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ZC4H2 Associated Rare Disorders (ZARD)

Definition

ZC4H2 Associated Rare Disorders (ZARD) [1] is an ultra-rare genetic condition with central and peripheral nervous system involvement caused by deleterious changes (pathogenic variants) of the *ZC4H2* gene. *ZC4H2* is located on the X chromosome and encodes the ZC4H2 (Zinc Finger C4H2-Type Containing) protein essential for normal development.
ZARD can manifest in a broad range of clinical severity. Male and female individuals can both be affected.

Important Note:

Many conditions have been described as associated with pathogenic variants in the ZC4H2 gene. [2,3,4]
These conditions are now thought to be included in the spectrum of ZARD.[1]

This previously used nomenclature describes limited populations of individual or family-specific cases, provides partial descriptions of the condition, and should no longer be used. These conditions include the following:

- *Wieacker-Wolff Syndrome, WRWF* [2]
- *Miles-Carpenter Syndrome* [3]
- *ZC4H2 Deficiency* [4]
- *Wieacker syndrome*
- *Contractures of the feet, muscle atrophy and oculomotor apraxia*
- *Apraxia, oculomotor with congenital contractures and muscle atrophy*
- *Miles-Carpenter X-linked mental retardation syndrome; MCS*
- *Mental retardation, X-linked, syndromic 4; MRXS4*
- *Mental retardation, X-linked with congenital contractures and low fingertip arches*
- *Wieacker-Wolff syndrome, female restricted; WRWFFR*

Disease mechanisms

The *ZC4H2* gene is expressed in all human tissues. Understanding of *ZC4H2*'s gene functions and the functions of its corresponding ZC4H2 protein is currently very limited. It is believed that the ZC4H2 protein plays an important role in the development of the neurologic system during the early stages of human development, particularly through the development of neuromuscular junctions, spinal cord motor-neuron differentiation and neural tube formation. [5,6,9]

Analysis of the *in vivo* expression pattern of the mouse *Zc4h2* gene during neurodevelopment in various brain regions and spinal cord of different developmental stages revealed that in all brain areas investigated, *Zc4h2* gene expression was highest during embryonic development and declined after birth, suggesting an important function during mouse brain development. [5]

In zebrafish zc4h2 is primarily expressed in brain cells called "myelinating oligodendrocytes", with decrease in expression as these mature into another type of brain cells. [6] This may suggest a function of *ZC4H2* in myelination – which has not been studied to date.

The spectrum of *ZC4H2* gene defects comprises novel (not reported before) and recurrent (present in at least two unrelated families), mostly inherited, missense variants which cause a single amino acid exchange in the ZC4H2 protein in affected male individuals, and *de novo* missense, splicing, frameshift, nonsense and partial *ZC4H2* deletions on one of the X chromosomes in heterozygous females and are predicted to be loss-of function alleles in affected female individuals. This suggests *ZC4H2* insuffiency as the most likely pathological mechanism leading to the clinical phenotype in females.

Thus far, missense variants cluster in the last exon of the *ZC4H2* gene, which encodes the zinc-finger domain and the most C-terminal part of the protein.

In both male and female individuals, severity of symptoms could possibly be determined by the impact of the pathogenic variant on the ZC4H2 protein product, its protein complex partners and associated signaling pathways. In addition, the individual's own genetic makeup could possibly contribute to the phenotypic variability and severity of ZARD. [1]

There is currently no evidence for a clear relationship between the genetic defect and the clinical phenotype. Also, clinical presentations of affected individuals who carry the same pathogenic *ZC4H2* variant can vary within families and between families. [1,5,6]

Arthrogryposis Multiplex Congenita and muscular atrophy, which are observed in the majority of affected males and females, could be a possible secondary consequence of reduced fetal movement. Similar to affected individuals with other types of Arthrogryposis Multiplex Congenita who develop joint contractures during pregnancy, abnormal fetal movement during pregnancy due to the pathogenic *ZC4H2* gene variant can be identified using real time ultrasound prenatally. However, AMC and fetal hypo-/akinesia can occur late during pregnancy and therefore the diagnosis can be easily missed. [1]

There is currently no evidence of any progressive or regressive nature in ZARD. Age expectancy is yet undetermined.

