REVIEW PAPER

GROWTH HORMONE DEFICIENCY (GHD) AND SMALL FOR GESTATIONAL AGE (SGA): GENETIC ALTERATIONS

Jancevska A.,1,2 Gucev Z.S.,1,2 Tasic V.,1,2 Pop-Jordanova N.1,2

1Medical Faculty, Skopje, R. Macedonia
2University Children's Diseases Clinic, Skopje, R. Macedonia

Abstract: Short stature associated with GH deficiency has been estimated to occur in about 1 in 4000 to 1 in 10,000 in various studies. In the last decade new genetic defects have been described in all the levels of the growth hormone–releasing hormone (GH-RH)–GH–IGF (insulin-like growth factor) axis. Genetic defects in the GHRH and in various parts of the Insulin-like growth factor system have been demonstrated. Genetic defects causing isolated GH deficiency (GHD), as well as multiple pituitary hormonal deficiencies have been analysed in detail. Signalling molecules and transcription factors leading to the development of the pituitary gland have been discovered and their function recognized. In animal models and in humans the importance of the transcription factors HESX1, PROP1, POU1F1, LHX3, LHX4, TBX19, SOX2 and SOX3 has been extensively studied. Genetic alterations of those transcription factors dictate the highly variable phenotype: from isolated hypopituitarism to multiple pituitary hormonal deficiencies with or without malformations (e.g. septo-optic dysplasia or holoprosencephaly). Small for gestational age (SGA) children are increasingly recognized to be a heterogeneous group in which new mechanisms of growth retardation and metabolic disturbances have been proposed. Since SGA is considered to be the main reason for the short stature in 10% of short adults this is a large group with a great potential for novel insights into mechanisms of growth and metabolic disturbances. A group of signalling proteins are involved in prenatal (SGA) growth retardation: IRS-1, PDK1, AKT1, and S6K1. In addition, an attractive modern theory supposes that a disturbed mother-placenta-foetus relation results in the activation of the so-called "thrifty phenotype" of which the IGF system is a vital part. The mechanisms assure short-term postnatal survival in conditions of deficient nutritional supply. However, as a consequence, the abundant postnatal nutritional supply and the "thrifty phenotype" result in increased adult risk of metabolic syndrome, diabetes mellitus type 2 (DM2) and cardiovascular disease.
The manuscript reviews in brief genetic alterations in humans leading to growth hormone deficiency (GHD), multiple pituitary hormone deficiencies (MPHD) and SGA.

**Key words:** Pituitary, genetic defects, IGF system, pituitary transcriptional factors, small for gestational age.

**Introduction**

The past couple of decades have seen a tremendous development in the understanding of the underlying mechanisms of growth hormone deficiency and hypopituitarism. The main regulatory axis GHRH-GH-IGF has been described in detail and genetic defects causing pituitary dwarfism have been discovered at every level of the axis. In addition, genetic alterations in a number of pituitary transcription factors: Pit1 / POU1F1, PROP1, HESX1, LHX3, LHX4, SOX2, SOX3, have been found to cause pituitary deficiencies. The ever-expanding knowledge about the causes of human short stature has been expanded on children born small for gestational age (SGA). Numerous defects in the IGF system and in particular signalling proteins were found to be involved in prenatal growth retardation: IRS-1, PDK1, AKT1, and S6K1. In addition, compelling evidence in mice shows that those genes are involved in glucose homeostasis, fat metabolism. Strikingly, some of these proteins are identified as oncogenes. This brief review describes the basic mechanisms of human growth retardation caused by the abovementioned genes, transcription factors and proteins.

**Classification of isolated growth hormone deficiency**

**Structure and function of GH and CS genes**

The GH gene cluster has five structurally similar genes: (GH-1, CSHP [chorionic somatomammotropin pseudogene], CSH-1 [chorionic somatomammotropin gene], GH-2, and CSH-2) 30. The length is ~65,000 bp (65 kb), the location: the long arm of chromosome 17 (bands q22–24) [1].

