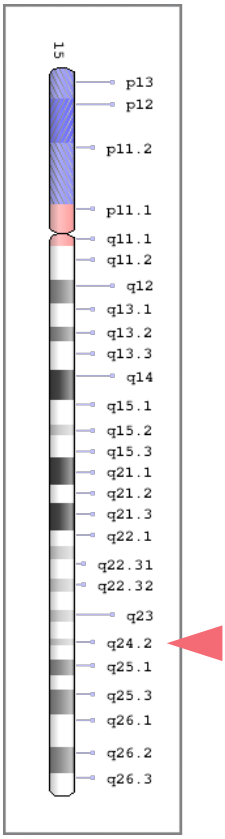
DELETION 15Q24.2

Deletion 15q24.2 and Witteveen-Kolk Syndrome (WITKOS)



In 2016 Witteveen and her colleagues[1] reported several patients with small deletions in 15q24.2 (in all cases involving the SIN3A gene) and with point mutations in this gene. Because clinical manifestations in the persons with deletions and with mutations were virtually identical, it was concluded that haploinsufficiency of the SIN3A gene is responsible for this condition. Later the term Witteveen-Kolk syndrome (WITKOS) was coined for this syndrome [Kolk is one of the authors of the original publication]. Of course, retrospectively several patients with deletions of this area reported before 2016[2] were attributed as patients with WITKOS.

Prevalence of this syndrome and the ratio between deletion-caused and mutation-caused cases are not known, but most likely it is not an extremely rare condition. Balasubramanian et al.[3] reported a cohort of 28 patients; all 28 had mutations in the SIN3A gene. The majority of patients in literature appear to have protein-truncating variants supporting the idea that haploinsufficiency is likely mechanism of pathogenicity[3]. SIN3A encodes a transcriptional regulatory protein, which is associated with the core histone deacetylase complex; it was previously shown that SIN3A is involved in cortical neurogenesis, supporting the hypothesis that variants in the gene that adversely affect its function lead to a broad range of developmental and neurological problems[1].

Main manifestations of the syndrome include microcephaly, short stature, mild intellectual disability with delayed cognitive and motor

development, characteristic distinctive facial features (a broad, tall forehead; small mouth, thin upper lip with pointed chin; down-slanting palpebral fissures), and subtle brain anomalies, including ventriculomegaly and corpus callosum dysgenesis[3]. Balasubramanian et al.[3] also reported that 1/3 of their cohort had psychiatric or behavioral condition, including aggressive behavior, attention deficit hyperactivity disorder, obsessive compulsive disorder, depression, psychosis, anxiety and schizoaffective disorder and 50% of patients had epilepsy, hypotonia, or both. Defects of the internal organs (heart, kidneys) are not characteristic. However, these defects may be found in patients with deletions also involving more proximal or more distal segments of 15q.

Until now, WITKOS has not formally been associated with congenital hypogonadotropic hypogonadism (CHH), a genetic condition noted for abnormal synthesis, secretion or action of gonadotrophin-releasing hormone. Schnöll et al.4 have suggested an overlap of WITKOS and CHH through novel patients with SIN3A defects and point out a possible clinical overlap between CHH and WITKOS and suggest the following shared manifestations: hypogonadotropic hypogonadism, hearing loss, and clinodactyly. These findings highlight the importance of detailed clinical evaluation of WITKOS patients to identify all possible syndromic phenotypes for the best management of the patient's condition. Because clinical manifestations in some patients may be mild, direct parental transmission of the deletion 15q24.2 or mutation of the SIN3A gene may be expected: therefore cytogenetic or molecular-genetic examination of the parents is necessary for genetic counseling.

REFERENCES

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[2] Samuelsson L, Zagoras T, Hafström M (2015). Inherited 15q24 microdeletion syndrome in twins and their father with phenotypic variability. Eur J Med Genet v. 58, 111-115.

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