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A 7- year old female with Arthrogryposis Multiplex Congenita, Duane Retraction Syndrome, and Marcus Gunn phenomenon due to a *ZC4H2* gene mutation: A Clinical Presentation of the Wieacker-Wolff Syndrome

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Abstract

Background: Duane retraction syndrome and arthrogryposis multiplex congenita have an incidence of approximately 1:1500–1:3000 live births. However the association of these two entities with a Marcus-Gunn might be a rare and until now and under recognized clinical presentation of the Wieacker-Wolff Syndrome.

Patient and methods: We report a 7-year-old female with dysmorphic features, global developmental delay, arthrogryposis multiplex congenita (AMC), Duane retraction syndrome (DRS), and unilateral Marcus Gunn jaw winking.

Results: Whole Exome Sequencing showed a *de novo* premature stop codon in *ZC4H2*. Extensive genetic and metabolic work was negative otherwise and Brain MRI showed delayed non-specific myelination abnormalities. She continues to have significant delays but does not have regression, seizures or other neurological complications. She has required multidisciplinary approach for the management of her multiple contractures.

Conclusion: This case confirms *ZC4H2* as a cause of syndromic DRS and extends the *ZC4H2* phenotype to include Marcus Gunn jaw winking.

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Keywords

Arthrogryposis; Duane; Marcus-Gunn; Wieacker-Wolff

We report a 7-year-old female with dysmorphic features, developmental disabilities, arthrogryposis multiplex congenita (AMC), Duane retraction syndrome (DRS), and unilateral Marcus Gunn jaw winking who harbors a de novo premature stop codon in ZC4H2. This case confirms ZC4H2 as a cause of syndromic DRS and extends the ZC4H2 phenotype to include Marcus Gunn jaw winking.

DRS is a form of congenital strabismus characterized by limited horizontal eye movement coupled with globe retraction and reduction in palpebral fissure height on attempted adduction and, in some cases, up or downshoots of the eye (1). DRS is caused by failure of abducens motor neurons to innervate the lateral rectus muscle, which is innervated instead by an aberrant branch of the oculomotor nerve (1). In DRS, co-contraction of the medial rectus and lateral rectus muscles occurs as a result of this aberrant neuronal innervation (1). AMC refers to congenital non-progressive joint contractures involving at least two different body areas (2). Most AMC cases are secondary to nervous system defects that arise from environmental or genetic factors (3). Thus, motor neuron maldevelopment can lead to contractures in AMC and restricted horizontal eye movement in DRS (4). Both DRS and AMC have an incidence of approximately 1:1500–1:3000 live births (1). Significant research has been directed towards uncovering the genetic etiology of DRS and AMC. Familial DRS can follow autosomal dominant or recessive inheritance patterns, with pathogenic variants being identified CHN1, MAFB, and SALL4 among other genes (5). AMC has been associated with autosomal dominant, autosomal recessive, and X-linked inheritance, and over 400 AMC genes have been reported (6). Here, we report a child with both AMC and DRS who harbors a de novo ZC4H2 mutation, thereby confirming this association that was previously reported in two teenaged females (7).

The proband is a 7-year-old female born to healthy, unrelated Hispanic parents. Prenatal ultrasounds revealed abnormal leg positions bilaterally. She was born at 38-weeks gestation via spontaneous vaginal delivery, with a birth weight of 6 lbs. 9oz and head circumference of 34 cm (90^{th} percentile). She was noted to have down-slanting small palpebral fissures, a prominent nasal bridge, small low-set ears, a high arched palate, microretrognathia, overlapping fingers, right hip dislocation, and bilateral proximal and distal contractures in all extremities. She had a 1-month NICU stay with feeding difficulties requiring gastrostomy tube placement.

At 2 months of age, her head circumference was 38cm (50^{th} percentile[6]). Ophthalmological examination revealed subnormal vision for age that could not be accounted for by the eye exam findings and was attributed to cortical/cerebral visual impairment. Anterior segment, maculae, and optic nerves appeared normal. Externally she had mild left-sided ptosis and elevation of the ptotic left eyelid with chewing. The sensorimotor exam revealed severely limited abduction and partially limited adduction of the right eye. These findings were less prominent in the left eye, but also present with limited abduction and trace limited adduction. She had narrowing of the palpebral fissure with globe retraction on attempted

adduction and widening of the palpebral fissure on attempted abduction in the right eye (Figure 1). Vertical gaze was normal. The ophthalmological diagnosis was bilateral DRS, left-sided ptosis, and Marcus Gunn jaw winking. She had multiple joint contractures; her legs were hyperextended, hips were abducted, and knees and ankles/feet had valgus deformities.

Developmental milestones were globally delayed. At four months of age, she was unable to use her hands, feed herself, or reach for a toy. At one year of age, she did not have a pincer grasp and was only able to grasp objects if placed in her hands. By two years of age, language development was limited to sounds and screams. She had decreased truncal tone and limited range of motion. Reflexes were 1+ in the upper extremities and difficult to assess in the lower extremities due to contractures.

