A Novel Partial Duplication of *ZEB2* and Review of *ZEB2* Involvement in Mowat-Wilson Syndrome

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Established Facts

- Mowat-Wilson syndrome is caused by heterozygous mutation of *ZEB2*.
- Over 180 different disease-causing mutations have been reported, including point mutations, deletions, and large chromosomal rearrangements.

Novel Insights

- We present the first reported case of Mowat-Wilson syndrome caused by a partial duplication of *ZEB2*.
- This case expands the types of mutations that can cause Mowat-Wilson syndrome and highlights the significance of partial gene duplications in the pathogenesis of genetic conditions.

Keywords

Mowat-Wilson syndrome · Partial duplication · *ZEB2*

Abstract

Mowat-Wilson syndrome is a rare genetic condition characterized by intellectual disability, structural anomalies, and dysmorphic features. It is caused by haploinsufficiency of the *ZEB2* gene in chromosome 2q22.3. Over 180 distinct muta-

tions in *ZEB2* have been reported, including nonsense and missense point mutations, deletions, and large chromosomal rearrangements. We report on a 14-year-old female with a clinical diagnosis of Mowat-Wilson syndrome. Chromosomal microarray identified a novel de novo 69-kb duplication containing exons 1 and 2 of the *ZEB2* gene. Sequence analysis identified no other variants in this gene. This is the first report of a partial duplication of the *ZEB2* gene resulting in Mowat-Wilson syndrome.

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Mowat-Wilson syndrome (MWS; OMIM 235730) is a rare genetic syndrome seen in 1:50,000–70,000 individuals [Mowat and Wilson, 2010]. First described by Mowat et al. in 1998, it is characterized by intellectual disability, structural anomalies, and dysmorphic features [Mowat et al., 1998; Adam et al., 2013]. Intellectual disability is typically in the moderate to severe range, expressive speech is particularly impaired, and about 70–75% of affected individuals have seizures [Wilson et al., 2003; Garavelli et al., 2009; Cordelli et al., 2013]. Common structural abnormalities include Hirschsprung disease and defects of the heart, genitourinary system, eyes, and brain (anomalies of corpus callosum, hippocampal abnormalities, enlargement of cerebral ventricles, white matter abnormalities, large basal ganglia, cortical and cerebellar malformations) [Adam et al., 2006; Garavelli and Mainardi, 2007; Ariss et al., 2012; Bouchany et al., 2015; Coyle and Puri, 2015; Garavelli et al., 2016]. Distinctive facial features include hypertelorism, broad medial eyebrows, low-hanging columella, prominent or pointed chin, and uplifted earlobes with a central depression [Zweier et al., 2005]. Additionally, individuals with this condition may have growth delay, microcephaly, and musculoskeletal anomalies [Mowat et al., 2003; Adam et al., 2006; Cordelli et al., 2013]. Birth weight and length are typically normal.

MWS is due to dominantly expressed, heterozygous mutations of the zinc finger E box-binding homeobox 2 gene (*ZEB2*, also called *ZFHX1B* or *SIP1*) located on chromosome 2q22.3 [Cacheux et al., 2001; Wakamatsu et al., 2001]. *ZEB2* has 10 exons (exon 1 is noncoding) and is about 165 kb in size [Wakamatsu et al., 2001]. Mutations leading to MWS are thought to result in truncated or absent protein products [Mowat et al., 2003].

More than 180 different disease-causing mutations of *ZEB2* have been reported [Ghoumid et al., 2013]. Loss-of-function point mutations account for 70–80% of MWS diagnoses, while deletions (ranging in size from exonic to multiple contiguous genes) represent another 15–20% [Garavelli and Mainardi, 2007; Saunders et al., 2009]. In rare cases (up to 2% of affected individuals), large chromosomal rearrangements, such as translocations, are identified [Adam et al., 2007]. A few individuals with MWS who harbor missense mutations in *ZEB2* have been reported [Heinritz et al., 2006; Dastot-Le Moal et al., 2007; Ghoumid et al., 2013; Wenger et al., 2014]. There is also a small proportion of individuals who have a clinical diagnosis of MWS but in whom a *ZEB2* mutation is not identified.