Clinical presentation

Patients with ZARD can have multiple disabilities and health concerns. These can include **orthopedic and musculoskeletal conditions** and **neurological/neuromuscular conditions**. The most common clinical features include:

- Motor planning impairments –either generalized or localized
- Arthrogryposis Multiplex Congenita, defined as multiple joint contractures that involve at least two different body areas before birth. One causal factor is decreased fetal movement during in utero (fetal hypo-/ akinesia).
- Joint and soft-tissue defects often expressed as contractures
- Hand and feet deformities
- Hip deformities
- Mobility impairments
- Variable muscle tone
- Muscular atrophy
- Osteopenia
- Scoliosis
- Difficulties to eat or breathe
- Speech disorders often including apraxia of speech
- Oculomotor apraxia
- Epileptic seizures
- Tethered cord
- Autism
- Global developmental delay
- Intellectual disabilities
- Learning difficulties

An affected individual can have the full range of symptoms or only some of them. [1-3,5-7]

MRI brain and spine images can show variable and global brain atrophy, delayed central nervous system myelination, abnormality of periventricular white matter, corpus callosum abnormality, abnormal cortical gyration, ventriculomegaly, tethered cord and hydromyelia. [1]

Of note, there are some gender specific clinical features, e.g. cardiovascular associated clinical features, hypogenitalism and hypoglycemia were so far only reported in affected males. [1]

Modes of Inheritance

ZC4H2 gene variants can be either **inherited** or arise spontaneously (***de novo***) in an individual.[1]

In inherited cases, variants of the *ZC4H2* gene can be passed on from the healthy or mildly affected mother who carries the variant on one of her X chromosomes[1].
Female carriers have a 25% chance with each pregnancy to pass on the *ZC4H2* variant to a daughter, a 25% chance to have a non-carrier daughter, a 25% chance to have a son affected with ZARD, and a 25% chance to have an unaffected son.

In very rare cases, healthy females who carry a *ZC4H2* variant in a small number of her body cells and sexual cells (gonosomal mosaicism) can pass the variant to their children. [1]

Reports so far show that females with a maternally inherited *ZC4H2* variant may be unaffected or mildly affected. In contrast, females who carry a *de novo* pathogenic *ZC4H2* variant can present with a highly variable clinical expression which ranges from mild to severe. [1]

Males have one X chromosome and one Y chromosome. If a male individual has a pathogenic *ZC4H2* gene variant (either inherited from his mother or *de novo*), he will express the condition.

In very rare cases, healthy males may have gonosomal mosaicism for a pathogenic *ZC4H2* variant. They will transmit this variant to all their daughters, who will be affected or unaffected carriers. Males cannot pass the *ZC4H2* gene variant to their sons because they always pass their Y chromosome instead of their X chromosome to male offspring.

Females have two X chromosomes but many genes of one of the X chromosomes are silenced to correct a dosage imbalance through a process which is called X-inactivation. *ZC4H2* is one of these many genes which is silenced through this process (in other words, the *ZC4H2* gene is subject to X-inactivation).[5]
However, results obtained so far by performing X-inactivation studies in blood and skin fibroblasts of heterozygous carrier females indicate that X-inactivation status does not predict the clinical outcome. [1]

Treatment

There is currently no cure or effective treatment for this ultra-rare condition. Current treatments consist mainly of different supportive therapies and medical interventions when necessary.

It is important to note that anecdotal evidence from the patient community worldwide shows a correlation between early and frequent therapeutic and supportive interventions and favorable short and long term outcomes, in particular Physical, Occupational and Speech & Language therapies. [7]
Pre-verbal, feeding, language & speech therapies, particularly those with an **oral-motor** focus and approach, have shown significant improvements in the prognosis of ZARD patients in the following areas: feeding and deglutition, respiratory health (through improvement of feeding aspiration), verbalization, and speech &

language development. This observation strengthens the thoughts of motor-planning impairments as one of the underlying mechanisms in the pathophysiology of ZARD. [7]

Orthopedic treatments and/or surgery may be necessary to treat specific congenital or structural malformations associated with ZARD.

Genetic counseling is recommended for affected individuals and their families to clarify the genetic and clinical characteristics, the inheritance, and the recurrence risks of the condition in their families.

Prevalence

Deleterious ZC4H2 gene defects have been identified in many ethnic groups, with both males and females being affected who present with a broad spectrum of severity.

To date, there have been 255 diagnosed patients with ZARD worldwide. [1,5-8,10-21]

Our records show that about 30% of the affected patients are male individuals and 70% are female individuals. [7]

Diagnosis

A diagnosis of ZARD may be considered based upon a thorough clinical evaluation, a detailed patient and family history, and the identification of characteristic findings. Molecular genetic testing for *ZC4H2* gene variants (gene sequencing, panel next generation sequencing and microarray analysis) is available to confirm the diagnosis.

The diagnosis of ZARD is established in a male proband with suggestive findings and a hemizygous *de novo* or inherited pathogenic variant in *ZC4H2* identified by molecular genetic testing.

The diagnosis of ZARD is usually established in a female proband with suggestive findings and a heterozygous *de novo* or inherited pathogenic variant in *ZC4H2* identified by molecular genetic testing.

Identification of a hemizygous *ZC4H2* variant in a male proband and a heterozygous variant in a female proband interpreted as variant of uncertain clinical significance (VOUS) does not establish the diagnosis or rule out the diagnosis of ZARD.

If a *ZC4H2* variant is not identified, molecular genetic testing for genes associated with similar conditions may be suggested.

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