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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]

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

A b s t r a c t: 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 191amino 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 – Табела 1

The various phenotypes caused by a defect of transcription factors of the pituitary
Различни фенотипови предизвикани од дефекти на питуитарните фактори на транскрипција

Gene	Phenotype	Inheritance
Pit1 / POU1F1	*Hormonal deficiences:* GH, PRL, TSH *Imaging* anterior pituitary gland: normal to hypo posterior pituitary gland: normal *Other manifestation*: none	R/D
PROP 1	*Hormonal deficiences:* GH, PRL, TSH, LH, FSH, (ACTH) *Imaging* anterior pituitary gland: hypo to hyper posterior pituitary gland: normal *Other manifestation*: none	R
HESX1	*Hormonal deficiences:* GH, PRL, TSH, LH, FSH, ACTH, IGHD, CPHD *Imaging* anterior pituitary gland:hypo posterior pituitary gland: ectopic *Other manifestation*: eyes, brain, septo-optic dysplasia	R/D
LHX3	*Hormonal deficiences:* GH, PRL, TSH, LH, FSH, (ACTH) *Imaging* anterior pituitary gland: hypo posterior pituitary gland: normal *Other manifestation*: neck rotation 75º–85º (?) (no: 160º–180º)	R
LHX4	*Hormonal deficiences:* GH, TSH, ACTH *Imaging* anterior pituitary gland: hypo posterior pituitary gland: normal *Other manifestation*: sella turcica/skull defects, cerebellar defects	D
SOX2	*Hormonal deficiences:* GH, LH, FSH *Imaging* anterior pituitary gland: hypo posterior pituitary gland: normal/hypo *Other manifestation*: bilateral anophtalmia, spastic, altered brain development esophage atresia	?/D
SOX3	*Hormonal deficiences:* 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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Abrevitations: 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 – Табела 2

Alteration of the growth hormone-realising hormone axis affecting growth in humans (differential diagnosis of insulin-like growth factor-I deficiency)
Промени во хормон за расш-рилизинг хормон оскаша кои влијаат на расшош кај луѓеше (диференцијално дијагносшички во однос на дефицишш на insulin-like growth factor-I)

Hypothalamus
Transcription factors
GHRH-gene
Pituitary gland
Transcription factors
TPIT
SOX2
SOX3
HESX1
LHX3
LHX4
PROP1
POU1F1
GH-RH-receptor
GH-gene cluster
GH-deficinecy/bioinactivity
GH-target organs
GH-receptor (primary: extracellular, transmembrane, intracelular)
GH-insensivity
Signalling (JAK2/STAT5b/ERK)
GH-insensivity (secondary)
Malnutrition (eg, anorexia)
Liver disease (eg, Byler's disease)
Chronic illness
Anti-GH antibodies
IGF-I defects
IGF-I transport/metabolism/clearence
IGF-I resistance
IGF-I receptor defect (type I)
IGF-I signalling

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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, consecutively, 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]. HESX1is 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 adrenocorticotrophin (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, hypogonadotrophic 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].

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 thyrotroph 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 heterozygous 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 variable 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 population (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 genes, the environment.

The National Center of Health Statistics has made an interesting comparison 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 psychosocial 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-I 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.

REFERENCES

1. Chen EY., Liao YC., Smith DH. *et al.* (1989): The human growth hormone locus: nucleotide sequence, biology, and evolution. *Genomics;* 4: 479–487.

2. Phillips JA. III. (1995): Inherited defects in growth hormone synthesis and action. In: Scriver CR, Beaudet AL, Sly WS, *et al*., editors. The Metabolic and Molecular Bases of Inherited Disease, vol. 2. 7th edition. New York: McGraw-Hill; 3023–44.

3. Rosenfeld RG., Cohen P. (2002): Disorders of growth hormone / insulin-like growth factor secretion and action. In: Sperling MA, editor. Pediatric Endocrinology. 2nd edition. Philadelphia: WB Saunders; 211–288.

4. Baumann G. (1991): Growth hormone heterogeneity: genes, isohormones, variants, and binding proteins. *Endocr Rev;* 12: 424–49.

5. Lewis UJ., Bonewald LF., Lewis LJ. (1980): The 20,000-dalton variant of human growth hormone: location of the amino acid deletions. *Biochem Biophys Res Commun;* 92: 511–6.