We present a case of a 14-year-old female with a de novo 69-kb duplication encompassing part of *ZEB2*. Specifically,

the duplication contained exons 1 and 2. She presented with developmental delays, multiple congenital anomalies, and a clinical diagnosis of MWS based on her medical history, physical features, and clinical presentation. She represents the first published case of an individual with a novel partial duplication of *ZEB2* resulting in MWS.

Patient and Methods

Clinical Report

Our patient was first evaluated genetically at age 14 years at which time she presented with multiple health problems, intellectual disability, and a clinical diagnosis of MWS made at 2 years of age. At age 14 years, her height was 148 cm (<3rd centile), weight was 41.4 kg (5th centile), and her head circumference was 49.3 cm (<3rd centile). Her BMI was 18.9. Congenital anomalies present at birth included cardiac defects (atrial septal defect, patent ductus arteriosus, and a bicuspid aortic valve), midline cutaneous pigment abnormalities, and a sacral dimple. Breast and bottle feeding were unsuccessful, so a nasogastric tube and, later, a G-tube were placed. Shortly after birth, she was diagnosed with global developmental delay and Hirschsprung disease. She has had 2 pull-through surgeries and one colostomy with 47 cm of her colon removed. She currently utilizes laxatives and a predigestive formula for treatment. She has a neurogenic bladder, kidney reflux, incontinence, and a tethered cord (for which surgery was recently performed). A head MRI showed agenesis of the corpus callosum and 3 frontal lobe cysts which diminished in size on repeated brain imaging studies. Seizures developed at age 2 years and are currently medically controlled. At age 10 years, she began consuming food by mouth but did not chew normally. She drinks liquid from a straw.

At age 14 years, her inner canthal distance was 3.7 cm (>97th centile); outer canthal distance was 8.8 cm (40th centile), and her ear length was 5.5 cm (20th centile). Hand length was 15.7 cm (3rd centile) and middle finger length was 6.6 cm (5th centile). She had a square face with medial flare to her eyebrows, a depressed and wide nasal root, hypertelorism with downslanting palpebral fissures, ptosis, strabismus, a short prominent nose with a broad nasal tip, prominent vertical philtral ridges with a short philtrum, full everted upper and lower lips with thinning of upper lip laterally, and downturned corners of the mouth with prognathism. Her ears were posteriorly rotated and fleshy with attached lobes and mild uplifting of the right earlobe (see Fig. 1). The pupils were round and equal in size without scleral icterus. There was a normal range of motion of the neck. The cardiopulmonary system was within normal limits without a heart murmur, rhythm irregularity, or abnormal breath sounds. Her abdomen was soft with no masses or hernias. Major joints had a normal range of motion, but she displayed increased reflexes and tone of both upper and lower body segments as well as poor coordination with a wide-based gait. She walked at age 5 years. She bruises easily and has a history of low platelet counts, first identified at age 10 years. She did not require transfusions but continues to have low platelet count. Cutis marmorata was noted. She was diagnosed with osteopenia and treated for hypothyroidism since age 10 years. She had not begun menstrual cycles.

Fig. 1. Facial frontal (a) and profile (b) views of our patient at age 14 years showing medial flare of the eyebrows, depressed and wide nasal root, hypertelorism with downsloping palpebral fissures, ptosis, short prominent nose with a broad nasal tip, short philtrum, full everted lips, downturned corners of mouth, and posteriorly rotated ears with attached earlobes.

A 3-generation pedigree found our patient's 20-year-old full sister and father are alive and well, and her mother has a history of arthritis, a positive antinuclear antibody titer, irritable bowel syndrome, and melanoma. There is a positive family history of hemophilia type A in a paternal uncle. Consanguinity was denied. Family history is otherwise unremarkable, and no other family members have MWS.

Chromosomal Microarray Analysis

Genetic testing was performed by Lineagen, Inc. (Salt Lake City, UT, USA) using a custom 2.8M probe whole genome chromosome microarray built upon the Affymetrix CytoScanHD® platform (Affymetrix, Santa Clara, CA, USA) with 88,435 additional probes designed to optimize testing for individuals with developmental delay/intellectual disability and/or autism spectrum disorder. The microarray contains both copy number and SNP probes. Coverage for *ZEB2* included 380 probes with an average probe spacing <500 bp. The Affymetrix Chromosome Analysis Suite (ChAS) software was used for copy number detection using standard protocols (Affymetrix). The proband's whole genome was evaluated by chromosomal microarray analysis (CMA) for clinical diagnostic testing. Parental DNA was subsequently submitted, and only the region of interest was evaluated by CMA on a research basis.