The GH-1 gene consists of five exons and four introns and encodes the GH (a 191 amino acid peptide) [1–3]. A major 22-kd product is found in 75% of the circulating GH, alternative splicing can result in minor forms [2–4]: a bioactive 20-kd GH peptide that results from the cryptic 30 splice site in exon 3, deleting amino acid 32–46 [4–7]. The expression of the GH-1 gene is further controlled by cis- and trans-acting elements and factors [8, 2].
### Table 1 – Таблица 1

<table>
<thead>
<tr>
<th>Gene</th>
<th>PhenoType</th>
<th>Inheritance</th>
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| Pitu / POU1F1 | *Hormonal deficiencies*: GH, PRL, TSH  
                     Imaging: Anterior pituitary gland: normal to hypo  
                     Posterior pituitary gland: normal  
                     *Other manifestation*: none        | R/D         |
| PROP 1        | *Hormonal deficiencies*: GH, PRL, TSH, LH, FSH, (ACTH)  
                     Imaging: Anterior pituitary gland: hypo to hyper  
                     Posterior pituitary gland: normal  
                     *Other manifestation*: none        | R           |
| HESX1         | *Hormonal deficiencies*: GH, PRL, TSH, LH, FSH, ACTH, IGHD, CPD  
                     Imaging: Anterior pituitary gland: hypo  
                     Posterior pituitary gland: ectopic  
                     *Other manifestation*: eyes, brain, septo-optic dysplasia | R/D         |
| LHX3          | *Hormonal deficiencies*: GH, TSH, ACTH  
                     Imaging: Anterior pituitary gland: hypo  
                     Posterior pituitary gland: normal  
                     *Other manifestation*: neck rotation 75°–85° (?),  
                     (no: 160°–180°)  
                     *Other manifestation*: sella turcica/skull defects, cerebellar defects | R           |
| LHX4          | *Hormonal deficiencies*: GH, LH, FSH  
                     Imaging: Anterior pituitary gland: hypo  
                     Posterior pituitary gland: normal  
                     *Other manifestation*: sella turcica/skull defects, cerebellar defects | D           |
| SOX2          | *Hormonal deficiencies*: GH, LH, FSH  
                     Imaging: Anterior pituitary gland: hypo  
                     Posterior pituitary gland: normal/hypo  
                     *Other manifestation*: bilateral anophthalmia, spastic, altered brain development esophage atresia | R/D         |
| SOX3          | *Hormonal deficiencies*: GH  
                     Imaging: Anterior pituitary gland: normal to hypo  
                     Posterior pituitary gland: normal, ectopic  
                     *Other manifestation*: mental retardation, abnormality of corpus callosum, absent infundibulum | XL          |

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**Abreviations**: ACTH, adrenocorticotropic hormone; CPHD, combined pituitary hormone deficiency; D, autosomal dominantly inherited; FSH, follicle-stimulating hormone; GH, growth hormone; IGHD, isolated growth hormone deficiency; LH, luteinising hormone; PRL, prolactin; R, autosomal recessively inherited; TSH, thyroid-stimulating hormone; XL, x-linked.
Familial isolated growth hormone deficiency

Since MRI examinations detect only about 12% to 20% of anomalies in either hypothalamus or pituitary gland in isolated growth hormone deficiency (IGHD), it is obvious that a higher proportion of sporadic cases may have a genetic cause [9]. In fact, 3% to 30% of cases have an affected first-degree relative suggesting a genetic etiology. So far, familial IGHD is shown to have at least four Mendelian forms [8, 2]: two forms that have autosomal-recessive inheritance (IGHD type IA, IB), an autosomal-dominant (IGHD type II) and, a X-linked (IGHD III) form.

Table 2 – Таблица 2

| Alteration of the growth hormone-realising hormone axis affecting growth in humans (differential diagnosis of insulin-like growth factor-1 deficiency) |
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<table>
<thead>
<tr>
<th>Hypothalamus</th>
<th>Transcription factors</th>
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<td>GHRH-gene</td>
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<tr>
<th>Pituitary gland</th>
<th>Transcription factors</th>
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<td>TPIT</td>
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<td>LHX3</td>
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<tr>
<td>PROP1</td>
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<td>GH-RH-receptor</td>
<td>GH-gene cluster</td>
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<td>GH-deficiency/bioinactivity</td>
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<thead>
<tr>
<th>GH-target organs</th>
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<td>GH-insensitivity (secondary)</td>
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<td>Malnutrition (eg, anorexia)</td>
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<td>Anti-GH antibodies</td>
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<th>IGF-1 defects</th>
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<td>IGF-1 transport/metabolism/clearance</td>
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Isolated growth hormone deficiency type IA. Illig [10] described three children with severe short stature and GHD. Short length at birth and hypoglycaemia in infancy were also described. Nevertheless, the most striking feature was that the initial good response to exogenous GH was compromised by the development of anti-GH antibodies which effectively stopped growth [2, 11].