6. DeNoto FM., Moore DD., Goodman HM. (1981): Human growth hormone DNA sequence and mRNA structure: possible alternative splicing. *Nucleic Acids Res;* 9: 3719–30.

7. Nuoffer JM., Fluck C., Deladoey J. *et al.* (2000): Regulation of human GH receptor gene transcription by 20- and 22-kDa GH in a human hepatoma cell line. *J Endocrinol;* 165: 313–20.

8. Mullis PE. (2005): Genetic control of growth. *Eur J Endocrinol;* 152: 11–31.

9. Cacciari E., Zucchini S., Carla G. *et al.* (1990): Endocrine function and morphological findings in patients with disorders of the hypothalamo-pituitary area: a study with magnetic resonance. *Arch Dis Child;* 65: 1199–1202.

10. Illig R. (1970): Growth hormone antibodies in patients treated with different preparations of human growth hormone (hGH). *J Clin Endocrinol Metab;* 31: 679–688.

11. Phillips JA III., Hjelle B., Seeburg PH. *et al*. (1981): Molecular basis for familial isolated growth hormone deficiency. *Proc Natl Acad Sci USA;* 78: 6372–6375.

12. Laron Z., Kelijman M., Pertzelan A. *et al.* (1985): Human growth hormone deletion without antibody formation or growth arrest during treatment: a new disease entity? *J Med Sci;* 21: 999–1006.

13. Mullis PE., Patel M., Brickell PM. *et al*. (1990): Isolated growth hormone deficiency: analysis of the growth hormone (GH) releasing hormone gene and the GH gene cluster. *J Clin Endocrinol Metab;* 70: 187–91.

14. Perez-Jurado LA., Phillips JA III., Francke U. (1994): Exclusion of growth hormone (GH)-releasing hormone gene mutations in family isolated GH deficiency by linkage and single strand con formation analysis. *J Clin Endocrinol Metab;* 78: 622–628.

15. Wajnrajch MP., Gertner JM., Harbison MD. *et al.* (1996): Nonsense mutation in the human growth hormone receptor causes growth failure analogous to the little (lit) mouse. *Nat Genet;* 12: 88–90.

16. Baumann G., Maheshwari H. (1997): The dwarfs of Sindh: severe growth hormone (GH) deficiency caused by a mutation in the GH-releasing hormone receptor gene. *Acta Paediatr* Suppl*;* 423: 33–38.

17. Maheshwari HG., Silverman BL., Dupuis J. *et al.* (1998): Phenotype and genetic analysis of a syndrome caused by an inactivating mutation in the growth hormone-releasing hormone receptor: dwarfism of Sindh. *J Clin Endocrinol Metab;* 83: 4065–4074.

18. Netchine I., Talon P., Dastot F. *et al.* (1998): Extensive phenotypic analysis of a family with growth hormone (GH) deficiency caused by a mutation in the GH-releasing hormone receptor gene. *J Clin Endocrinol Metab;* 83: 432–436.

19. Salvatori R., Hayashida CY., Aguiar-Oliveira MH. *et al.* (1999): Familial dwarfism due to a novel mutation of the growth hormone-releasing hormone receptor gene. *J Clin Endocrinol Metab;* 84: 917–923.

20. Salvatori R., Fan X., Phillips JA III. *et al.* (2001): Three new mutations in the gene for the growth hormone (GH)-releasing hormone receptor in familial isolated GH deficiency type Ib. *J Clin Endocrinol Metab;* 86: 273–279.

21. Alba M., Hall CM., Whatmore AJ. *et al.* (2004): Variability in anterior pituitary size within members of a family with GH deficiency due to a new splice mutation in the GHRH receptor gene. *Clin Endocrinol (Oxf);* 60: 470–475.

22. Mullis PE., Eble A., Wagner JK. (1994): Isolated growth hormone deficiency is associated with a 211bp deletion within RAR a gene [abstract]. *Horm Res;* 41: 61.

23. Binder G., Ranke MB. (1995): Screening for growth hormone (GH) gene splice-site mutations in sporadic cases with severe isolated GH deficiency using ectopic transcript analysis. *J Clin Endocrinol Metab;* 80: 1247–1252.

