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Genetically Determined Central Hypothyroidism

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Abstract

Central, secondary or low TSH hypothyroidism can be congenital or acquired. Congenital Central hypothyroidism (CH-C), either isolated or (unlike primary hypothyroidism) combined with deficiency of other pituitary hormones, is usually caused by mutations in genes related either to TSH synthesis or pituitary ontogenesis. The prevalence of CH-C is higher than previously considered, ranging from 1:16000 to 1:20000 live births. Isolated CH-C is most frequently caused by mutations in the *TSHβ*-subunit and in rare cases by *TRHR* gene mutations. Either one of these mutations are inherited as a recessive trait. In patients with multiple pituitary hormone deficiency, molecular defects have been detected in the following genes: *IGSF1*, *PROP1*, *POU1F1*, *LHX3*, *LHX4*, *HESX1*, *SHH*, *TGIF*, *GLI2*. The resulting phenotype varies and the mode of inheritance could be autosomal dominant, autosomal recessive or X-linked, depending on the specific gene involved. In patients with CH-C, the timely identification of the underlying genetic defect is crucial because it leads to early and appropriate management that improves prognosis and determines genetic counseling.

Keywords: Pituitary; Thyroid; TSHβ-subunit; Central hypothyroidism; PROP1; SHH; TGIF; TRHR

Introduction

Central hypothyroidism (CH) refers to hypothyroidism that is not caused by anatomical or functional defects of the thyroid gland per se (primary hypothyroidism) but by inefficient synthesis of TSH (secondary hypothyroidism) [1,2]. Central hypothyroidism might be congenital (CH-C) or acquired. The TSH values in individuals with central hypothyroidism would be expected to be subnormal. Although that is usually the case, normal or mildly elevated TSH values can also be detected in certain cases, leading to an erroneous diagnosis of primary hypothyroidism. This phenomenon has been attributed to an aberrant TSH molecule, which is measurable by applied methodology but is biologically inactive [3-5]. Regardless of the mechanism involved one should be aware of this phenomenon in order to avoid misinterpretation and diagnose primary instead of secondary (central) hypothyroidism.

A distinction between primary and secondary hypothyroidism is also important because in many CH-C cases TSH deficiency is accompanied by deficiency of other pituitary hormones (multiple pituitary hormone deficiency – MPHD). In such cases the concomitant deficiency of growth hormone (GH) and/or cortisol may cause hypoglycemia with adverse effects on brain function. One should also consider that in most screening programs for congenital hypothyroidism, only TSH is determined and hence CH-C escapes detection. Importantly, even if the neonatal screening procedure is enriched with T4 determination, not all cases will be identified because in a significant number of CH-C cases the thyroid function at birth is normal. Consequently, the screening results can be falsely normal or falsely re-assuring [6]. In such cases, only a high index of suspicion will lead to prompt identification of affected individuals.

Prevalence of CH-C

A more precise estimate of the prevalence of CH-C has been obtained in recent years based on the application of more efficient neonatal screening tests, which are also supplemented by an adequate follow-up period. The initial estimates of the prevalence of CH-C in the United States and Canada ranged from 1:106304 to 1:29.000 [7,8]. In a more recent study from The Netherlands, a CH-C prevalence of 1:20263 was reported [9]; 78% of these subjects had MPHD, 53% had a pituitary malformation on magnetic resonance imaging (MRI). In this particular report, it was also mentioned that delay in the detection of MPHD resulted in significant morbidity, and a mortality rate of 14%, possibly accounted for by the co-existence of GH and/or cortisol deficiency. Moreover, the CH-C cases constituted 13.5% of all cases of permanent congenital primary and secondary hypothyroidism [9]. Analogous were the results of a study by Kempers et al. [10] in which a prevalence of CH-C of 1:21.000 was estimated. In another study by Lanting et al. [11] the prevalence of CH-C, based on T4, TSH and T4/TBG ratio determination was 1:16404. Thus, current data indicate that the prevalence of CH-C is higher than previously considered and ranges from 1:16400 to 1:20.000 live births, most of the cases having besides central CH, deficiency of other pituitary hormones (MPHD). Herein, we will review the molecular defects causing CH-C, isolated or in the context of MPHD (Table 1).

Isolated CH-C

This form of CH-C can be caused by mutations in the *TSHβ*-subunit, or thyrotropin releasing hormone receptor (*TRHR*) genes.

