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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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Copy Number Variant Analysis in Next-Generation Sequencing Panels for Germline Disorders

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A copy number variant (CNV) analysis is widely performed in next-generation sequencing (NGS) tests for germline disorders, such as NGS panels or whole exome sequencing. The CNVs provide a high proportion of positive results and the frequency of the CNVs varies depending on the NGS panel categories. To provide accurate CNV results from NGS data, we need to select appropriate analysis methods and manage quality control (QC) metrics of NGS testing. This review briefly introduces the CNV analysis methods associated with NGS panels, investigates the frequency of CNVs among the different NGS panel categories, and suggests factors that need to be considered before performing a CNV analysis as part of an NGS test.

Key words: Next-generation sequencing panel, Copy number variant, Germline disorder

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INTRODUCTION

Importance of copy number variant detection in next-generation sequencing panels for germline disorders

The primary purpose of next-generation sequencing (NGS) panel testing for hereditary diseases is to detect sequence variants in target genes. However, advances in the bioinformatics analysis pipeline and quality control (QC) management of the wet bench process mean that it is now possible to accurately detect copy number variants (CNVs), such as deletions or duplications in genomic regions, by statistically analyzing sequencing depth data [1,2]. Currently, such analysis pipelines are almost routine. They allow a CNV analysis to be actively conducted even in clinical laboratories that perform NGS panel testing. The literature on CNV analyses of targeted NGS panels suggests that CNVs are detected in about 1%–2% of all NGS panel tests. However, the CNVs account for a higher proportion, at approximately 9%–10%, among the cases reported as positive due to pathogenic variants [3,4]. The distribution of reported CNVs also varies depending on the type of panel used. For example, neurologic disease panels show a high reporting rate of 30%–40% [3]. Thus, a CNV analysis of a NGS panel will provide useful complementary information, especially for cases where making a diagnosis is challenging.

Copy number variant detection methods used in NGS tests for germline disorders

Statistical data analysis methods for target gene regions

Deletions or duplications in the coding regions of target genes can be identified using a statistical analysis if there are 10 or more samples in a batch. Representative statistical indicators include the z-score and z-ratio [5]. Algorithms, such as

VisCap, are also frequently used in NGS panels to detect CNVs [6]. One of the recently developed CNV detection tools such as CABANA shows highly accurate intragenic CNVs according to base-level normalization [7].

CNV detection methods in whole exome sequencing tests

Most hereditary disease NGS panel tests now use whole exome sequencing (WES), which means that it is possible to perform a CNV analysis based on WES data, including NGS panel test data. Algorithms commonly used in WES tests include XHMM, CODEX, and Conifer [8-10] and the results of the CNV analysis can be visualized on a genome-wide basis using z-score and z-ratio plots. This allows the identification of large-scale deletions and duplications at similar levels to a chromosomal microarray (CMA).

Off-target analysis

Sequencing data from off-target regions can be utilized in CNV analyses of data from targeted NGS panels or WES tests. This method, known as an off-target CNV analysis, is particularly useful for detecting large deletions or duplications. Additionally, it offers the advantage of being able to estimate breakpoints to some extent [11].

Analysis using the Integrative Genomics Viewer program

When a CNV is suspected after a statistical analysis, the Integrative Genomics Viewer (IGV) program can, in some cases, be used to identify the split reads. This enables the precise localization of deletions or duplications at the base pair level. Additionally, though rare, it is also possible to detect genomic rearrangement [12].

Distribution of CNVs in NGS panels for hereditary disease

The NGS panel with the highest detection rate for CNVs is the Charcot-Marie-Tooth disease panel, where pathogenic CNVs have been identified in approximately 50% of total positive cases [3]. This is because the major causative factor for this disease is a heterozygous duplication in the PMP22 gene region. Additionally, other tests in which CNVs are frequently detected include panels for neurodevelopmental disorders such as epilepsy, where CNVs are found in over 10% of all positive cases [3]. Furthermore, in panels for hereditary cancer, cardiomyopathy, arrhythmia, and connective tissue disease, CNVs are detected in approximately 5%–10% of the total positive cases [3,4]. Interestingly, in hereditary cancer and dyslipidemia panels, most reported CNVs are small and occur at the exon level. However, in panels for autism, epilepsy, and skeletal dysplasia, large CNVs—such as several hundred kilobase CNVs associated with microdeletion syndromes or several megabase CNVs that are related to chromosomal unbalanced translocations—are frequently reported [4,13].