GH-1 gene deletions. Phillips et al. [11] analysed the genomic DNA from the children reported by Illig and discovered that the GH-1 gene was missing. Additional cases of GH-1 gene deletions have been described subsequently. Interestingly, development of anti GH antibodies was an inconsistent finding and some children respond well to the GH treatment despite having identical molecular defects [12]. The sizes of the deletions differ, but the most frequent (70%–80%) is 6.7 kb [8, 2]. 7.6, 7, 45 kb, and double deletions within the GH gene cluster are also described [8, 2].

In addition, single base pair deletions and nonsense mutations of the signal peptide were found to result in an absent production of GH and, consequently, in the production of anti-GH antibodies [8].

Isolated growth hormone deficiency type IB. Patients are found to have low but detectable levels of GH (> 7 mU/L; > 2.5 ng/mL). Their stature is remarkably short (> -2 standard deviation score [SDS] for age and sex), the height velocity is less than 25th percentile for age and sex. The bone age is significantly delayed, and an autosomal-recessive inheritance (two parents of normal height, two siblings affected) was supposed. Exogenous GH caused good growth response and no immunologic intolerance. Later, splicing sites mutations of the GH gene and a lack of GH have been demonstrated. The phenotype of IGHD type IB is more variable than IA and GH may be nearly lacking or low [8].

GHRH-gene. GHRH gene mutations or deletions causing IGHD have been reported [13, 14].

GHRH-receptor gene. A nonsense mutation in India and a point mutation in the GHRH-receptor gene in Pakistan have been described [15, 16]. Patients are very short (-7.4 SDS), normally proportioned, have normal intelligence, and some are fertile. GH-RH and GHBP concentrations are normal, but GH is undetectable and IGF-I is extremely low. Further patients and families from Sri Lanka, Brazil, Spain, the United States and Pakistan were reported [17–20]. This is a syndrome of autosomal-recessive IGHD and anterior pituitary hypoplasia (139, 190). Strikingly, even in siblings with the same mutation some variability in anterior pituitary size was reported [21].

In addition, alterations of the specific transcriptional regulation of the GH-1 gene may produce IGHD type IB. A heterozygous 211-bp deletion within...
the retinoic acid receptor-a gene was found to produce an IGHD type IB phenotype [22].

**Isolated growth hormone deficiency type II.** Type II (IGHD II) is mainly caused by mutations within the first six base pairs of intervening sequences 3 (50 IVS-3) [8], which result in a missplicing and loss of exon 3, producing a 17.5-kd GH isoform [8, 23], which lacks amino acid 32–71 (del32-71). Skipping of exon 3 caused by other GH-1 splice gene alterations has also been described: mutations in exon 3 (E3) splice enhancer ESE1 (E3 þ 1G-O T:ESE1m1; E3 þ 2A-O C:ESE1m2, E3 þ 5A-O G:ESE1m3) and ESE2 (downstream of the cryptic splice site in E3; ESE2: D721-735) and within suggested intron splice enhancers (ISE) (IVS-3 þ 28 G-O A: ISEm1; IVS-3del þ 28-45: ISEm2) sequences [8,24–31]. Some nonsense mutations might cause skipping of one or more exons during mRNA splicing: a so-called "nonsense-mediated altered splicing" [32]. Three other mutations within the GH-1 gene (missense mutations) are also reported as responsible for IGHD II: the substitution of leucine for proline, histidine for arginine, and phenylalanine for valine at amino acid positions 89 (P89V), 183 (R183H), and 110 (V110F) [33–35]. The 17.5-kd isoform exhibits a dominant-negative effect on the secretion of the 22-kd [36–38]. The variable phenotype of autosomal-dominant GHD may reflect a threshold and a dose dependency effect to the amount of 17.5-kd relative to 22-kd hGH [37, 38, 39], with variable impact on pituitary size, on onset and severity of GHD [40, 41].

