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Case Report

Delineation of CLINICAL PHENOTYPE with Interstitial Deletion on Chromosome 2 Including *ZEB2* Gene

Frenny Sheth*, Krati Shah and Jayesh Sheth

FRIGE's Institute of Human Genetics, Ahmedabad, India

***Corresponding Author:** Frenny J Sheth, Cytogenetic and Molecular Cytogenetic Department, FRIGE's Institute of Human Genetics, Ahmedabad, India.

Received: November 17, 2017; **Published:** December 16, 2017

Abstract

Objective: Mowat-Wilson syndrome (MWS) is a rare congenital disorder with specific facial features and multiple congenital anomalies including Hirschsprung disease (HD). In absence of Hirschsprung disease affected individuals may not be recognized until childhood or adulthood.

Case Report: A six-year-old girl presented with multiple congenital anomalies, developmental delay and epilepsy. On examination, she had microcephaly and specific dysmorphic features: telecanthus, deeply set eyes, wide nasal bridge with prominent and rounded nasal tip and thick lower lip. Neuroimaging detected micro bleeds in cerebrum. She had been operated for atrial septal defect. Chromosomal microarray (CMA) detected 6.9 Mb interstitial deletion on chromosome 2 (2q22.12q22.3) encompassing *ZEB2*.

Conclusion: A systematic evaluation is warranted in cases of multiple congenital anomalies with neonatal encephalopathy. The availability of current advanced molecular diagnostic modalities have been extremely fruitful in reaching a definitive diagnosis thereby helping the family understand the prognosis, management and recurrent risk for subsequent pregnancies.

Keywords: *Mowat-Wilson Syndrome; CMA; Hirschsprung Disease; ZEB2*

Abbreviations

MWS: Mowat-Wilson Syndrome; CMA: Chromosomal Microarray; EEG: Electroencephalography; HD: Hirschsprung Disease; HIE: Hypoxic-Ischemic Encephalopathy; MRI: Magnetic Resonance Imaging; *ZEB2*: Zinc Finger E-Box-Binding Homeobox 2

Introduction

Mowat-Wilson syndrome (MWS: # 235730) is a rare genetic syndrome, with a reported prevalence of 1 in 50,000 to 70,000 live births [1]. MWS is inherited as an autosomal dominant pattern and results in to deletions/truncating mutations involving Zinc finger E-box-binding homeobox 2 (*ZEB2*) gene at chromosome 2q proposing haploinsufficiency as the basic pathogenic mechanism of MWS. MWS is characterized by distinctive facial features, heart defects, microcephaly, anomalies of eye and Hirschsprung disease [2,3]. The facial features of MWS include hypertelorism, medial large eyebrows, deep set eyes, large, uplifted and cup shaped ear lobes with prominent rounded nasal tip with low hanging columella. The associated anomalies are: congenital heart defects (patent ductus arteriosus, ventricular septal defect, pulmonary valvular stenosis), cerebral (agenesis of the corpus callosum), pulmonary (artery sling with or without tracheal stenosis), genitourinary (hypospadias, cryptorchidism, vesicoureteric reflux and hydronephrosis), and ocular (microphthalmia) with Hirschsprung disease (HD) [3].

The idiosyncratic facial features such as open mouth, deep seated eyes and triangular face becomes more prominent as the child grows which provide strong clinical suspicion leading to an accurate diagnosis. Features such as severe developmental delay and microcephaly clinically overlaps with features of neonatal encephalopathy. The features overlap with other syndromes like Pitt-Hopkins, Goldberg-Shprintzen megacolon and Smith-Lemli-Opitz syndrome.

Neonatal Encephalopathy, caused by lack of oxygen or intrapartum asphyxia hypoxic-ischemic encephalopathy (HIE) severely modifies the neurological outcome leading to multiple developmental abnormalities. Other causes could be congenital infections, haemorrhage, neurometabolic and undeciphered genetic aetiologies [4]. Genetic aetiologies can only be diagnosed accurately with the help of molecular modalities like clinical exome and/or comparative genome hybridization.

The patient under report is a proband of six years who presented with multiple congenital abnormalities and developmental delay. She was referred to the clinical genetics clinic since the couple was planning for the next pregnancy.

