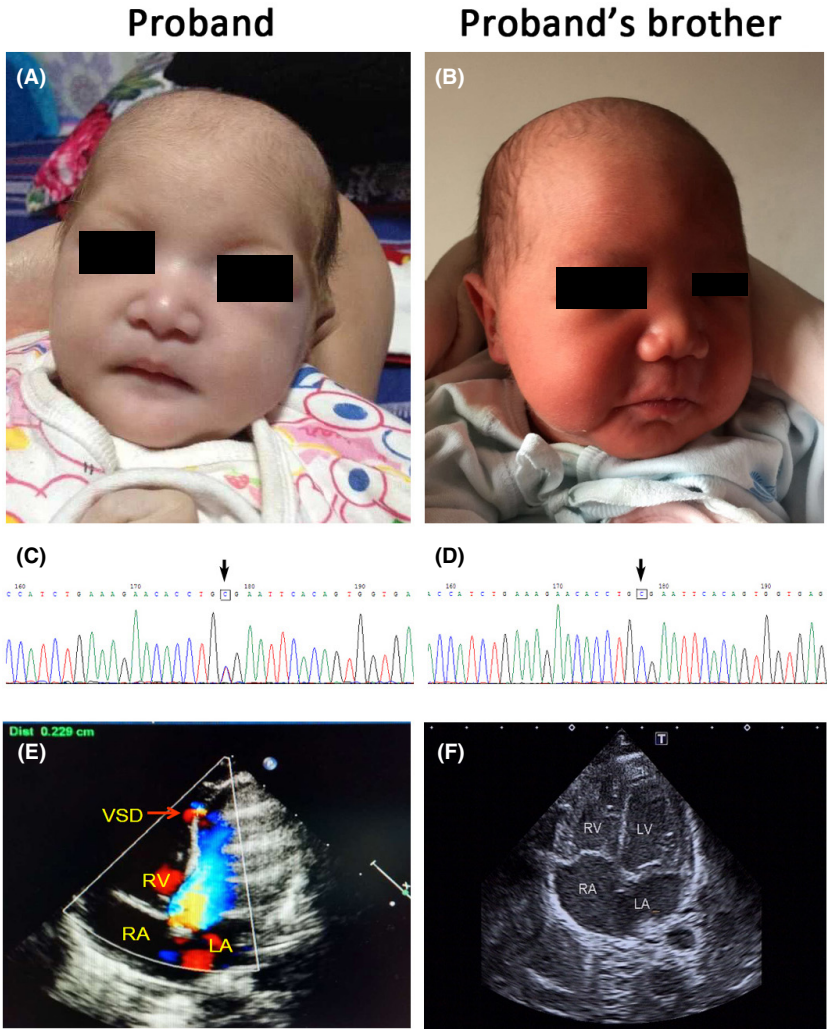

Figure 1. Comparison between the proband and her healthy brother. A–B, facial appearance of the MWS patient and her brother. The patient has large and deep-set eyes, telecanthus, round nasal tip with a prominent columella (beaked nose), short philtrum, frontal bossing, and micrognathia. C–D, a heterozygous mutation of c.904 C>T was detected by target gene NGS and verified by Sanger sequencing in the patient. Amniocentesis was performed at 19 + 1 weeks for her brother and genetic testing demonstrated him to be wild type. E–F, representation of the newborn echocardiogram examination on the patient and her brother. The patient has multiple muscular ventricular septal defect (VSD), multiple ostium secundum atrial septal defect (ASD), persistent ductus arteriosus (PDA), and pulmonary stenosis (PS).

clues to exclude complete agenesis of the corpus callosum (coronal and sagittal planes were not caught to show the corpus callosum because of the fetal breech presentation). Evaluation of the fetal face showed intact upper lip and the presence of nasal bone. Normal male genitalia were seen without hypospadias. Fetal echocardiography screening for cardiac abnormalities at 21 weeks apparently excluded obvious congenital heart defects. Follow-up prenatal scans at 30 and 36 weeks presented no abnormal findings associated with MWS (Fig. 2). Amniocentesis was performed at 19 + 1 weeks for genetic testing which revealed a normal 46, XY karyotype, and wild-type status of the p.Arg302 (Fig. 1D). The mother gave birth to a healthy boy (Fig. 1B) in March 2016 with a birthweight of 3870 g (between the 75th and 85th centile), length of 52 cm (between the 85th and 95th centile) and head circumference of 35 cm (between the 50th and 75th centile). The baby passed meconium at 3 h after birth, and the newborn echocardiogram examination revealed no obvious heart defects (Fig. 1F).