**Isolated growth hormone deficiency type III.** This is an X-linked recessively inherited form of IGHD. The affected males are immunoglobulin and GH deficient [42, 43]. The disorder may be caused by mutations or deletions of a portion of the X chromosome [44]. McGuinness and co-workers [37] showed that the most severely affected lines rapidly developed severe GHD, dwarfism, profound pituitary hypoplasia and near total loss of somatotrophs. In addition, high-copy lines rapidly developed profound GHD, while low-copy mice showed a milder adult-onset GHD [29, 37]. Prolactin, TSH, and luteinizing hormone in males only were all significantly reduced in adult high-copy transgenic mice, whereas these deficits were absent or mild, with a later onset, in low-copy lines.

There is an evident variability in onset, severity, and progression, evident between mutation genotypes and more interestingly within families with the same mutation. It is to be stressed that other hormone deficits can develop in IGHD II patients.

The development of the pituitary gland is an extremely complex process. Its alterations can cause defects leading to pituitary deficiency and to various associated anomalies [45].
HESX1. Abnormalities of the pituitary gland and the forebrain can be linked in human disease. Septo-optic dysplasia (SOD) [46, 47] is defined by any combination of the triad of optic nerve hypoplasia (ONH), midline neuroradiological abnormalities (agenesis of the corpus callosum and absence of the septum pellucidum) and pituitary hypoplasia with panhypopituitarism [46–50]. The incidence of SOD is 1/10 000 live births [51]; it is equally prevalent in males and females, and sporadic and familial cases have been reported.

The phenotype is highly variable: ~30% of SOD cases have complete manifestations, 62% have hypopituitarism and 60% have an absent septum pellucidum [52]. The etiology is unknown, with the predominant hypothesis of a genetic defect underlying the developmental mechanisms. The SOD is more frequently associated with an autosomal recessive manner of inheritance [53–55]. Dominant inheritance has also been described [56, 57, 58, 59].

HESX1 is a member of the paired-like class of homeobox genes [60]. HESX1 is a transcriptional repressor, having repression domains within the N-terminal region and the DNA-binding homeodomain [61, 62]. In mice, homozygous disruption of Hesx1 is associated with a SOD phenotype. Mice have a reduction in forebrain tissue, absence of developing optic vesicles, decreased head size, craniofacial dysplasia with a short nose, absence of olfactory placodes, hypothalamic abnormalities and aberrant morphogenesis of the Rathke’s pouch [63]. In addition, 5% of the Hesx1-null mutants had no anterior pituitary [64].

In humans, a homozygous missense mutation (R160C) in the homeobox of HESX1 was identified in a highly consanguineous family, in which two affected siblings presented SOB features with optic nerve hypoplasia, hypoplastic corpus callosum and hypoplasia of the anterior pituitary gland with an undescended/ectopic posterior pituitary and panhypopituitarism [53, 63]. Since the parents were heterozygous for the mutation and phenotypically normal the autosomal recessive mode of inheritance was presumed. Subsequently additional homozygous mutations have been identified with variably severe phenotypes [64, 65].

Heterozygous mutations within HESX1 were found to be associated with milder phenotypes when compared with the homozygous mutations, leading to growth hormone deficiency (GHD) with or without an undescended posterior pituitary [57]. Optic nerve hypoplasia as well as midline forebrain abnormalities may be associated [58].

SOX3. SOX3 is a member of the SOX (SRY-related high mobility group (HMG) box) family of transcription factors [66]. Approximately 20 different SOX genes have been identified in mammals, and variation in homology exhibited within the HMG box between different members allows them to be grouped into different subfamilies [67]. SOX3 was among the first of the SOX
genes to be cloned, and together with SOX1 and SOX2, belongs to the SOXB1 subfamily exhibiting the highest degree of similarity to SRY [66].

Members of the SOXB1 subfamily of genes are expressed throughout the developing central nervous system (CNS) and are some of the earliest neural [68].