Mutations in the *TSHβ*-subunit gene: Mutations in the *TSHβ*-subunit gene constitute the most common genetic defect of isolated CH-C. TSH is a member of the glycoprotein hormone family, the other members being follicle-stimulating hormone (FSH), luteinizing hormone (LH), and chorionic gonadotropin (CG). These glycoprotein hormones share a common α-subunit and a β-subunit, the latter

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Forms of central congenital hypothyroidism	
A) Isolated CH-C	
I.	*TSHβ*-subunit
II.	*TRHR*
B) CH-C caused by *IGSF1* gene	
C) CH-C as part of MPHD[1]	
I.	Genes related to pituitary organogenesis
1.	*PROP1*
2.	*POU1F1/PIT1*
3.	*LHX3*
4.	*LHX4*
5.	*HESX1*
II.	Genes related to PSIS[2] or isolated pituitary hypoplasia
1.	*SHH*
2.	*TGIF*
3.	*GLI2*

[1]MPHD: Multiple Pituitary Hormone Deficiency
[2]PSIS: Pituitary stalk interruption syndrome

Table 1: Synopsis of genes related to central congenital hypothyroidism (CH-C).

conferring the specificity to their action. The TSH β-subunit is encoded by the *TSH β-subunit* gene located in the short arm of chromosome 1 (1p13) and is consisting of three exons, the first one being non coding [12]. Mutations in this gene cause isolated CH-C, an autosomal recessive disorder, first reported as a distinct clinical entity in 1971 by Miyai et al. [13]. The molecular basis of the disease was unraveled almost 20 years later [14-16]. The initially detected mutations were p.G29R in three Japanese families and p.E12X in two Greek families. The affected subject's present symptoms of hypothyroidism and low thyroxin values associated with inappropriately low TSH. If not recognized and treated early, this disorder leads to mental subnormality.

Following initial reports on the molecular defect of *TSHβ*-subunit gene, various mutations have been described with an interesting geographical clustering. Thus, in a study of patients with isolated CH-C from European countries [17,18] it was found that the mutation 313 delT (p.C105Vfs114X) is the most frequent cause of the *TSHβ*-subunit gene defects in western and central Europe as well as in Latin America. Interestingly, in eight patients with CH-C from seven unrelated Argentinean families, the same mutation (p.C105Vfs114X) was identified [19]. On the other hand, the p.Q49X mutation seems to predominate in the Mediterranean countries (Turkey, Egypt, Taskend, France) [20]. The clustering of these two mutations might reflect a founder effect or a mutational hot spot [21]. The splice site mutation IVS2 + 5G>A (p.1152+5G>A) has been reported in three Turkish families and was shown to be the result of founder effect [22,23]. This mutation was also detected in our laboratory in a Kurdish family (unpublished observation). The mutation p.G29R has been detected in Japanese patients [15]. The p.E12X and p.C85R mutations have exclusively been detected in Greek patients and, quite interesting, in subjects from Greek islands and not from the mainland [16,24]. This should not be attributed to elected referrals because other molecular defects detected in our laboratory (e.g. *PROP1*) have a more generalized geographic distribution [25]. Further population genetic studies might offer a plausible interpretation for the "journey" and distribution of the *TSHβ*-subunit gene mutations.

Mutations in the thyrotropin-releasing hormone receptor (*TRHR*) gene: TRHR belongs to the G-protein – coupled seven transmembrane domain type of receptor that, after TRH binding, activates the inositol phosphate-calcium protein kinase C transduction pathway. The gene encoding *TRHR* maps to chromosomal locus 8q23 and has three exons. Collu et al. [26] in 1997 first reported a boy born to non-consanguineous Caucasian parents, who was examined for short stature at age 9yrs. The evaluation disclosed low TSH hypothyroidism with no response of TSH and prolactin to TRH. DNA analysis revealed compound heterozygosity with inheritance of a differently mutated allele from each parent. Both mutated receptors, when transferred to eukaryotic cells, resulted in greatly reduced or absent TRH binding and TRH stimulation of inositol phosphate accumulation. The clinical manifestations were rather mild; short stature and delayed bone maturation. The poor school performance of this child was most likely not related to the hypothyroidism since his two unaffected brothers had the same difficulties in school and had comparable IQ values. In 2009, Bonomi et al. [27] reported a family with two members affected by CH-C but having a different phenotype. The proband was examined for short stature, lethargy and fatigue at age 11yrs. The evaluation showed low TSH hypothyroidism with no response of TSH and prolactin to TRH. DNA analysis showed a homozygous mutation of the *TRH* gene in the proband and his 22 yrs old sister who had no symptoms of hypothyroidism and had three pregnancies two of which resulted in the birth of normal children and one resulted in a spontaneous abortion. The parents were heterozygous for the same mutation. Thus, from the available data this form of CH-C is inherited in a recessive mode, which is either rare or underdiagnosed at present and results in a mild phenotype especially as far as mental development is concerned.

