Reference: Statement

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Progression/degeneration 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*).

There is no evidence of primary progression/degeneration in patients with ZARD[1]. It is important to notice though, the definition of 'progression' appearing in the early literature (Wieacker, 1985)[2], where the author described 5 males of one single family, who later appeared to carry an inherited form of a pathogenic variant of the *ZC4H2* gene[4]. These 5 males presented slowly progressive distal muscle atrophy. In addition, a second early publication (Hennekam 1991)[8] described one single family showing a late adult-onset mild form of slowly progressive spastic paraplegia in females carrying an inherited form of a pathogenic variant of the *ZC4H2* gene[4]. It should be noted that in none of these families, other forms of genetic late-onset of progressive syndromic spastic paraplegia (SPG) or any other (neuro) muscular degenerative condition were ever investigated. Moreover, studies on the morphological and physiological nature of the progressive peripheral muscular impairments described in these families were either absent[2] or inconclusive[8]. Therefore, one cannot exclude comorbidity with other conditions in those described families[1] nor attribute these undefined progressive phenotypes to the ZC4H2 mutation.

In contrast to the late-onset neurodegenerative adult phenotype reported so far in these two families [2,8], **there is no evidence of early-onset of progressive neurodegenerative phenotype known in affected children**[1]
In addition, there is no evidence or known reported cases of progression/degeneration of systemic nature in ZARD patients, including degeneration of gastroenterological nature. ZARD is not considered to be a primarily degenerative disorder. However, secondary neurologic and/or neuromuscular degeneration can possibly develop in the absence of appropriate supportive therapeutic and medical interventions.

We attribute these conclusions to both the available literature, as cited in this statement, as well as to anecdotal evidence from all currently diagnosed cases of ZARD belonging to our patient community worldwide.

References:

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