In humans, tandem duplications involving chromosome Xq26-27 have been identified in several pedigrees with mental retardation and hypopituitarism (69–72). The phenotypes of affected males are variable. All affected males manifest GH deficiency and varying degrees of developmental delay or mental retardation. Some individuals have been reported to have varying combinations of deficiencies of other hormones including adrenocorticotropic (ACTH), TSH or gonadotrophins, and complete panhypopituitarism has been documented in some cases. Unaffected carrier females in these pedigrees show preferential inactivation of the duplicated X chromosome; however, a rare family with five affected females presenting with short stature secondary to hypopituitarism, speech and language problems, hearing impairment and facial dysmorphism has also been reported with a 7.5 Mb duplication of chromosome Xq26.2-q27.1 [73]. Woods et al. [74] described a pedigree with two half-brothers manifesting evidence of X-linked hypopituitarism, in the absence of developmental delay, and harbouring a submicroscopic duplication on chromosome Xq27.1, further refining the critical interval to ~690 kb. The first child manifested GHD and borderline low FT4 concentrations, with hypoplasia of the lower half of the infundibulum and an abnormal corpus callosum, which contained a cyst within the splenium. The second sibling manifested a more severe phenotype of combined pituitary hormone deficiency (CPHD) with complete absence of the infundibulum and hypoplastic genitalia; however, his corpus callosum appeared normal. Both patients had anterior pituitary hypoplasia and an undescended posterior pituitary as revealed by magnetic resonance imaging (MRI). The duplication identified in this family is the smallest described to date encompassing SOX3 and two additional transcripts of unknown function, neither of which is expressed in the developing infundibulum [74], suggesting that the phenotype in these patients is due to the presence of an additional copy of SOX3.

Further implication of SOX3 in X-linked hypopituitarism comes from the identification of patients harbouring an expansion of one of the polyalanine tracts within the gene [74, 75]. Laumonnier et al. [75] identified an in-frame duplication of s33 bp occurring between nucleotides 711 and 743 and co-segregating in affected males in a large family with X-linked mental retardation and GH deficiency. This mutation encodes an additional 11 alanine residues and is predicted to cause expansion of the normal polyalanine tract from 15 to 26 residues. Additionally, a second novel expansion of seven alanine residues within the same tract has been identified in three siblings of a consanguineous pedigree presenting with profound and complete panhypopituitarism in association with anterior pituitary hypoplasia, an absent or hypoplastic infundibulum.
and an undescended posterior pituitary. There was no evidence of mental retardation or craniofacial dysmorphism in these individuals.

In summary, both duplications of Xq27 encompassing SOX3 and loss-of-function polyalanine expansion mutations are essentially associated with similar phenotypes, predominantly infundibular hypoplasia, suggesting that gene dosage of SOX3 is critical for normal development of the diencephalon and infundibulum, and consequently the anterior pituitary.

**SOX2.** SOX2 is also a member of the same SOXB1 subfamily. Homozygous loss of SOX2 results in peri-implantation lethality. SOX2 heterozygous mice show a reduction in size, male fertility [76], or in anophthalmia [77].

In humans, heterozygous de novo mutations in SOX2 were associated with bilateral anophthalmia or severe microphthalmia, learning difficulties, developmental delay, oesophageal atresia and genital abnormalities [78, 79–82]. In males SOX2 mutations were also found to be associated with anterior pituitary hypoplasia, hypogonadotropic hypogonadism, and genital abnormalities. Hippocampal and corpus callosum defects, oesophageal atresia and sensorineural hearing loss have also been reported [83, 84].

**LHX3/LHX4.** Lhx3 is a member of a homeobox gene family. The LIM family is characterized by the presence of a unique cysteine/histidine-rich zinc-binding domain. LHX3 is one of the earliest transcription factors expressed within the developing pituitary and is maintained in the adult pituitary, suggesting a role in the maintenance of mature anterior pituitary cell types [85, 86].

In humans, homozygous mutations in LHX3 have been identified in 12, all of which resulted in loss of LHX3 function [87–91]. The endocrine phenotype was similar to that described in patients with PROP1 mutations. All anterior pituitary hormones except ACTH were deficient. In addition, 9 out of 12 patients had a short, rigid cervical spine with limited head rotation and trunk movement. Two patients exhibited a small anterior on MRI. Interestingly, a patient was found to have a markedly enlarged anterior pituitary that was not evident in a previous MR scan performed 10 years previously [87].