Case Report

The proband was the first child born to non-consanguineous parents. Mother had uncomplicated pregnancy with no history of abortions. Child was born of caesarean section with an APGAR score of 6 at 36 weeks of pregnancy. The child was admitted in NICU for 9 days due to premature delivery and neonatal encephalopathy. The parents and younger sibling of the proband had apparently normal phenotype. The proband was able to hold head by one year, started turning over by 3 years and sitting by 4 years with no history of repeated infections. At the age of six years, her weight, height and head circumference was 13.3 kg, 105 cm and 45 cm (< 3rd centile) respectively. Clinical features include proportionate stature, dysmorphic face and microcephaly. On clinical examination, the proband had widely spaced eyes with broad medial eyebrows and upward gaze, small cup shaped ears with lifted earlobes, prominent nasal bridge with low hanging columella, long face with open mouth appearance, long slender fingers and hypotonia. The skin was normal. Child was operated for atrial septal defect at one year of age. Brain Magnetic Resonance Imaging (MRI) showed remote micro-bleeds in brain stem, cerebellar hemisphere, right basal ganglia, right occipital and temporal lobe without oedema. Abnormal sleep pattern was detected on EEG.

The karyotype was normal at 550-band resolution (46,XX). The child was labelled with "cerebral palsy" and was rehabilitated in a centre for children with intellectual disability due to hypoxic ischemic encephalopathy.

To delineate the cause of the aforesaid features, CMA was planned which detected a 6.9 Mb interstitial deletion on chromosome 2 (2q22.12q22.3) i.e. arr[GRCh37] 2q22.1q22.3 (141,124,951-148,067,216)x1 using CytoScan750K (Affymetrix) array platform following standard and manufacturer's recommendations (Figure 1A). Monosomy for this region encompasses 8 genes*; LRP1B, KYNU, ARHGAP15, GTDC1, ZEB2, ZEB2-AS1, TEX41* and *PABPC1P2*. Haploinsufficiency of the gene *ZEB2* causes Mowat Wilson syndrome. Quantitative-PCR (qPCR) further confirmed 'de novo' origin of the deletion as parents were genotypically normal (Figure 1B). Clinical exome did not find any mutation/s in that region which further established the deletion as the sole cause for the phenotypic manifestation leading to "Mowat Wilson syndrome".

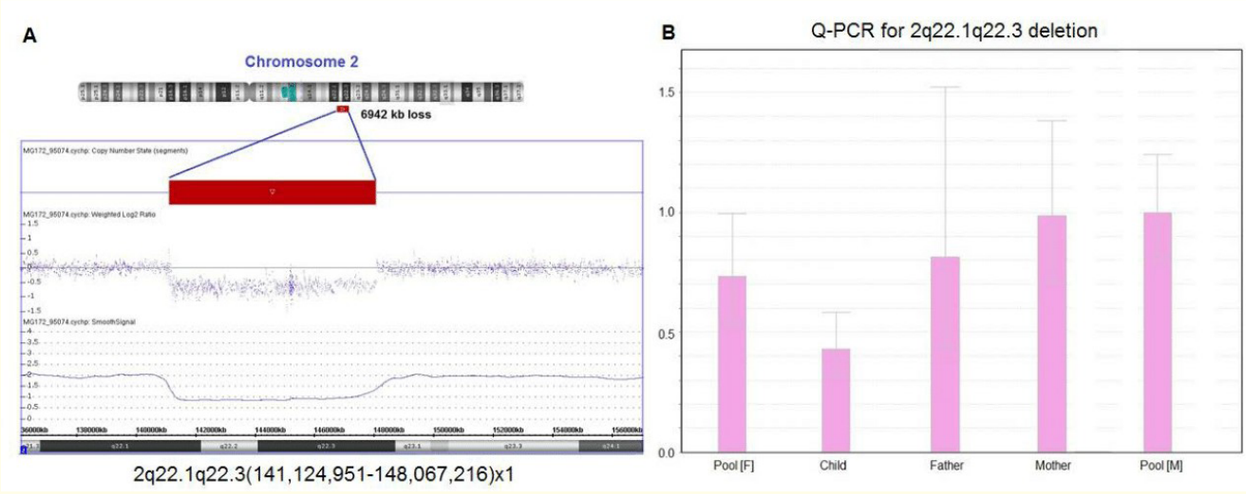

Figure 1: *A) Array-CGH profile of the patient showing a 6.9 Mb loss at 2q22.12q22.3 i.e. arr[GRCh37] 2q22. 1q22.3(141,124,951-148,067,216). B) Deletion was further analysed by qPCR and compared to be of de novo origin as parents were normal.*

