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Is *ZNF462* at 9q31.2 a Novel Kallmann Syndrome Gene?

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ZNF462 haploinsufficiency is the recognized cause of Weiss-Kruszka syndrome, a neurodevelopmental disorder characterized by global developmental delay, craniofacial anomalies, hypotonia, and midline brain defects. So far, ZNF462 has not been implicated in reproductive endocrinology or congenital hypogonadotropic hypogonadism. However, new clinical evidence challenges this view. A Finnish boy reported by Iivonen et al. carried a 9q31.2 microdeletion encompassing *ZNF462* and displayed both Weiss-Kruszka syndrome and Kallmann syndrome. Because *ZNF462* had not been associated with reproductive phenotypes at the time, the authors proposed that an unknown Kallmann syndrome gene within the deleted interval must explain the endocrine findings. Subsequently, Park et al. described a Korean boy with a truncating *ZNF462* variant who exhibited Weiss-Kruszka syndrome together with an empty sella, growth hormone deficiency, and markedly delayed puberty. In this case, isolated ZNF462 loss-of-function variant-without a multigene deletion-should account for the endocrine abnormalities. More recently, Zhou et al. reported a prepubertal Chinese boy harboring a heterozygous truncating ZNF462 variant who presented with bilateral cryptorchidism and complete growth hormone deficiency, further supporting a role for ZNF462 haploinsufficiency in hypothalamic-pituitary-gonadal axis dysfunction. Together, these cases provide converging evidence that ZNF462 disruption can affect development and function of the hypothalamic-pituitary-gonadal axis. This mini-review synthesizes current data, explores biological plausibility based on ZNF462 molecular interactions, and discusses how neurodevelopmental disorders and delayed puberty frequently co-occur due to shared developmental pathways. We propose that ZNF462 should now be considered a strong candidate gene for Kallmann syndrome and highlight the need for systematic reanalysis of genomic datasets to define its role more precisely.

Key words: ZNF462, Kallmann syndrome, Weiss-Kruszka syndrome, 9q31.2, Delayed puberty, Hypogonadotropic hypogonadism, Neurodevelopmental disorder

REVIEW ARTICLE

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INTRODUCTION

Kallmann syndrome (KS) is a form of congenital hypogonadotropic hypogonadism (CHH) characterized by absent or delayed puberty in combination with anosmia or hyposmia. It arises from impaired development, migration, or function of gonadotropin-releasing hormone neurons, which originate in the olfactory placode and migrate to the hypothalamus during embryogenesis. The condition demonstrates how disruptions in early brain development can impair the hypothalamic-pituitary-gonadal axis [1]. Neurodevelopmental disorders, in contrast, encompass global developmental delay, cognitive impairment, and structural or functional brain abnormalities. While historically treated as separate clinical domains, neurodevelopmental disorders and reproductive endocrine disorders share extensive developmental biology. Many genes involved in neural patterning, midline development, chromatin regulation, and neuronal differentiation have parallel roles in establishing the hypothalamic-pituitary-gonadal axis. With the advent of next generation sequencing, patients with combined neurodevelopmental and pubertal disorders are increasingly recognized, prompting re-examination of genes previously assigned to a single phenotype category.

Table 1. Individuals harboring pathogenic *ZNF462* variants with reproductive endocrine phenotypes

Case	Sex	Age	Ethnicity	Genotype	Neurodevelopmental Features	Endocrine/Reproductive Phenotype	Reference
1	male	16 year 9 months	Finnish	2.38 Mb heterozygous *de novo* deletion encompassing *ZNF462, FKTN, TAL2, TMEM38B, RAD23B, KLF4*	Weiss-Kruszka Syndrome	Kallmann Syndrome (hypoplastic scrotum, small testes, anosmia, low reproductive hormone level, absence of olfactory bulb)	Iivonen et al. Eur J Endocrinol 2021 [3]
2	male	16 years	Korean	Heterozygous c.4185del / p.Met1396Ter in *ZNF462*	Weiss-Kruszka Syndrome	Delayed puberty, growth hormone deficiency, empty sella syndrome, flattened pituitary gland	Park et al. J Korean Med Sci 2021 [4]
3	male	8 years 6 months	Chinese	Heterozygous c.6311dup/ p.Val2015Glyfs*32 in *ZNF462*	Weiss-Kruszka Syndrome	Bilateral cryptorchidism, complete growth hormone deficiency without pituitary lesions	Zhou et al. Front Genet 2022 [5]

ZNF462 located at 9q31.2 encodes a zinc-finger transcription factor. Heterozygous loss-of-function variants cause Weiss-Kruszka syndrome, a neurodevelopmental disorder characterized by craniofacial anomalies, metopic ridging, ptosis, developmental delay, hypotonia, and midline brain malformations, including abnormalities of the corpus callosum [2]. Prior to 2021, endocrine abnormalities were not described among individuals with Weiss-Kruszka syndrome, and *ZNF462* was not considered a candidate gene for KS or CHH. Thus, the gene was categorized strictly within the neurodevelopmental spectrum.