Special considerations

QC management

The primary objective of NGS panel tests for germline disorders is the analysis of sequence variants. However, sufficient average coverage is required for a sequence variants analysis and the CNV analysis requires additional QC management. For efficiency reasons, the sequencing depth should be uniformly distributed across all target regions. This is referred to as coverage uniformity and is assessed using various indicators, such as the coefficient of variation [14]. In particular, coverage uniformity must meet a certain threshold and values such as the median absolute pair-wise difference (MAPD) must be within an acceptable range [15]. However, these QC values may fall outside the acceptable range due to specimen quality issues or other unknown factors. Consequently, maintaining the QC for CNV analyses as high as that achieved for a CMA is challenging and can sometimes lead to difficulties in performing accurate CNV analyses.

Confirmation test for detected CNVs in NGS tests

Even if CNVs detected through NGS tests have been reported, additional confirmatory testing may still be required in some cases. Confirmation using an alternative method is recommended, particularly when a CNV is suspected in cases where there has been a single exon deletion or where CNVs have been found in regions that are difficult to analyze by NGS, such as homologous regions or areas with insufficient coverage. Multiplex ligation-dependent probe amplification (MLPA) is commonly used as a confirmatory test, but it cannot confirm all genes due to limitations in the available probes. An alternative is a CMA-based test, such as the CytoScan Xon array, which can detect exon-level regions [16,17]. In clinical practice, the validation of the CNVs in NGS result by MLPA or CMA is important to confirm the genetic diagnosis.

CONCLUSION

A CNV analysis is often performed concurrently in current NGS-based genetic testing for germline disorders because CNVs play a significant role in genetic diagnosis and substan-

tially improve the diagnostic yield. Most NGS panels for hereditary diseases are performed using WES and CNV analyses based on WES data have become increasingly accurate. Notably, CNVs can be detected across a broad range, from the single exon level to Mb-scale large deletions. In particular, accurate interpretation and reporting of CNV—supported by the interpreting specialist's extensive clinical experience and analytical expertise—greatly enhance the diagnostic accuracy for hereditary diseases.

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Genetics of Thyroid Dyshormonogenesis: From Molecular Mechanisms to Precision Management

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Congenital hypothyroidism (CH) is one of the most common endocrine disorders in newborns and an important preventable cause of intellectual disability. Thyroid dyshormonogenesis accounts for approximately 15%–20% of CH cases and results from defects in thyroid hormone synthesis. Recent advances in molecular genetics have identified several key genes involved in this process, including *SLC5A5, TPO, DUOX2, DUOXA2, TG, SLC26A4*, and *IYD*. These genes affect different steps of hormone production, such as iodide transport, organification, thyroglobulin synthesis, and iodide recycling. Clinical presentations vary widely, ranging from transient to permanent hypothyroidism, depending on the type and severity of genetic defects. A precise genetic diagnosis has important clinical implications. It can guide individualized treatment strategies and help predict disease courses, including the likelihood of transient versus permanent hypothyroidism. In addition, early identification of affected family members enables timely intervention and prevention of developmental complications. In conclusion, thyroid dyshormonogenesis represents a genetically heterogeneous group of disorders. Integrating genetic, biochemical, and clinical data is essential for precision management and may improve long-term outcomes in patients with congenital hypothyroidism.