ZEB2 Gene Sequence Analysis

This patient's genomic DNA specimen was used for next-generation sequencing. DNA was sheared into small fragments that were end-ligated oligo-adapters, target-enriched for coding exons along with 10 bp of flanking intronic sequence in *ZEB2* (RefSeq NM_014795.3), and amplified by PCR and sequenced using bridge amplification. This targeted gene sequencing strategy interrogates the coding regions and splice site junctions of *ZEB2* only.

Results

CMA identified a novel 69-kb duplication of 2q22.3 including *ZEB2*, arr[hg19] 2q22.3(145,218,807–145,287,401)×3, encompassing exons 1 and 2 as well as intron 1 and part of intron 2 (see Fig. 2, 3). *ZEB2* was the only gene that was partially included in this duplication. Next-generation sequencing of *ZEB2*, performed to rule out the presence of sequence variants contributing to the patient's phenotype, identified no *ZEB2* sequence variants. Parental CMA assessing only the region of interest on chromosome 2 did not identify any CNVs, indicating that the patient's duplication is de novo.

Fig. 2. Chromosomal microarray analysis showing the 69-kb interstitial duplication of chromosome 2q22.3 (chr2: 145,218,807–145,287,401 with hg build 19) found in our patient performed by Lineagen, Inc. *ZEB2* is partially duplicated in this region.

Discussion

A variety of mutations have been described in individuals with MWS. The majority of individuals with MWS have point mutations within *ZEB2* that cause protein truncation and, therefore, loss of function [Dastot-Le Moal et al., 2007]. Within this cohort, germline mosaicism has been suggested and low-level somatic mosaicism reported. The estimated recurrence is 1% when parents test negative for a familial mutation [Zweier et al., 2005]. Additionally, another 15–20% of individuals with MWS have exonic or complete gene deletions of *ZEB2* [Adam et al., 2013].

Most features seen in our patient, including microcephaly, seizures, distinctive facies, and Hirschsprung disease, are consistent with loss or altered function of *ZEB2*. However, chromosomal microarray cannot in itself determine if a partial duplication as observed in this case has disrupted gene function. Interpretation of duplications is always challenging as they may not alter gene function or could lead to increased dosage, gene disruption,

or novel function due to gene fusion [Newman et al., 2015]. This has been demonstrated to be true for duplications of *ZEB2* as well.

Phenotypic consequences from increased dosage of *ZEB2* have been suggested (see Fig. 4; Table 1). Yuan et al. [2015] reported a boy with a de novo 2.9-Mb triplication/duplication involving chromosome 2q22.3 which encompassed the entire *ZEB2* gene as well as *GTDC1*, *TEX41*, and part of *ARHGAP15*. This boy presented with hypotonia, cognitive impairment, behavioral abnormalities, dysmorphic features, and an atrial septal heart defect. While his severe speech impairment and open-mouth appearance are commonly reported in those with MWS, his facial features were significantly different than those seen in MWS.

A duplication of an overlapping 2.1-Mb region was recently reported by Mak et al. [2016]. Just as the duplication reported by Yuan et al. [2015], this duplication fully included *ZEB2* as well as *GTDC1*, *TEX41*, and part of *ARHGAP15*. This 32-year-old woman presented with tetralogy of Fallot, patent foramen ovale, mild intellectual

Fig. 3. Diagram of the putative interstitial duplication within the *ZEB2* locus encompassing exons 1 and 2 and intron 1 with part of intron 2 identified in our patient with Mowat-Wilson syndrome identified with high-resolution chromosomal microarray analysis.

Fig. 4. UCSC Genome Browser view showing the current patient and previously reported copy number gains involving *ZEB2*.

disability, adjustment disorder, dysmorphic features, and a hypernasal voice. Notably, her dysmorphic features were not similar to those seen in MWS.