So far, only a single mutation within LHX4 has been reported in a family with GH, TSH, ACTH deficiency and anterior pituitary hypoplasia with an ectopic posterior pituitary and absent pituitary stalk [92]. Nevertheless, other family members had short stature, isolated GH deficiency and a normal posterior pituitary.

**TBX19.** TBX19 is a member of the T-box family of transcription factors that contain a homologous DNA-binding domain. TBX19 is expressed within the developing anterior pituitary gland, in the ventral diencephalon, the POMC expressing corticotrophs in the anterior lobe and melanotrophs forming the intermediate lobe [93–95].

Приложение. Оцил. біол. мед. наук, XXX/2 (2009), 33–55
Mutations in TBX19 are associated with neonatal isolated ACTH deficiency. Interestingly it has not been reported in cases of juvenile-onset deficiency.

Twelve independent mutations have been identified as resulting in loss of TBX19 function, and implying a recessive mode of inheritance [96–99]. An additional three patients were identified as carrying only one mutant TBX19 allele, with a pedigree suggesting that other mutations may be present in the regulatory regions of the gene in some cases [97]. TBX19 mutations are found in patients with a homogeneous clinical phenotype with very low basal plasma ACTH and cortisol levels, and no significant ACTH response to corticotrophin-releasing hormone. Neonates have severe hypoglycaemia, seizures, and prolonged cholestatic jaundice [97]. About 25% of families with segregating TBX19 mutations suffered a neonatal death.

**PROP1**. Prop1 is a paired-like homeodomain transcription factor, expressed within the embryonic pituitary gland. In humans, PROP1 mutations are the most common cause of CPHD reported, accounting for ~50% of familial cases [100, 101, 102, 103]. 22 distinct mutations have been identified in more than 170 patients, all exhibiting recessive inheritance. With one exception, all mutations identified to date involve the DNA-binding homeodomain [104]. The most common mutation is a 2 bp deletion among three tandem GA repeats (296-GAGAGAG-302) within exon 2 resulting in a frameshift at codon 101 and the introduction of a termination codon at position 109 [101, 102, 105, 106]. A PROP1 mutation downstream of the homeo-domain involving a substitution of a tryptophan residue for a stop codon at position 194 (W194X) was also described [107].

PROP1 mutations are associated with GH, TSH, PRL and gonadotrophin deficiencies. Interestingly, the time of initiation and severity of pituitary hormone deficiencies is highly variable. Early-onset GH deficiency and growth retardation are common. Nevertheless, there has been normal growth in early childhood [108]. TSH deficiency is highly variable, being reported as the first symptom presenting in rare cases [101, 109–111]. In early life ACTH/cortisol levels are normal, but often cortisol deficiency occurs later in life [111–116]. Hypogonadism with a complete lack of pubertal development and spontaneous, albeit delayed, onset of puberty with subsequent development of gonadotrophin deficiency have been reported [101, 109, 110, 113]. Most individuals have a normal pituitary stalk and posterior lobe, with a small or normal size anterior pituitary gland on MRI. Rarely, an enlarged anterior pituitary gland has been reported [100, 111, 117].

A significant number of patients demonstrated pituitary enlargement in early childhood with subsequent regression and involution [114, 118].

**POU1F1**. POU1F1 (previously known as PIT1) is a pituitary-specific transcription factor belonging to the POU homeodomain family of transcription.
Pou1f1 is essential for the development of somatotroph, lactotroph and thyro-
troph cells [119]. R271W (Arg271Trp) is presumed to be a hot spot. Most of the
mutations reported in POU1F1 to date are recessive. Rarely, a number of hetero-
zygous point mutations have been identified [120]. A total of 27 POU1F1
mutations have been described including 22 recessive and 5 dominant mutations
in over 60 patients originating from 19 different countries [121]. GH and PRL
deficiencies generally present early in life. TSH deficiency can be highly vari-
able with presentation later in childhood [122, 123, 124]. Magnetic resonance
imaging demonstrates a small or normal anterior.