24. Cogan JD., Prince MA., Lekhakula S. *et al.* (1997): A novel mechanism of aberrant pre-mRNA splicing in humans. *Hum Mol Genet;* 6: 909–912.

25. Cogan JD., Ramel B., Lehto M. *et al.* (1995): A recurring dominant negative mutation causes autosomal dominant growth hormone deficiency: a clinical research center study. *J Clin Endocrinol Metab;* 80: 3591–3595.

26. Takahashi I., Takahashi T., Komatsu M. *et al.* (2002): An exonic mutation of the GH-1 gene causing familial isolated growth hormone deficiency type II. *Clin Genet;* 61: 222–225.

27. Moseley CT., Mullis PE., Prince MA. *et al.* (2002): An exon splice enhancer mutation causes autosomal dominant GH deficiency. *J Clin Endocrinol Metab;* 87: 847–852.

28. Mullis PE., Deladoey J., Dannies PS. (2002): Molecular and cellular basis of isolated dominant-negative growth hormone deficiency, IGHD type II: Insights on the secretory pathway of peptide hormones. *Horm Res;* 58: 53–66.

29. Ryther RC., McGuinness LM., Phillips JA III. *et al.* (2003): Disruption of exon definition produces a dominant-negative growth hormone isoform that causes somatotroph death and IGHD II. *Hum Genet;* 113: 140–148.

30. McCarthy EMS., Phillips JA III. (1998): Characterization of an intron splice enhancer that regulates alternative splicing of human GH pre-mRNA. *Hum Mol Genet;* 7: 1491–1496.

31. Ryther RC., Flynt AS., Harris BD. *et al.* (2004): GH1 splicing is regulated by multiple enhancers whose mutation produces a dominant-negative GH isoform that can be degraded by allele-specific siRNA. *Endocrinology;* 145: 2988–2996.

32. Dietz HC. (1997): Nonsense mutations and altered splice-site selections. *Am J Hum Genet;* 60: 729–730.

33. Deladoey J., Stocker P., Mullis PE. (2001): Autosomal dominant GH deficiency due to an Arg183His GH-1 gene mutation: clinical and molecular evidence of impaired regulated GH secretion. *J Clin Endocrinol Metab;* 86: 3941–3947.

34. Binder G., Keller E., Mix M. *et al.* (2001): Isolated GH deficiency with dominant inheritance: new mutations, new insights. *J Clin Endocrinol Metab;* 86: 3877–3881.

35. Duquesnoy P., Simon D., Netchine I. *et al.* (1998): Familial isolated growth hormone deficisen-cy with slight height reduction due to a heterozygote mutation in GH gene. In: Program of the 80th Annual Meeting of the Endocrine Society. New Orleans: Endocrine Society; 2–202.

36. Lee MS., Wajnrajch MP., Kim SS. *et al*. (2000): Autosomal dominant growth hormone (GH) defi-ciency type II: the Del32–71-GH deletion mutant suppresses secretion of wild-type GH. *Endocrinology;* 141: 883–890.

37. McGuinness L., Magoulas C., Sesay AK. *et al.* (2003): Autosomal dominant growth hormone deficiency disrupts secretory vesicles *in vitro* and *in vivo* in transgenic mice. *Endocrinology;* 144: 720–731.

38. Hayashi Y., Yamamoto M., Ohmori S. *et al.* (1999): Inhibition of growth hormone (GH) secretion by a mutant GH-I gene product in neuroendocrine cells containing secretory granules: an implication for isolated GH deficiency inherited in an autosomal dominant manner. *J Clin Endocrinol Metab;* 84: 2134–2139.

39. Millar DS., Lewis MD., Horan M. *et al.* (2003): Novel mutations of the growth hormone 1 (GH1) gene disclosed by modulation of the clinical selection criteria for individuals with short stature. *Hum Mutat;* 21: 424–440.

40. Mullis PE., Robinson IC., Salemi S. *et al.* (2005): Isolated autosomal dominant growth hormone deficiency: an evolving pituitary deficit? A multicenter follow-up study. *J Clin Endocrinol Metab;* 90: 2089–2096.