Key words: Congenital hypothyroidism, Thyroid hormone synthesis disorders, Thyroid dyshormonogenesis

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INTRODUCTION

Congenital hypothyroidism (CH) is the most common congenital endocrine disorder and an important preventable cause of intellectual disability [1]. CH is classified into two main categories: thyroid dysgenesis and thyroid dyshormonogenesis. Thyroid dyshormonogenesis causes 15%–20% of congenital hypothyroidism, while thyroid dysgenesis accounts for the majority [2]. Thyroid dyshormonogenesis has been associated with mutations in seven genes: *SLC5A5 (NIS)*, *SLC26A4 (PDS)*, *TG*, *TPO*, *DUOX2*, *DUOXA2*, and *IYD (DEHAL1)*. Defects can occur at any step of thyroid hormone synthesis, including iodine uptake *(SLC5A5)*, iodine organification (*TPO, DUOX2, DUOXA2, SLC26A4*), thyroglobulin synthesis (*TG*), and iodine recycling by iodotyrosine deiodinase (*IYD/DEHAL1*) [3]. A definite genetic diagnosis in CH offers several clinical benefits. It can guide treatment decisions, as some hormonogenesis defects may respond effectively to iodide supplementation rather than levothyroxine (L-T4). In addition, genetic testing can help identify patients with transient CH caused by partial defects in hormonogenesis and may also predict those who will require lifelong thyroid hormone replacement therapy [1].

THYROID HORMONE BIOSYNTHESIS

Thyroid hormone synthesis starts with the uptake of iodine (I) from the diet, which is absorbed in the form of iodide (I^-) and transported into thyroid cells by

Table 1. Clinical characteristics of thyroid dyshormonogenesis according to genetic defects

Gene	Biosynthesis Step	Goiter	Serum TG level	Radioiodine Uptake in Thyroid scintigraphy	Perchlorate discharge test	Treatment
SLC5A5	Iodide uptake	Present	Elevated	Decreased or absent	Negative	Iodide ± LT4
TPO	Iodine organification	Present (often large)	Elevated	Increased	Positive	Lifelong LT4
DUOX2	H_2O_2 generation (for organification)	Present	Elevated	Normal or increased	Positive	Iodide or LT4
DUOXA2	DUOX2 maturation	Present	Elevated	Normal or increased	Positive	LT4
SLC26A4	Iodide efflux (apical transport)	Present	Elevated	Normal or increased	Positive	LT4 if needed
TG	Thyroglobulin synthesis	Present (often large)	Low	Increased (high uptake)	Negative	Lifelong LT4
IYD	Iodide recycling	Present	Elevated	Initially increased, then declines	Negative	Iodide or LT4

Perchlorate discharge test positive: indicating a defect in converting accumulated iodide to organically bound iodine.

the sodium/iodide symporter (NIS) [4]. Inside the cells, thyroglobulin (Tg), a large glycoprotein, is secreted into the follicle lumen [5], while thyroid peroxidase (TPO) at the apical membrane uses H_2O_2, generated by Duox, to oxidize iodide and attach it to Tg tyrosyl residues [6,7]. This iodination produces monoiodotyrosine (MIT) and diiodotyrosine (DIT), and the coupling of two DIT residues forms T4 [8]. When needed, Tg is endocytosed and degraded in endosomes and lysosomes, releasing T4 and T3 into the circulation. Non-hormonal iodide, about 70% of Tg iodine, is recovered by iodotyrosine deiodinase (IYD) or reuse within the gland [9]. Thyroid-stimulating hormone (TSH) regulates nearly every step, controlling both enzyme activity in the short term and gene expression in the long term. Imbalances in iodine or genetic defects in key proteins such as NIS, TPO, Duox, or Tg can lead to goiter or hypothyroidism. Clinical characteristics of thyroid dyshormonogenesis according to genetic defects are described in Table 1.

IODIDE TRANSPORT DEFECT: *SLC5A5(NIS)* MUTATIONS (OMIM #274400, THYROID DYSHORMONOGENESIS-1)

Thyroid dyshormonogenesis-1 (TDH1) results from homozygous or compound heterozygous mutations in the *SLC5A5* gene, which is located on chromosome 19p13. The NIS, encoded by the *SLC5A5* gene, is a 13-transmembrane protein that enables iodide to enter thyroid follicular cells via the basolateral membrane [1]. TDH1 is characterized by a failure of the thyroid gland to establish and maintain an iodide concentration gradient between the plasma and thyroid tissue. Therefore, patients usually present with goiter and show reduced or absent radioactive iodine uptake (RAIU) on thyroid scintigraphy. RAIU directly reflects residual NIS activity [10]. Patients can be treated with iodide supplementation alone or combined with L-T4 replacement therapy. Hypothyroidism may develop from the neonatal period through childhood and is influenced by the remaining functional activity of the mutant transporter. Identification of an index case enables early detection in other family members, preventing delayed diagnosis and potential developmental delay [11].