Mutations in the *IGSF1* gene: The immunoglobulin super family member 1 (*IGSF1*) gene maps to chromosomal locus Xq25. IGSF1 mRNA is abundantly expressed in Rathke's pouch, the developing and adult pituitary gland and the testes. IGSF1 protein is detected in murine thyrotrophs, somatotrophs and lactotrophs but not in gonadotrophs or in testes. Mutations in the *IGSF1* gene were recently identified in a newly defined, X-linked disorder characterized by central hypothyroidism, macroorchidism and variable prolactin and GH deficiency. This molecular defect in humans impairs trafficking of the IGSF1 C-terminal domain to the cell surface, consistent with loss of protein function. The exact mechanism causing macroorchidism is not apparent at present [28]. The authors attribute the central hypothyroidism to a reduced TRH signaling, which, however, does not fully explain the phenotype. In a subsequently reported case from Japan [29], macroorchidism was not present, while there was no response of TSH and prolactin to TRH, consistent with reduced TRH signaling.

Central Hypothyroidism in the Context of Multiple Pituitary Hormone Deficiency

Genetic defects related to pituitary organogenesis

The various pituitary cell lineages of the adenohypophysis emerge from a common primordium. Different transcription factors are involved in precursor proliferation, cell lineage determination and terminal differentiation leading to distinct cell phenotypes. Mutations in genes encoding these transcriptions factors may lead to MPHD, which usually includes central – low TSH – hypothyroidism [30-32]. Besides hypothyroidism, the clinical manifestations include short stature, as well as, failure to thrive, hypoglycemia, and liver dysfunction in the neonatal period. In males, small penis and testes are also detected [33,34]. It is thus important to identify these defects promptly and treat appropriately in order to ensure the best outcome and especially to prevent hypoglycemic seizures.

Mutations in the *PROP1* gene: *PROP1* gene maps to chromosomal

locus 5q35.3. It is expressed in the anterior pituitary (adenohypophysis) during the early stages of pituitary organogenesis and is essential for the specification and proliferation of somatotrophs, lactotrophs and the terminal differentiation of gonadotrophs. Inactivating mutations of the *PROP1* gene constitutes the most frequent cause of genetically determined pituitary hormone deficiency including TSH, GH, prolactin and gonadotrophins deficiency. The disorder is inherited as a recessive trait, the heterozygous carriers being asymptomatic. The most frequent *PROP1* mutation is a GA deletion at nucleotide 296 [31,32]. Patients with *PROP1* gene defects are usually evaluated later in childhood for short stature or subclinical hypothyroidism since pituitary deficiency gradually evolves. Nevertheless, *PROP1* gene defects can cause jaundice, raised liver transaminases, hypoglycemic episode and small penis in the neonatal period [33,34]. Such clinical features may obscure and delay the diagnosis if there is not a high index of suspicion. Patients with this defect, if appropriately managed, have a good outcome with respect to somatic growth, fertility and mental development.

Mutations in the *POU1F1/PIT1* gene: *PIT1* gene maps to chromosomal locus 3p11.2 and encodes a pituitary specific homeodomain transcription factor, which is important for the determination of pituitary cells producing GH, TSH and prolactin. Mutations in this gene are associated with GH and prolactin deficiency and various degrees of central hypothyroidism. The first mutation in humans was reported in 1992 and up to date more than 30 mutations have been identified [35-37]. The clinical phenotype is characterized by hypothyroidism, short stature as a result of GH deficiency, while gonadotrophic function is preserved. Pituitary atrophy constitutes an age dependent phenomenon [38]. *PIT1* gene defects are inherited either as a dominant or recessive trait without apparent phenotypic differences between the two forms.

Mutations in the *LHX3* gene: The LIM-homeodomain transcription factor, LHX3, is transiently expressed in the developing neural cord and brainstem, while, subsequently, is restricted to the developing and adult pituitary gland. *LHX3* gene maps to chromosomal locus 9 (9q34.3) in humans and contains seven coding exons and six introns. The produced protein is a key regulator of pituitary development and spinal cord motor neurons in fetal life. The abnormal proteins resulting from *LHX3* mutations demonstrate reduced capacity to activate promoters of genes expressed in the pituitary gland, while retaining a certain degree of activity on the nervous system promoters. Mutations in this gene lead to a phenotype characterized by MPHD, which includes central hypothyroidism. In certain cases limitation of neck rotation and hearing loss are also observed. The latter characteristic could be explained by the fact that *LHX3* is located in the sensory epithelium of the developing inner ear [39-42]. The disorder is inherited as a recessive trait.