41. Salemi S., Yousefi S., Baltensperger K. *et al.* (2005): Variability of isolated autosomal dominant GH deficiency (IGHD II): impact of the P89L GH mutation on clinical follow-up and GH secretion. *Eur J Endocrinol;* 153: 791–802.

42. Fleisher TA., White RM., Broder S. *et al.* (1980): X-linked hypogammaglobulinemia and isolated growth hormone deficiency. *N Engl J Med;* 302: 1429–34.

43. Sitz KV., Burks AW., Williams LW. *et al.* (1990): Confirmation of X-linked hypogammaglo-buliemia with isolated growth hormone deficiency as a disease entity. *J Pediatr;* 116: 292–4.

44. Conley ME., Burks AW., Herrod HG. *et al.* (1991): Molecular analysis of X-linked agammaglobulin emia and isolated growth hormone deficiency. *J Pediatr;* 119: 392–7.

45. Kelberman D., Dattani MT. (2007): Hypothalamic and pituitary development: novel insights into the aetiology. *Eur J of Endocrinol;* 157 (1): 3–14.

46. de Morsier G. (1954): Studies in cranio-encephalic dysraphia. I. Agenesia of the olfactory lobe (lateral telencephaloschisis) and of the callous and anterior commissures (median telencephaloschisis); olfacto-genital dysplasia. *Schweizer Archiv Für Neurologie und Psychiatrie;* 74: 309–361.

47. Reeves DL. (1941): Congenital absence of the septum pellucidum. *Bulletin of the Johns Hopkins Hospital;* 69: 61–71.

48. Hoyt WF., Kaplan SL., Grumbach MM. *et al.* (1970): Septo-optic dysplasia and pituitary dwarfism. *Lancet;* 1: 893–894.

49. Arslanian SA., Rothfus WE., Foley TP Jr. *et al.* (1984) Hormonal, metabolic, and neuroradiologic abnormalities associated with septo-optic dysplasia. *Acta Endocrinologica;* 107: 282–288.

50. Stanhope R., Preece MA., Brook CG. (1984): Hypoplastic optic nerves and pituitary dysfunction. A spectrum of anatomical and endocrine abnormalities. *Archives of Disease in Childhood;* 59: 111–114.

51. Patel L., McNally RJ., Harrison E. *et al.* (2006): Geographical distribution of optic nerve hypoplasia and septo-optic dysplasia in Northwest England. *Journal of Pediatrics;* 148: 85–88.

52. Morishima A., Aranoff GS. (1986): Syndrome of septo-optic–pituitary dysplasia: the clinical spectrum. *Brain and Development;* 8: 233–239.

53. Wales JK., Quarrell OW. (1996): Evidence for possible Mendelian inheritance of septo-optic dysplasia. *Acta Paediatrica;* 85: 391–392.

54. Blethen SL., Weldon VV. (1985): Hypopituitarism and septo-optic 'dysplasia' in first cousins. *American Journal of Medical Genetics;* 21: 123–129.

55. Benner JD., Preslan MW., Gratz E. *et al.* (1990): Septo-optic dysplasia in two siblings. *American Journal of Ophthalmology;* 109: 632–637.

56. McNay DE., Turton JP., Kelberman D. *et al.*. (2007) *HESX1* mutations are an uncommon cause of septooptic dysplasia and hypopituitarism. *Journal of Clinical Endocrinology and Metabolism;* 92: 691–697.

57. Thomas PQ., Dattani MT., Brickman JM. *et al.* (2001): Heterozygous *HESX1* mutations associated with isolated congenital pituitary hypoplasia and septo-optic dysplasia. *Human Molecular Genetics;* 10: 39–45.

58. Cohen RN., Cohen LE., Botero D. *et al.* (2003): Enhanced repression by *HESX1* as a cause of hypopituitarism and septooptic dysplasia. *Journal of Clinical Endocrinology and Metabolism;* 88: 4832–4839 .

59. Tajima T., Hattorri T., Nakajima T. *et al.* (2003): Sporadic heterozygous frameshift mutation of *HESX1* causing pituitary and optic nerve hypoplasia and combined pituitary hormone deficiency in a Japanese patient. *Journal of Clinical Endocrinology and Metabolism;* 88: 45–50.