Spine MRI at 11 months revealed mild dextroscoliosis centered in the mid thoracic spine. Brain MRI scans revealed bilateral absence of the abducens cranial nerves, myelination less than expected for age, increased periventricular white matter signal intensity in the centrum semiovale, increased fluid in the middle cranial fossa, and mild cystic dysplasia of the vestibules.

Evaluation for congenital disorders of glycosylation, Gaucher type II, and glycine encephalopathy with normal serum glycine were undertaken because these have been associated with AMC (6, 8, 9). CBC, CMP, and blood lactate, pyruvate, ammonia, and amino acids, and acylcarnitine profile were normal. Two initial blood studies revealed mild elevation in one or several very long chain fatty acids and/or their ratios, while a third follow-up study was normal. Urine oligosaccharides, mucopolysaccharides, organic acids, and acylglycines studies were normal and did not suggest a specific inherited metabolic defect.

The proband had a normal female karyotype (46, XX) and, by microarray, a 723 kb gain in the Xp22.33 pseudoautosomal region of unknown significance. The Distal Arthrogryposis Panel (University of Chicago) reported a paternally inherited variant in FBN2 of unknown significance. Clinical whole exome trio sequencing (≥ 20x coverage, > 98% of bases covered, Ambry Diagnostics) followed by standard filtering assuming autosomal and X-linked dominant and recessive modes of inheritance revealed a de novo heterozygous c.199C>T ZC4H2 variant (NM_018684) predicted to introduce a premature stop codon in exon 2 (p.R67*), with a CADD pathogenicity prediction score of 37 (10). The variant was absent from the gnomAD database and was previously reported in a child with AMC, facial asymmetry, cleft palate, severe developmental delay and growth retardation; there was no mention of Duane syndrome or strabismus (Frints et al, family 17) (7). Based on clinical overlap of the patient's reported signs and symptoms and existing evidence, this alteration was classified as pathogenic (7).

Heterozygous loss-of-function mutations in X-linked ZC4H2 cause ZC4H-associated rare disorders (ZARD); while there is a wide spectrum of associated phenotypes, AMC and central and peripheral nervous system involvement are prominent (10, 11, 12, 13, 14, 15). Ptosis and strabismus are each found in approximately 50% of affected

individuals (7). In males, phenotypes of ZARD range from intellectual disability to AMC with intellectual disability, fetal hypo-/akinesia, postnatal growth retardation, spasticity, tetraplegia, microcephaly, and hypogonadism (7). In females, phenotypes of ZARD range from unaffected carriers to AMC with intellectual disability, postnatal growth retardation, poor or absent speech, spasticity, inability to walk, distal muscle wasting/atrophy, short neck with limited rotation, narrow chest, and limited shoulder movements (7). Two females with de novo truncating ZC4H2 variants (Gln23* and Lys81Asnfs*6) were recently reported to have DRS in addition to AMC, dysmorphic features, and developmental disabilities (Frints et al, families 16 and 22) (7). We report the third female with DRS and AMC thereby confirming the role of ZC4H2 in disease pathogenesis and expanding the phenotypic presentation to include the ophthalmological finding of Marcus Gunn jaw winking phenomenon.

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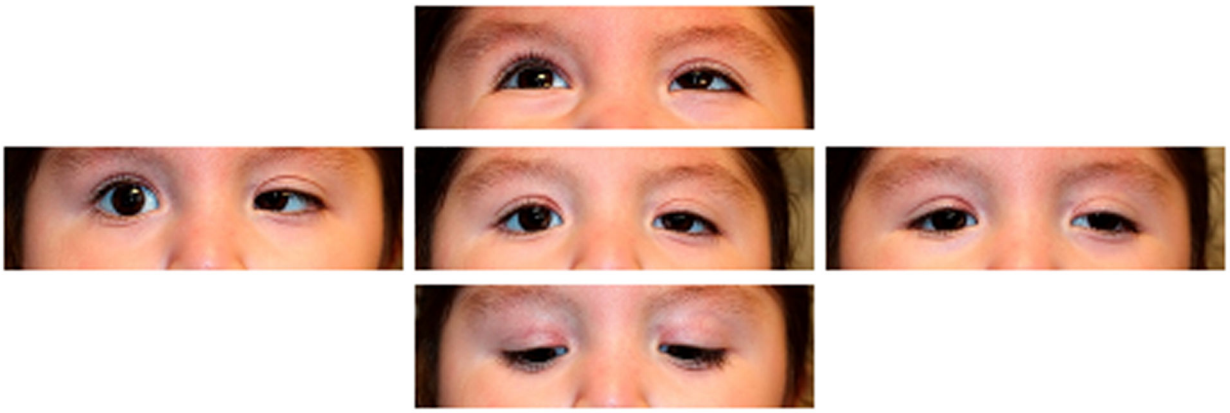

Figure 1: External Photos of Ocular Motility.

Proband in primary gaze (center) and right-, left-, up-, and downgaze. Note marked limitation of abduction greater in the right eye. On gaze right, there is widening of the palpebral fissure on attempted abduction of the right eye and narrowing on adduction of the left eye. Note the ptosis of the left eye. MGJW is not demonstrated in the static photos.