**SGA.** SGA is a child born within the delivery term with birth weight
and/or length (BW/BL) which is under two standard deviations for the popula-
tion (Lee et al, 2003). Although this is the most widely accepted definition there
is a tendency to define it as a BW/BL below 10. 5 or 3 percentile of the growth
curve. In addition, there is still the problem of specifying the gestational age.

IUGR (Intrauterine growth retardation) is defined as a growth failure
during the intrauterine development. As a result of the intrauterine delay the
child is born with small length and low weight – SGA (small for gestational age).
The cause of this occurrence may be various – the mother, the placenta, the
genesis, the environment.

The National Center of Health Statistics has made an interesting compa-
rison between the SGA incidence and that of the Turner Syndrome. Namely,
with 2.3 SD below the mean for weight/length 91,000 children are expected to
be SGA in comparison to only 800 children with the Turner Syndrome (if the
TS incidence of 1/2500 live-born is presumed). Most of these children start to
make up for the lost intrauterine growth with a postnatal catch-up growth which
is most obvious in the first six months of their life. More than 80% of these
children reach the normal adult growth by the end of their second year. Yet, 10–
15% of these children, especially those born with a height less than 3 SDS, do
not catch up on their growth by the end of their second year and they remain
considerably short.

SGA is considered to be the main reason for the short stature in ~ 10%
of short adults. SGA children have increased perinatal mortality, and psychoso-
cial and mental problems. In addition, adult problems such as diabetes mellitus
type 2, metabolic syndrome, PCOS in girls, and cardiovascular complications
are a consequence of SGA.

Most of the cases of SGA are still idiopathic. The causes of the growth
failure in the SGA children include the low spontaneous secretion of the growth
hormone, the reduced sensitivity to the growth hormone and reduced sensitivity
to IGF1.
Insulin-like growth factors (IGF-I and IGF-II). IGF-I and IGF-II have a significant homology for insulin, and exhibit a high affinity for a family of binding proteins (IGFBPs). So far, six binding proteins (IGFBP 1–6) have been cloned and sequenced. At least 5 IGFBP-related proteins have been sequenced too (IGFBP-rp). The various IGFBPs share a common structure in that they contain similar N- and C-terminal cysteine domains separated by a less conserved domain, and they appear to be encoded by a gene family. In the circulation, IGFBPs prolong the biological half-life of the IGFs and protect against the acute insulin-like action of these peptides. IGFBP-3 is the major binding protein in human serum, forming a 150-kDa complex with an acid labile subunit (ALS) and IGF. IGFBPs in the interstitial fluid are thought to regulate the bioavailability of locally secreted IGFs to their target cells and to modulate the biological effects of the IGFs by altering their interaction with the IGF receptor. There are two receptors that specifically recognize the IGFs: type 1 IGF receptor and type 2 IGF receptor. With lower affinity, the insulin receptor can also bind the IGFs.

Levels of IGFBP-3 complex are determined by age as well as hormonal and nutritional status. IGFBP-3 concentrations increase from birth to puberty, with a gradual decline throughout adulthood. Dependence on GH has been demonstrated from the decreased levels in hypopituitary subjects and GH-deficient children and increased levels in acromegalic patients. IGFBP-3 concentrations are decreased in conditions of hepatic cirrhosis, protein deprivation, and poorly controlled diabetes.

An increasing number of mutations is found in the growth hormone insulin-like growth factor axis (GH-IGF) (Table 1). Interestingly, 60 mutations have been found in humans for GH, and even more were determined for GHR – 75. On the other hand, only three IGF mutations were described [125, 126]. A STAT5b mutation in the signalling pathway down-stream IGF-1 receptor was also reported [127].

Mutations of several genes may underlie in some children with SGA. A patient was shown to have a partial gene deletion of the IGF-1 gene [128]. Among 42 IUGR children two had IGF-1R mutations in exon2 [125].

The IGF-1 resistance in SGA children seems to be frequent in SGA. In vitro and in vivo studies show that the IGF-1 resistance might originate from monogenic causes or deregulation of intrauterine adaptive processes.

"Thrifty phenotype". An attractive modern theory supposes that the disturbed mother-placenta-fetus relation results in the activation of the so-called "thrifty phenotype" of which the IGF system is a vital part. The mechanisms assure short term postnatal survival in conditions of deficient nutritional supply. On the other hand, the abundant postnatal nutritional supply and the "thrifty
phenotype" result in increased adult risk of metabolic syndrome, DM2 and cardiovascular disease.