Seven other individuals with copy number gains involving part or all of *ZEB2* were identified within the

DECIPHER (<https://decipher.sanger.ac.uk>) [Firth et al., 2009; Swaminathan et al., 2012] and ISCA (International Standards for Cytogenomic Arrays) clinical genomic resource databases (<http://dbsearch.clinicalgenome.org>). Direct comparisons between these previous reports and

Table 1. Summary of current patient and previously reported copy number gains involving ZEB2

Current patient	Yuan et al. [2015]		Mak et al. [2016]		DECIPHER		ISC-A		Jiang et al. [2011]			
	chr2:	chr2:	chr2:	chr2:	chr2:	chr2:	chr2:	chr2:	chr2:	chr2:	chr2:	chr2:
Genomic location (hg19)	145,218,807–145,287,401	143,886,436–146,831,592	144,223,416–146,233,601	143,871,587–146,250,058	144,872,506–151,071,331	143,289,922–151,513,185	139,199,730–151,305,514	144,657,717–145,425,705	144,657,717–145,425,705	145,273,511–145,275,501	145,273,849–145,275,269	372.3
Size	69 kb	2.9 Mb	2.1 Mb	2.38 Mb	6.20 Mb	8.22 Mb	12.11 Mb	768 kb	768 kb	203 kb	1.99 kb	1.42 kb
Gain type	triplication/ duplication		duplication		duplication		triplication		duplication		duplication	
	duplication	duplication	duplication	duplication	duplication	duplication	duplication	duplication	duplication	duplication	duplication	duplication
Genes involved	ZEB2	ARHGAP15, LOC101928386, ZEB2-AS1, LINC01412, LOC105373656	ARHGAP15, LOC101928386, ZEB2-AS1, LINC01412, LOC105373656, TEX41	ARHGAP15, LOC101928386, ZEB2-AS1, LINC01412, LOC105373656, TEX41	ARHGAP15, LOC101928386, ZEB2-AS1, LINC01412, LOC105373656, TEX41	ARHGAP15, LOC101928386, ZEB2-AS1, LINC01412, LOC105373656, TEX41	ARHGAP15, LOC101928386, ZEB2-AS1, LINC01412, LOC105373656, TEX41	ARHGAP15, LOC101928386, ZEB2-AS1, LINC01412, LOC105373656, TEX41	ARHGAP15, LOC101928386, ZEB2-AS1, LINC01412, LOC105373656, TEX41	ARHGAP15, LOC101928386, ZEB2-AS1, LINC01412, LOC105373656, TEX41	ARHGAP15, LOC101928386, ZEB2-AS1, LINC01412, LOC105373656, TEX41	ARHGAP15, LOC101928386, ZEB2-AS1, LINC01412, LOC105373656, TEX41
	ZEB2 (part of exon 1 and all of exon 2)	ZEB2 (part of exon 1 and all of exon 2)	ZEB2 (part of exon 1 and all of exon 2)	ZEB2 (part of exon 1 and all of exon 2)	ZEB2 (part of exon 1 and all of exon 2)	ZEB2 (part of exon 1 and all of exon 2)	ZEB2 (part of exon 1 and all of exon 2)	ZEB2 (part of exon 1 and all of exon 2)	ZEB2 (part of exon 1 and all of exon 2)	ZEB2 (part of exon 1 and all of exon 2)	ZEB2 (part of exon 1 and all of exon 2)	ZEB2 (part of exon 1 and all of exon 2)
Other identified genetic changes	none	none	none	none	none	none	none	none	none	none	none	none
	DD/ID +	DD/ID +	DD/ID +	DD/ID +	DD/ID +	DD/ID +	DD/ID +	DD/ID +	DD/ID +	DD/ID +	DD/ID +	DD/ID +
Clinical features	Dysmorphic features	(distinct from MWS features)	(distinct from MWS features)	(distinct from MWS features)	(distinct from MWS features)	(distinct from MWS features)	(distinct from MWS features)	(distinct from MWS features)	(distinct from MWS features)	(distinct from MWS features)	(distinct from MWS features)	(distinct from MWS features)
	Hirschsprung +	Hirschsprung +	Hirschsprung +	Hirschsprung +	Hirschsprung +	Hirschsprung +	Hirschsprung +	Hirschsprung +	Hirschsprung +	Hirschsprung +	Hirschsprung +	Hirschsprung +
Other	Heart defect +	Heart defect +	Heart defect +	Heart defect +	Heart defect +	Heart defect +	Heart defect +	Heart defect +	Heart defect +	Heart defect +	Heart defect +	Heart defect +
	Seizures +	Seizures +	Seizures +	Seizures +	Seizures +	Seizures +	Seizures +	Seizures +	Seizures +	Seizures +	Seizures +	Seizures +
Pathogenicity	Behavior -	Behavior -	Behavior -	Behavior -	Behavior -	Behavior -	Behavior -	Behavior -	Behavior -	Behavior -	Behavior -	Behavior -
	feeding problems, neurogenic bladder, kidney reflux, pigment abnormalities, brain MRI abnormalities	hypotonia, severe speech impairment, open-mouth appearance	hypotonia, severe speech impairment, open-mouth appearance	hypotonia, severe speech impairment, open-mouth appearance	hypotonia, severe speech impairment, open-mouth appearance	hypotonia, severe speech impairment, open-mouth appearance	hypotonia, severe speech impairment, open-mouth appearance	hypotonia, severe speech impairment, open-mouth appearance	hypotonia, severe speech impairment, open-mouth appearance	hypotonia, severe speech impairment, open-mouth appearance	hypotonia, severe speech impairment, open-mouth appearance	hypotonia, severe speech impairment, open-mouth appearance
Inheritance	pathogenic	pathogenic	pathogenic	pathogenic	pathogenic	pathogenic	pathogenic	pathogenic	pathogenic	pathogenic	pathogenic	pathogenic
	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo
ISC-A, International Standards for Cytogenomic Arrays; MWS, Mowat-Wilson syndrome; NA, not available; DD, developmental delay; ID, intellectual disability.												