Stanbury and Chapman first reported iodide transport defect in 1960 [12]. Fujiwara [13] subsequently clarified the molecular mechanism underlying this defect, identifying a mutation in the *SLC5A5* gene in 1997. To date, 66 mutations in *SLC5A5* have been documented in the Human Gene Mutation Database (HGMD) [14].

IODIDE ORGANIFICATION DEFECT: *TPO* MUTATIONS (OMIM #274500, THD2A)

TDH2A results from homozygous or compound heterozygous mutation in the *TPO* gene located on chromosome 2p25. TPO catalyzes the iodination of tyrosine residues in thyroglobulin using H_2O_2 and mediates their coupling to generate thyroid hormones. *TPO* defects cause severe congenital hypothyroidism with goiter and a total or partial iodine organification defect. After sodium perchlorate administration, accumulated radioiodide is rapidly released from the thyroid, reflecting failure of iodide oxidation and binding to tyrosine residues in thyroglobulin [15]. *TPO* deficiency is the most common cause of thyroid dyshormonogenesis with permanent

CH [16]. If a newborn with congenital hypothyroidism has biallelic *TPO* mutations, lifelong thyroid hormone treatment is needed, and careful monitoring for fetal goiter is recommended in future pregnancies [17]. Although the condition follows a recessive inheritance pattern, about 20% of cases show only monoallelic *TPO* mutations are identified, likely due to undetected variants in intronic or regulatory regions [18]. Niu et al. [19] reported that even monoallelic *TPO* mutations may be associated with transient neonatal hypothyroidism.

Haddad and Sidbury reported the first *in vitro* demonstration of impaired thyroid peroxidase activity in a patient with a thyroid hormone organification defect in 1959 [20]. Abramowicz et al. [21] identified a *TPO* gene mutation in 1992 in a patient presenting with partial iodide organification defect. To date, the HGMD has documented 287 mutations in the *TPO* gene [14].

IODIDE ORGANIFICATION DEFECT, H_2O_2 GENERATION DEFECT: *DUOX2* MUTATIONS (OMIM #607200, TDH6)

TDH6 is caused by homozygous or compound heterozygous mutations in the *DUOX2* gene located on chromosome 15q21. Duox plays a key role by producing H_2O_2 required for TPO-driven iodination and coupling reactions [22]. CH due to *DUOX2* mutations typically presents with goiter and elevated Tg, and most patients demonstrates a partial iodide organification defect (PIOD) on the perchlorate discharge test. Several studies have reported that biallelic *DUOX2* mutations are associated with permanent CH accompanied by PIOD. Iodide supplementation may be considered as an alternative to lifelong thyroid hormone replacement therapy [1]. Although most dyshormonogenesis defects follow an autosomal recessive inheritance pattern, a single defective *DUOX2* allele can cause transient CH due to haploinsufficiency, particularly during the neonatal period or pregnancy when thyroid hormone synthesis demand is highest [23].

Moreno et al. [23] first described patients with CH with total/partial iodide organification defect caused by *DUOX2* mutations in 2002. In the Korean populations, *DUOX2* variants represent a relatively common cause of CH, often accompanied by normal-sized or enlarged eutopic thyroid glands [24]. The HGMD currently lists 527 different *DUOX2* mutations [14].

IODIDE ORGANIFICATION DEFECT, H_2O_2 GENERATION DEFECT: *DUOXA2* MUTATIONS (OMIM #274900, TDH5)

TDH5 is caused by homozygous or compound heterozygous mutation in the *DUOXA2* gene on chromosome 15q21. DUOXA2 functions as a maturation factor for DUOX2 [22]. Zamproni et al. [7] identified homozygous *DUOXA2* mutation in a patient with permanent CH and dyshormonogenic goiter in 2008. The mutant protein failed to reconstitute DUOX2 activity *in vitro*. A perchlorate discharge test revealed partial iodide discharge [7]. However, a monoallelic *DUOXA2* mutation linked to transient CH was reported in 2015, highlighting the need for additional investigation. To date, 89 different mutations in *DUOXA2* have been reported in the HGMD [14].