Discussion

Mowat Wilson syndrome is a rare genetic entity characterized by distinctive facial features, structural anomalies and intellectual disability with microcephaly [3]. MWS, was first clinically described in 1998 and molecularly delineated in 2001 as heterozygous deletions or truncating mutations of the *ZEB2* (*ZFHX1B*, *SIP1*) gene [1]. Around 200 cases of MWS have been described in the literature with only one from Indian sub-continent pertaining to the anesthetic management of MWS patient [5]. Recently, a case of MWS has also been diagnosed with partial duplication for the first time [6]. Hirschsprung disease is known to occur in 67.6% MWS cases; hence is often diagnosed through HD. However, its absence does not rule out MWS. Twenty percent of patients diagnosed with Mowat-Wilson syndrome have large deletion and can only be diagnosed by FISH (Fluorescence in situ Hybridisation) encompassing that gene or by aCGH [7,8]. Further, Saunders., *et al*. have suggested an economical strategy for the molecular diagnostics of MWS [9].

The deleted *ZEB2* gene is a member of the Drosophila Zfh1 family of 2-handed zinc finger/homeodomain proteins; functions as a DNA-binding transcriptional repressor and has critical roles in normal embryonic neural and neural crest development; usually presents with neurocristopathies at cephalic, cardiac and vagal levels where the formation of midline structures is affected [10,11]. Experiments carried out in the knock-out mice with similar mutations have demonstrated that Smad interacting protein 1 is essential for the development of vagal neural crest precursors and the migratory behaviour of cranial neural crest in the mouse [12].

The distinctive clinical features described in Mowat Wilson syndrome - widely spaced eyes, broad medial eyebrows, low hanging columella, prominent chin and uplifted earlobes with a central depression, and without the classical HD, are present in proband under report. These features clinch the diagnosis of Mowat Wilson syndrome encompassing deletion of the entire *ZEB2* gene [13].

The molecular cytogenetic testing showed a deletion of 6.9 MB with these 8 genes involved: Low Density Lipoprotein Receptor-Related Protein 1B, Kynureninase, Rho GTPase Activating Protein 15, Glycosyltransferase Like Domain Containing 1, *ZEB2* antisense RNA1, Testis Expressed 41 (Non-Protein Coding) and Poly(A) Binding Protein Cytoplasmic 1 Pseudogene 2; few of them like ARHGAP15 are involved in the formation of midline structures.

The deletion sizes and breakpoints vary widely in MWS. There is no correlation between phenotype and the size of deletion up to 5MB, except for individuals with extremely large deletions (>5 Mb) who were more severely affected [14,15].

Recently, Garavelli., *et al*. described a neuroimaging phenotype through MRI Brain where most of the MWS patients had abnormal MRI in the form of anomalies of corpus callosum, hippocampus, white matter and enlargement of cerebral ventricles. However, the patient under report had micro bleeds in various parts of the brain raising suspicion towards HIE [16]. The proband was labelled to have "cerebral palsy" due to neonatal encephalopathic event during birth but the genetics consultation and molecular cytogenetic work up along with its facial gestalt yielded the diagnosis of Mowat-Wilson syndrome.

Conclusion

The diagnosis of Mowat Wilson syndrome in the proband highlights the need to diagnose and pinpoint the etiology in cases of "cerebral palsy" with dysmorphic features. It would not only help discern the prognosis but also the need for further preventive measures. In the present case the systematic analysis of clinical phenotype and molecular karyotype helped to counsel the family that the recurrence risk is low; provided germline mosaicism was excluded. The molecular investigations in a child with neonatal encephalopathy thus expands our understanding of the pathogenic mechanisms, help the family through precise genetic counselling and planning of subsequent pregnancies.

Acknowledgements

We thank the patient and the parents for their cooperation. Authors thanks to Dr. Sunil Trivedi and Dr. Stuti Tiwari for valuable suggestions. This work is partly supported by Gujarat State Biotechnology Mission (GSBTM) [grant no.: GSBTM/MD/PROJECTS/SSA/505/4865/2016-17].

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Volume 6 Issue 4 December 2017