This view began to shift when Iivonen et al. [3] reported a Finnish girl presenting with both Weiss-Kruszka syndrome and KS in 2021. Genetic studies revealed a *de novo* 2.38-Mb deletion at 9q31.2 encompassing *ZNF462* and five additional genes. Because *ZNF462* had no known association with reproductive phenotypes and because the deletion interval contained multiple uncharacterized genes, the authors concluded that a separate, unidentified KS gene must lie within the deleted region (Table 1). Their interpretation was reasonable given the absence of published endocrine phenotypes in Weiss-Kruszka syndrome at the time.

A crucial development occurred when Park et al. [4] described a 16-year-old Korean boy with a heterozygous truncating *ZNF462* variant in 2021. This individual exhibited typical features of Weiss-Kruszka syndrome, including developmental delay, hypotonia, and craniofacial anomalies, but his clinical presentation also included an empty sella, growth hormone deficiency, and markedly delayed puberty. Unlike the Finnish patient, the Korean boy did not harbor a multigene deletion. Instead, he possessed a nonsense variant c.4185del /p.Met1396Ter in *ZNF462* [4]. Since the protein is 2,462 amino acids, this disruption/truncation strongly supports pathogenicity (Table 1). As the only disrupted gene identified by exome sequencing, *ZNF462* is highly likely to be responsible for both the neurodevelopmental and endocrine abnormalities. This is further supported by the report in 2022 of an 8-year-6-month-old Chinese boy carrying a heterozygous *ZNF462* truncating variant who presented with bilateral cryptorchidism, a typical feature of KS, although his pubertal phenotype could not yet be fully evaluated because of his prepubertal age [5]. This boy also had growth hormone deficiency in the absence of structural pituitary lesions, so a direct role of ZNF462 in the regulation of pituitary hormone production and secretion cannot be completely ruled out (Table 1). Taken together, these cases provide strong evidence that ZNF462 haploinsufficiency alone can impair development and function of the hypothalamic-pituitary-gonadal axis.

Re-evaluating the Finnish case in light of the Korean patient produces an alternative interpretation of the data. The earlier assumption that *ZNF462* could not contribute to KS is now brought into question. Instead, the Korean case suggests that *ZNF462* disruption may directly impair pituitary morphology and pubertal development. It is therefore plausible that the endocrine phenotype in the Finnish deletion case could also be driven by ZNF462 haploinsufficiency rather than by another unknown gene within the deletion interval. Given that no other genes in the region have a clear mechanistic link to KS, *ZNF462* becomes the most biologically and genetically credible explanation for the combined phenotype observed in the Finnish patient.

Biological data further support the plausibility of *ZNF462* as a candidate gene for KS. ZNF462 interacts with a set of chromatin regulators and epigenetic modifiers, including EHMT1 and CHD4, according to curated protein–protein in-

teraction data (BioGRID, https://thebiogrid.org/). These proteins participate in transcriptional programs essential for early brain development. EHMT1 haploinsufficiency causes Kleefstra syndrome, a neurodevelopmental disorder characterized by intellectual disability, childhood hypotonia, and a high frequency of genital anomalies such as micropenis, cryptorchidism, and hypospadias in affected males [6]. Detailed endocrine evaluation in at least one adolescent boy with a pathogenic *EHMT1* variant has demonstrated partial hypogonadotropic hypogonadism with low gonadotropins and isolated micropenis, supporting a direct contribution of EHMT1 dysfunction to impaired hypothalamic-pituitary-gonadal axis development in addition to its neurodevelopmental effects [7]. *CHD4* encodes an ATP-dependent chromatin remodeler that is a core component of the NuRD complex, and *de novo* missense and truncating variants cause Sifrim-Hitz-Weiss syndrome, a multisystem neurodevelopmental disorder with intellectual disability, brain malformations, and congenital heart defects. In the largest published cohort of 32 individuals with *CHD4*-related syndrome, hypogonadism was documented in about forty percent of affected males, most often presenting with cryptorchidism, micropenis, or abnormal gonadotropin levels, and several patients also had growth hormone deficiency, prompting the authors to recommend systematic endocrine evaluation at diagnosis and again during puberty [8]. Taken together, the observation that pathogenic variants in *EHMT1* and *CHD4*-two direct interactors of ZNF462-can produce phenotypes consistent with partial hypogonadotropic hypogonadism and delayed pubertal development reinforces the broader concept that chromatin remodelers involved in neurodevelopment may also modulate pubertal timing.

Co-occurrence of neurodevelopmental disorders and pubertal disorders is increasingly recognized in human genetics, and *CHD7* is a prime example of this dual involvement. *De novo* pathogenic variants in *CHD7* cause CHARGE syndrome, a multisystem neurodevelopmental disorder with characteristic craniofacial, ear, cardiac, and brain anomalies, while a substantial proportion of affected individuals also exhibit CHH or frank KS. Moreover, *CHD7* variants have been identified in patients with isolated CHH without full CHARGE features [9], underscoring that the same chromatin remodeler can independently disrupt both higher-order neurodevelopment and sexual maturation.