Mutations in the *LHX4* gene: The *LHX4* gene maps to chromosome 1 (1q25.2) in humans and includes six coding exons. It encodes a 390-aminoacid protein, which is highly homologous to LHX3 protein except for the N-terminal region. Studies in humans and rodents have demonstrated expression of the *LHX4* gene in the developing hindbrain, cerebral cortex, pituitary gland and spinal cord. The LHX4 LIM homeodomain transcription factor has essential roles in pituitary gland development. Heterozygous mutations in this gene have been associated with variable phenotypes, which include short stature, GH, ACTH and TSH deficiency, hypoplastic pituitary, ectopic neurohypophysis and hindbrain defects [43-46].

Mutations in the *HESX1* gene: *HESX1* gene maps to chromosomal locus 3p14.3 and encodes the HESX1 transcription factor. This transcription factor is a member of the paired like homeodomain proteins, functions as a transcriptional repressor and is essential for normal forebrain development. Mutations in *HESX1* gene have been described in patients with various forms of hypopituitarism with or without septo-optic dysplasia (SOD) [47-50]. Depending on the mutation, the disorder is inherited either as a dominant trait with incomplete penetrance or as a recessive trait.

Pituitary Stalk Interruption Syndrome (PSIS) or Isolated Pituitary Hypoplasia

The phenotype of PSIS is clinically characterized by short stature associated with MPHD, which includes central hypothyroidism. MRI discloses a distinct anatomical defect namely absent or faint pituitary stalk, adenohypophysial hypoplasia with or without ectopic neurohypophysis. The pathogenetic mechanism involved remains uncovered in most cases [51]. Based on distinct clinical phenotypes, we recently proved that, at least in some cases with *PSIS* or isolated pituitary hypoplasia, HPE-related gene mutations are causative factors [52]. Holoprocencephaly (HPE) is the most common developmental brain anomaly in humans and is caused by various genetic and environmental factors. The most commonly encountered HPE-related molecular defects are in the *SHH*, *ZIC2*, *SIX3* and *TGIF* genes, which are detected in 5-10% of HPE cases [52]. The extended spectrum of clinical manifestations even in the case of specific defects in HPE-related genes is probably a result of the synergistic effect of other co-existing genetic variants as well as environmental factors.

Mutations in the *SHH* gene

SHH gene maps to chromosomal locus 7q36, and constitutes a major developmental morphogen, widely expressed during embryonic development [53]. With respect to the role of *SHH* in pituitary development it has been shown that *SHH* is implicated in cell proliferation and differentiation of the pituitary gland in zebra fish and has a role in Rathke's pouch development [54]. A heterozygous mutation C1279G>A (p.G427R) in the *SHH* gene has been uncovered in one patient with pituitary hypoplasia and MPHD including central hypothyroidism, without HPE brain defects [55]. Furthermore, a variant of the *SHH* gene (c* 8G>T) was recently reported in a patient with MPHD and PSIS anomaly but without HPE findings [56].

Mutations in the *TGIF* gene

TGIF gene maps to chromosomal locus 18p11.3 and encodes a transcription factor that represses TGIF-activated *SMAD* target genes and the response to retinoids. It is expressed in many areas of the developing embryo including the forebrain and cerebral cortex as well as the optic pit and is also involved in the development of midline structures [57]. A novel heterozygous mutation of the *TGIF* gene was detected in a patient with MPHD including CH-C, in whom the MRI disclosed PSIS without HPE related anomalies [55].

Mutations in the *GLI2* gene

GLI2 gene maps to chromosomal locus 2q14 and encodes a transcription factor downstream the SHH signaling pathway and is related to HPE anomaly. Heterozygous mutations in *GLI2* gene were recently reported in patients with MPHD associated with PSIS and without HPE brain anomalies [58].

Central hypothyroidism is managed by daily oral administration of L-thyroxin as a substitution therapy for life, irrespective of the specific genetic cause and mode of inheritance. Again, we should underline

the fact that in most neonatal screening programs for congenital hypothyroidism, central hypothyroidism escapes detection. The latter is important because early recognition and prompt initiation of therapy in the neonatal life results in a normal somatic and mental development of the patient. L-thyroxin replacement therapy is extremely easily accessible at very low cost, with high rates and ease of compliance and very efficient. Therefore, there is no room for a gene therapy alternative like in the case of other hormone deficiencies such as GH, EPO, insulin etc [59,60].

Low TSH (secondary) congenital hypothyroidism, unlike primary hypothyroidism, is in most cases a well-documented familial disorder. Therefore, defining the molecular defect in the index case should always be a priority for appropriate management and improved prognosis. For the initial etiologic classification, which will be very helpful in the search for the underlying molecular defect, accompanying clinical manifestations and the hormonal response to TRH should be defined [1]. Genetic studies in the extended family tree could lead to early recognition and proper management of other affected members or detection of carriers, a very useful process in genetic counseling.

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