Reference: Statement

Update: May 2022

Supportive Therapies in ZARD

ZC4H2 Associated Rare Disorders (ZARD) [1] (previously referred by as *"Wieacker-Wolff Syndrome"* [2] or *"Miles-Carpenter Syndrome"* [3]*)* 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.

Understanding of the *ZC4H2* gene functions and the functions of its corresponding ZC4H2 protein is currently 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. [4,5,6]

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: Arthrogryposis Multiplex Congenita, joint defects, muscular atrophy, osteopenia, scoliosis, tethered cord, motor planning impairments, mobility impairments, difficulties to eat or breathe, speech disorders, vision problems, epilepsy, global developmental delay. An affected individual can have the full range of symptoms or only a few of them. [1-4,7]

There is currently no cure or effective treatment for this ultra-rare condition. Current treatments consist mainly of different supportive therapies, medical interventions and medications when necessary. [1,7]

To date, there have been 255 diagnosed patients with ZARD worldwide (familiar or de-*novo*).

Currently, from all reported interventions in ZARD, supportive therapies have consistently been stated among our community to result in the most significant improvements in the primary and secondary symptoms associated with ZARD[7].

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]

Although there is no study or clinical consensus regarding supportive therapies in ZARD, based on the current evidence on ZARD disease mechanism and the anecdotal evidence from our community, we recommend early (as soon as birth), frequent (daily) and consistent delivery of these therapies to patients affected by ZARD, either in a professional setting or at home [7].

References

1. Frints, S.G.M. *et al.* Deleterious de novo variants of X-linked ZC4H2 in females cause a variable phenotype with neurogenic arthrogryposis multiplex congenita. *Hum Mutat* **40**, 2270-2285 (2019).
2. Wieacker, P., Wolff, G., Wienker, T.F. & Sauer, M. A new X-linked syndrome with muscle atrophy, congenital contractures, and oculomotor apraxia. *Am J Med Genet* **20**, 597-606 (1985).
3. Miles, J.H. & Carpenter, N.J. Unique X-linked mental retardation syndrome with fingertip arches and contractures linked to Xq21.31. *Am J Med Genet* **38**, 215-23 (1991).
4. https://en.wikipedia.org/wiki/ZC4H2 deficiency.
5. Hirata, H. *et al.* ZC4H2 mutations are associated with arthrogryposis multiplex congenita and intellectual disability through impairment of central and peripheral synaptic plasticity. *Am J Hum Genet* **92**, 681-95 (2013).
6. May, M. *et al.* ZC4H2, an XLID gene, is required for the generation of a specific subset of CNS interneurons. *Hum Mol Genet* **24**, 4848-61 (2015).
7. The ZC4H2 Research Foundation.