SOX10-related Waardenburg-Hirschsprung disease results from defects in neural crest development rather than central neurodevelopment. However, pathogenic variants in *SOX10* can also impair migration of gonadotropin-releasing hormone neurons, leading to CHH or KS in a subset of affected individuals, providing another example of a gene affecting multiple functional systems [10]. Deafness is a common accompaniment to *SOX10* pathogenic variants.

Although direct functional studies examining the mechanism by which ZNF462 may influence GnRH neuron development are not yet available, its proposed role is supported by parallels with established genes implicated in CHH and KS. Several CHH/KS-associated genes, including *CHD4*, *CHD7*, *EHMT1*, and *SOX10*, encode chromatin regulators or transcription factors that are essential for early neurodevelopment, forebrain patterning, neuronal differentiation, and migratory processes critical for GnRH neuron specification and integration into the hypothalamic-pituitary-gonadal axis. Disruption of these shared chromatin-based and transcriptional regulatory pathways represents a well-established pathogenic mechanism underlying combined neurodevelopmental and reproductive phenotypes. In this context, *ZNF462*, which encodes a zinc-finger transcription factor involved in chromatin organization and transcriptional regulation, may contribute to CHH/KS through similar developmental mechanisms. Further functional studies will be required to define the precise role of *ZNF462* in GnRH neuron biology.

Structural variation analysis offers a promising path to clarify the role of *ZNF462* in KS. Identifying small deletions that either include only *ZNF462* or exclude it while removing neighboring genes would help delineate the minimal interval required to produce delayed puberty. A similar comparative genomic approach has already been applied at the neighboring 9q31.3 region, where our own study combined a 4.78 Mb familial microdeletion spanning 9q31.2-9q31.3 with a *de novo* balanced translocation t(7;9)(p14.1;q31.3) in a patient with KS to narrow the candidate interval to approximately 3.7 Mb and to highlight *ACTL7A* and *ACTL7B* as plausible KS gene candidates, although a definitive causal gene in this region has not yet been identified [11]. High-resolution chromosomal microarray or genome sequencing datasets contain many individuals with copy-number variants in this region, but their pubertal phenotypes have not been systematically analyzed. Examination of these cases could identify recurrent patterns or refine genotype-phenotype correlations. If small deletions limited to *ZNF462* consistently produce endocrine abnormalities, the gene's causal role would be strongly supported. Conversely, if deletions excluding *ZNF462* but including other

genes also yield KS, alternative candidate genes would emerge. Fine mapping at 9q31.2 therefore represents an important future direction for refining the mechanistic basis of this association.

Given the emerging evidence, reanalysis of existing genomic datasets is critical. Large CHH cohorts, many of which already have whole-exome or whole-genome sequencing data, should be screened systematically for *ZNF462* variants. Retrospective review of sequencing data from clinical diagnostic laboratories may also reveal individuals previously labeled with Weiss-Kruszka syndrome who have unrecognized delayed puberty. In parallel with genomic reanalysis, careful clinical examination of patients with Weiss-Kruszka syndrome and pathogenic *ZNF462* variants is needed, particularly during pubertal age, to determine whether delayed puberty or other reproductive phenotypes have been under-recognized or overlooked. Gene matching platforms and international registries for KS and CHH could help consolidate rare cases. Even a small number of additional individuals with pathogenic *ZNF462* variants and endocrine abnormalities would substantially strengthen the case for *ZNF462* as a *bona fide* KS gene. Functional studies, including model organism work and stem cell–based differentiation assays, will be essential to define the pathways through which *ZNF462* operates.

CONCLUSION

Current evidence positions *ZNF462* as a credible and compelling candidate gene for KS. The Finnish 9q31.2 deletion case and the Korean truncating variant case together demonstrate that *ZNF462* disruption can produce both neurodevelopmental abnormalities and impaired maturation of the hypothalamic-pituitary-gonadal axis. Although additional data are needed, the biological plausibility of *ZNF462*, supported by its interactions with chromatin regulators involved in early neural and hypothalamic development, provides a mechanistic framework for this dual phenotype. Identifying small, precisely defined deletions at 9q31.2 will be crucial in refining genotype–phenotype relationships, as will systematic reanalysis of existing exome and genome sequencing datasets from CHH cohorts. Careful longitudinal assessment of pubertal development in patients with Weiss-Kruszka syndrome may uncover additional reproductive phenotypes that have previously been overlooked. In light of the emerging data, *ZNF462* merits targeted screening in KS patients, and further research is likely to clarify and possibly confirm its role in the molecular architecture of pubertal development.

AUTHOR CONTRIBUTIONS

HG Kim conceived the study and drafted the manuscript. SH Kim and MH Jang contributed to literature search and manuscript preparation, and LC Layman reviewed reproductive and endocrine data from the literature and revised the manuscript.

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