IODIDE EFFLUX DEFECT: PENDRED SYNDROME, *SLC26A4* MUTATIONS (OMIM #274600, TDH2B)

Pendred syndrome (PDS) is caused by homozygous or compound heterozygous mutation in the *SLC26A4* gene on chromosome 7q22.3. Pendrin is expressed in the thyroid, inner ear, and kidney. In the thyroid, pendrin is in the apical membrane of follicular cells, where it is thought to play a role in transporting iodide across the apical surface [25]. PDS is the most common syndromic cause of deafness. It is characterized by sensorineural hearing loss, developmental abnormalities of the cochlea and diffuse thyroid goiter [26]. In perchlorate discharge test, patients exhibit partial discharge of iodide [27], and they typically develop enlarged thyroid glands beginning in childhood. Although most patients are euthyroid, an exaggerated response to thyrotropin-releasing hormone indicate compensated for hypothyroidism [28], and approximately 10% of patients have elevated TSH levels [29]. With sufficient dietary iodide, most patients are euthyroid.

Pendred syndrome was first described by Vaughan Pendred in 1896 [30]. Everett et al. [26] identified the gene mutated in Pendred syndrome, *SLC26A4*, using a positional cloning strategy in 1997. Currently, the HGMD lists 763 different mutations in *SLC26A4* [14].

THYROGLOBULIN SYNTHESIS: *TG* MUTATIONS (OMIM #274700, TDH3)

TDH3 is caused by homozygous or compound heterozy-

gous mutation in the *TG* gene on chromosome 8q24. Thyroglobulin (Tg), a glycoprotein generated within the endoplasmic reticulum of thyroid follicular cells, is delivered to the colloid by exocytotic vesicles through the apical membrane [5]. It functions as a structural platform for hormone production by offering tyrosyl residues, which form the non-iodide portion of thyroid hormones. The severity of thyroid dysfunction differs among individuals with impaired Tg production. The condition is characterized by undetectable or very low serum Tg levels despite elevated TSH, often accompanied by markedly enlarged goiter [5]. Thyroid scintigraphy typically shows high uptake in an enlarged gland, and no perchlorate discharge is observed because iodide organification remains intact [1]. CH caused by *TG* mutations is usually permanent, requiring lifelong L-T4 medication [31]. Sugisawa et al. reported that monoallelic variants in *DUOX2*, *TSHR*, *TG*, and *TPO* are more frequent in hypothyroidism patients (16.8%) than in the general population (3.3%) and act as risk factors rather than direct causes of disease [32].

Riddick et al. reported hypothyroidism patients with absence of Tg in 1969 [33], and the first *TG* gene mutation was reported by Ieiri et al. in 1991 [34]. The HGMD currently lists 480 different mutations in *TG* [14].

IODIDE RECYCLING DEFECT: *IYD* MUTATIONS (OMIM #274800, TDH4)

TDH4 is caused by homozygous mutation in the iodotyrosine deiodinase gene (*IYD*) on chromosome 6q25. Deiodinases are membrane-bound isoenzymes that require NADPH and FAD for activity and are expressed in multiple tissues, including the thyroid, kidney, and liver. In affected patients, the inability to deiodinate radiolabeled MIT and DIT leads to ongoing urinary loss of iodine and tyrosine. On scintigraphy, an enlarged thyroid usually demonstrates a rapid and high initial uptake of ^{123}I, followed by a spontaneous decline without perchlorate administration. Elevated urinary MIT and DIT detected by tandem mass spectrometry may aid in diagnosis [1]. Iodine supplementation, such as Lugol's solution, has been reported as a potential alternative to L-T4 treatment in patients with *IYD* deficiency [35]. Iodide deficiency due to biallelic *IYD* mutations may not manifest at birth. Affected patients can have normal neonatal CH screening results but later present between 1.5 and 8 years of age with complications of untreated hypothyroidism. Therefore, even if initial thyroid function is normal, careful follow-up is clinically important [36]. A heterozygous carrier of an inactivating mutation was recently reported to develop overt hypothyroidism, suggesting a possible dominant pattern of inheritance [37].