Discussion

To the best of our knowledge, this is the first report describing the prenatal diagnosis provided for a family in mainland China after identifying the causal mutation

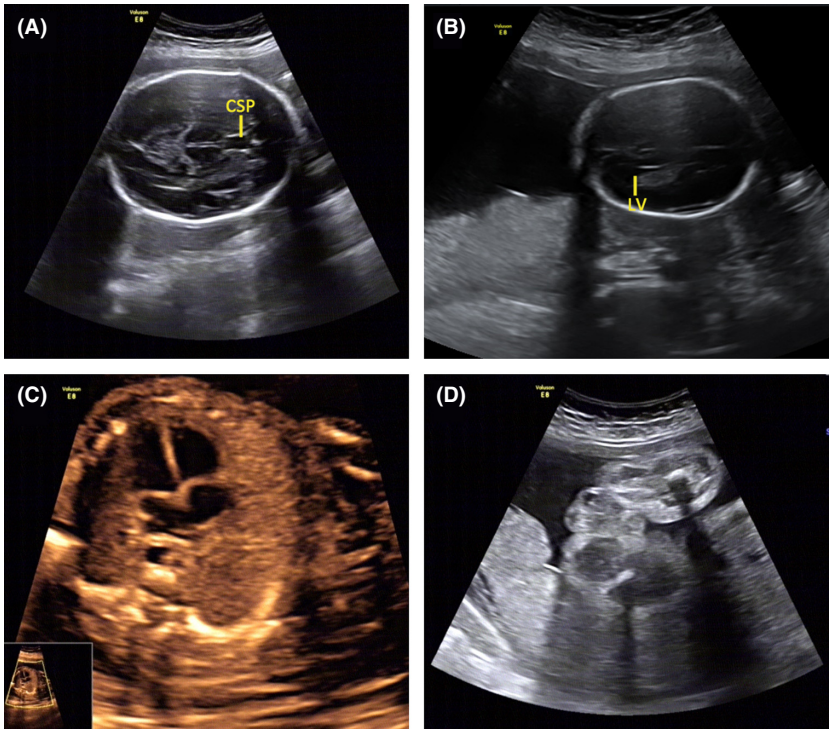

Figure 2. Prenatal ultrasound examinations of the proband's sibling. (A) Axial plane showed the cavum septi pellucid (CSP) in prenatal scan at 30 weeks of gestation. (B) Axial plane showed the lateral ventricle (LV) in prenatal scan at 21 weeks of gestation. (C) Fetal echocardiography at 21 weeks of gestation showed normal four-chamber view. (D) Normal male genitalia showed in scan at 30 weeks of gestation.

for the proband. Our female patient here exhibits mild facial gestalt, HSCR, and severe congenital heart defects. After the molecular genetic diagnosis was made by NGS, we retrospectively reviewed her embryonic examination but all prenatal ultrasound examinations were reported to be "normal". She had a NT record of 1.2 mm for a crown-rump length of 36.4 mm at 10 + 4 weeks of gestation which is too early to provide credible information. Besides, all routine fetal ultrasound scans were normal and no special signs were found prompting the diagnosis of MWS. There is limited knowledge available regarding the prenatal ultrasound features associated with MWS, and this can inevitably result in the delayed diagnosis until postnatal. Up to now, there have been only three reported cases of prenatally diagnosed MWS: two males with copy number deletion from Hong Kong and one male with point mutation from France [10, 11]. Considering the gravity of the situation, molecular diagnosis of the proband and special focus on MWS-related organs (tissues) during prenatal ultrasound scan hence become extremely important for genetic counseling of parents, given the truth that majority of patients with MWS are sporadic cases with a low recurrence risk. We believe that genetic screening of the fetus in the high-risk individuals will become more widely acceptable in the future.

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prenatal and postnatal morphology findings associated with the Mowat–Wilson syndrome. Our purpose, thereafter, is hoping that this observation will ultimately help clinicians to raise their suspicion of MWS when similar features are encountered clinically. We believe that these two papers are essentially different and the current one should not be regarded as a duplicate submission.

Conflict of Interest

None declared.

Authorship

QJ, XZ, HP, and LL: designed the research; XZ: collected all prenatal ultrasound examination images; YM: performed the genetic testing; QL, CZ, YY, ZZ, and PX: collected essential clinical information on both the proband and her younger brother; LS: extracted the genomic DNA; QJ and WC: wrote the paper.

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