A group of signalling proteins involved in prenatal growth retardation have recently been under intense scrutiny: IRS-1, PDK1, AKT1, and S6K1. Given the animal data, these proteins (and their genes) might play an important role in growth retardation. Moreover, compelling evidence in mice shows that those genes are involved in glucose homeostasis and in fat metabolism [129]. A number of proteins of the pathway are identified as oncogenes. For example, PTEN a negative coregulator of PIP3 generation, was found to be the second most frequently mutated protein in cancer after p53 [130, 131]. Therefore, at least three genes, IGF-IR, PDK1 and AKT are targets for anti-cancer pharmacological intervention [132, 133, 134].

Conclusions

Genetic information about pituitary development and isolated or multiple pituitary defects is reported with ever-increasing frequency. Nevertheless, no genetic aetiology has been established to date in most patients. The complex nature of most growth disorders remains to be elucidated. So far, the greatest clinical implication of the novel genetic alterations is the need for clinical follow-up for new pituitary deficiencies and for the development of pituitary enlargement as a potential for visual damage.

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Резиме

ДЕФИЦИТ НА ХОРМОНОТ ЗА РАСТ И SMALL FOR GESTATIONAL AGE (SGA): ГЕНЕТСКИ АЛТЕРАЦИИ

Jančevska A.,1,2 Gucev Z. S.,1,2 Tasić V.,1,2 Pop-Jordanova N.1,2

1Медицински Факултет, Скопие, Р. Македонија,

2Универзитетска клиника за дейски болесни, Скопие, Р. Македонија

Низок раст асоцииран со дефисцит на хормонот за раст (ХР) се појавува кај 1–4 000 до 1–10 000 новородени. Нови генетски дефекти на сите нивоа на GH-RH–GH–IGF оскарата со опишани во последните десетина години. Генетските дефекти кои предизвикуваат изолиран дефисцит на ХР, како и мултипли питуитарни дефисцити се предмет на детална анализа. Откривени се и сигналините молекули и транскрипционските фактори кои влијаат на развоя на питуитарната жлеза, како и нивните функции. Кај животини и луѓе значењето на транскрипционските фактори HESX1, PROP1, POU1F1, LHX3, LHX4, TBX19, SOX2 и SOX3 е предмет на детално испитување. Генетските алтерации на овие транскрипционски фактори диктираат различни фенотипови: од изолиран хипопитуитаризам, до мултипли питуитарни хормонски дефисцити со или без малформацији (на пример септо-оптичка дисплазија или холопрозеницефалија). Од друга страна, децата родени мали за гестационата возраст (SGA) се хетерогена група каде што се посочени нови механизми на ретардација на растот и метаболни нарушувања. Бидејки SGA се смела за главна причина

за низок раст кај 10% од возрасните, оваа голема група нуди можность за нови сознание за механизмот на раст и метаболните нарушувања. Групата на сигнализации протеини се вклучени во прекинателната ретардација на растот: IRS-1, PDK1, Akt1, and S6K1. Денес, атрактивната модерна теорија тврди дека нарушениата релација мајка-плацената-фетус резултира со активација на т.н. "thrifty phenotype" ("штедлив фенотип") од кој витален дел е и IGF системот. Овие механизми обезбедуваат постинално преживување на кус рок во состојби со намален внес на храна. Но, постинално, изобилната исхрана кај "штедливот фенотип" доведува до зголемен адултен ризик од метаболен синдром, шеќерна болест тип 2 (DM2) и кардиоваскуларна болест.

Овој труд накусо, ревијално, ги опишува генетските промени кај луѓето кои водат до дефицит на хормонот за раст, мултипли питаутарни хормонални дефицити и SGA.

Клучни зборови: питаутарни генетски дефекти, IGF систем, питаутарни транскрипцииски фактори, мали за гестациска возраст.

**Corresponding Author:**

Zoran S. Gucev,
Medical Faculty,
50 Divizija BB,
1000 Skopje, R. Macedonia,

E-mail: gucevz@gmail.com