SIN3A Witteveen-Kolk syndrome WITKOS

https://pubmed.ncbi.nlm.nih.gov/36758531/

Introduction:

Congenital hypogonadotropic hypogonadism (CHH) is a rare condition caused by GnRH deficiency. More than 40 genes have been associated with the pathogenesis of CHH, but most cases still remain without a molecular diagnosis. Mutations involving the same gene (e.g., FGFR1, PROK2/PROKR2, CHD7) were found to cause normosmic CHH and Kallmann syndrome (KS), with and without associated phenotypes, illustrating the coexistence of CHH with signs of other complex syndromes. The Witteveen-Kolk syndrome (WITKOS), caused by defects of the SIN3A gene, is a heterogeneous disorder characterized by distinctive facial features, microcephaly, short stature, delayed cognitive, and motor development. Although micropenis and cryptorchidism have been reported in this syndrome, WITKOS has not been formally associated with CHH so far.

Patients and methods:

A man with KS associated with mild syndromic features (S1) and a boy with global

developmental delay, syndromic short stature, micropenis and cryptorchidism (S2), in whom common genetic defects associated with CHH and short stature had been previously excluded, were studied by either chromosomal microarray analysis or whole exome sequencing.

Results:

Rare SIN3A pathogenic variants were identified in these 2 unrelated patients with CHH phenotypic features. A 550 kb deletion at 15q24.1, including the whole SIN3A gene, was identified in S1, and a SIN3A nonsense rare variant (p.Arg471*) was detected in S2.

Conclusion:

These findings lead us to propose a link between SIN3A defects and CHH, especially in

syndromic cases, based on these 2 patients with overlapping phenotypes of WITKOS and CHH.