Moreno et al. identified *IYD* mutations in patients with hypothyroidism in 2008 [36]. A total of 32 mutations in *IYD* have been reported in the HGMD [14].

CONCLUSIONS

CH due to thyroid dyshormonogenesis represents a genetically heterogeneous group of disorders affecting multiple steps of thyroid hormone synthesis. Mutations in genes such as *SLC5A5*, *TPO*, *DUOX2*, *DUOXA2*, *TG*, *SLC26A4*, and *IYD* lead to variable clinical phenotypes, ranging from transient to permanent hypothyroidism. Recent advances in molecular genetics have improved understanding of genotype–phenotype correlations and revealed that some defects may show atypical inheritance patterns or partial functional impairment. A precise genetic diagnosis can guide individualized treatment strategies, predict disease course, and allow early identification of affected family members. In addition, distinguishing transient from permanent hypothyroidism can help avoid unnecessary lifelong treatment. Future studies integrating genetic, biochemical, and clinical data will further improve risk stratification and support the development of precision medicine approaches in congenital hypothyroidism.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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JIG Journal of Interdisciplinary Genomics

Instruction for Authors

Revised 3rd: June 23, 2023

Enacted in January 31, 2019 and most recently revised in June 23, 2023 and applied from Vol 5, No 2 (October 2023)

STUDY CONDUCT AND POLICIES

1. Research and publication ethics

In regard to the process of reviewing and assessing the manuscripts, including the ethical guidelines and plagiarism/duplicate publication and study misconduct, it should conform to the ethical guidelines specified in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/recommendations/), which were established by the International Committee of Medical Journal Editors (ICMJE). For the policies on the research and publication ethics not stated in this instruction, Good Publication Practice Guidelines for Medical Journals 3rd (Korean Association of Medical Journal Editors, KAMJE; http://kamje.or.kr/intro.php?body=publishing_eth-ics) or Guidelines on Good Publication (Committee on Publication Ethics, COPE; http://publicationethics.org/resources/guidelines) can be applied.

2. Disclosure of conflicts of interest

Financial sponsorship should be stated in the conflicts of interest. Any other financial support associated with the study, including stocks or consultation arrangements with pharmaceutical companies should be stated at the end of the text, under a subheading "Conflicts of interest."

3. Statement of informed consent

Human study must conform to ethical standards, and be approved by the appropriate Institutional Review Board (IRB). A statement concerning IRB approval and consent procedures must appear at the beginning of the "Methods" section. Any systematic data gathering effort in patients or volunteers must be approved by an IRB or adhere to appropriate local/national regulations. Authors may be questioned about the details of consent forms or the consent process. On occasion, the Editor-in-Chief may request a copy of the approved IRB application from the author.

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Clinical research studies must state that the work was done in accordance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki in 1975 (revised in 2013; http:// www.wma.net/en/30publications/10policies/b3/index. html). Clinical studies that do not meet the Declaration of Helsinki will not be considered for publication. Human subjects must not be identifiable. Patients' name, initial, hospital number, date of birth, or other protected health-care information must not be disclosed.

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A corresponding author should be designated when there are two or more authors. The corresponding author is primarily responsible for all issues to the editor and audience. Any comment of the corresponding author is regarded as opinion of all coauthors.

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct re-

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- Review article
- Editorial
- Brief report
- Image
- Letters to the editor

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   (2) Abstract and keywords.
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   (4) Notes:
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Nonessential tables and figures may accompany articles as online-only supplemental files. All online-only supplementary files should be combined in one document file (whenever possible) and uploaded separately during the submission process. This file must be clearly labeled as "Online-Only Supplemental Material." In addition, supplemental online-only files must be referenced in the main text of the manuscript at least once (e.g., "Supplemental Table S1").

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- Each author took a certain role and contributed to the study and the manuscript.
- The corresponding author signed electronically a statement disclosing any conflict of interest on behalf of all author(s) at the time of submission.
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