the current patient may be difficult as most of the previous duplications are much larger and contained additional genes. Six of these gains were de novo and 1 did not have parental testing information available. Six of these individuals had clinical features that overlapped with those seen in MWS (intellectual disability, developmental delay, dysmorphic features, multiple congenital anomalies, and seizures). One patient presented only with hearing impairment (DECIPHER 238286).

Also, 1 patient (nssv578831) found in the ISCA database had a reportedly pathogenic de novo 203-kb duplication which included exons 1 and 2 and intron 1 with part of intron 2 within *ZEB2* (larger but similar duplication region as seen in our patient; see Fig. 3). This patient was reported to have seizures. It is unknown if the patient had or developed any other features of MWS that were not reported in the ISCA database.

Additionally, Jiang et al. [2011] described 4 unrelated individuals with Hirschsprung disease who had 2q22.3 duplications (ranging from 1.42–1.99 kb in size) involving part of exon 1 and all of exon 2. Three of these individuals had additional physical anomalies, but 1 individual had a mutation in *RET* and 2 had a *SOX2* duplication with a mutation in *RET* that likely contributed to their clinical features. These reports indicate that partial duplications of *ZEB2* likely contribute to pathogenesis of Hirschsprung disease, one of the core features of MWS.

All of these previously reported cases demonstrate that both partial and full duplications of *ZEB2* can be pathogenic, resulting in abnormal clinical features. Previous reports of partial duplications of *ZEB2* have been identified in individuals with some clinical features of MWS, but none of these previously reported individuals were actually specifically diagnosed of MWS or presented with all of the key features of this condition.

Causative partial gene duplications have been reported in several other conditions that are typically caused by point mutations. These include neurofibromatosis type 1, Rubinstein-Taybi syndrome, Cornelia de Lange syndrome, and Kleeftstra syndrome [Roelfsema et al., 2005; Russo et al., 2012; Nemethova et al., 2013; Schwaibold et al., 2014]. These cases provide evidence that a partial duplication of *ZEB2* could similarly result in a haploinsufficient condition.

In conclusion, our patient represents the first report of a partial duplication of *ZEB2* in an individual with an established clinical diagnosis of MWS. This highlights the significance of partial gene duplications in the pathogenesis of genetic conditions and expands the types of mutations that can cause MWS.

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Statement of Ethics

Informed consent was obtained for this report from the parents of the patient in accordance with institutional standards for the protection of human research subjects.

Disclosure Statement

The authors have no conflicts of interest to declare.

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