60. Thomas PQ., Johnson BV., Rathjen J. *et al.* (1995): Sequence, genomic organization, and expression of the novel homeobox gene *Hesx1*. *Journal of Biological Chemistry;* 270: 3869–3875.

61. Dasen JS., Barbera JP., Herman TS. *et al.* (2001): Temporal regulation of a paired-like homeodomain repressor/TLE corepressor complex and a related activator is required for pituitary organogenesis. *Genes and Development;* 15: 3193–3207.

62. Brickman JM., Clements M., Tyrell R. *et al.* (2001): Molecular effects of novel mutations in *Hesx1*/*HESX1* associated with human pituitary disorders. *Development;* 128: 5189–5199.

63. Dattani MT., Martinez-Barbera JP., Thomas PQ. *et al.* (1998): Mutations in the homeobox gene *HESX1*/*Hesx1* associated with septo-optic dysplasia in human and mouse. *Nature Genetics;* 19: 125–133.

64. Sobrier ML., Netchine I., Heinrichs C. *et al* (2005): Alu-element insertion in the homeodomain of *HESX1* and aplasia of the anterior pituitary. *Human Mutation;* 25: 503.

65. Sobrier ML., Maghnie M., Vie-Luton MP. *et al.* (2006): Novel *HESX1* mutations associated with a life-threatening neonatal phenotype, pituitary aplasia, but normally located posterior pituitary and no optic nerve abnormalities. *J of Clin Endocrin and Metab;* 91: 4528–4536.

66. Stevanovic M., Lovellbadge R., Collignon J. *et al.* (1993): *SOX3* is an X-linked gene-related to *Sry*. *Human Molecular Genetics;* 2: 2013–2018.

67. Pevny LH., Lovell-Badge R. (1997): *Sox* genes find their feet. *Current Opinion in Genetics and Development;* 7: 338–344.

68. Pevny L., Placzek M. (2005): *SOX* genes and neural progenitor identity. *Current Opinion in Neurobiology;* 15: 7–13.

69. Hamel BC., Smits AP., Otten BJ. *et al.* (1996): X-linked mental retardation and isolated growth hormone deficiency: clinical and molecular findings. *Am J of Med Genet;* 64: 35–41.

70. Lagerstrom-Fermer M., Sundvall M., Johnsen E. *et al.* (1997): X-linked recessive panhypopituitarism associated with a regional duplication in Xq25-q26. *American Journal of Human Genetics;* 60: 910–916.

71. Hol FA., Schepens MT., van Beersum SE. *et al*. (2000): Identification and characterization of an Xq26-q27 duplication in a family with spina bifida and panhypopituitarism suggests the involvement of two distinct genes. *Genomics;* 69: 174–181.

72. Solomon NM., Nouri S., Warne GL. *et al.* (2002): Increased gene dosage at Xq26-q27 is associated with X-linked hypopituitarism. *Genomics;* 79: 553–559.

73. Stankiewicz P., Thiele H., Schlicker M. *et al.* (2005): Duplication of Xq26.2-q27.1, including *SOX3*, in a mother and daughter with short stature and dyslalia. *American Journal of Medical Genetics. Part A;* 138A: 11–17.

74. Woods KS., Cundall M., Turton J. *et al*. (2005): Over- and underdosage of *SOX3* is associated with infundibular hypoplasia and hypopituitarism. *American Journal of Human Genetics;* 76: 833–849.

75. Laumonnier F., Ronce N., Hamel BCJ. *et al.* (2002): Transcription factor SOX3 is involved in X-linked mental retardation with growth hormone deficiency. *American Journal of Human Genetics;* 71: 1450–1455.

76. Avilion AA., Nicolis SK., Pevny LH. *et al.* (2003): Multipotent cell lineages in early mouse development depend on *SOX2* function. *Genes and Development;* 17: 126–140.

77. Taranova OV., Magness ST., Fagan BM. *et al.* (2006): *SOX2* is a dose-dependent regulator of retinal neural progenitor competence. *Genes and Development;* 20: 1187–1202.

78. Williamson KA., Hever AM., Rainger J. *et al.* (2006): Mutations in *SOX2* cause anophthalmia-esophageal–genital (AEG) syndrome. *Human Molecular Genetics;* 15: 1413–1422.

79. Fantes J., Ragge NK., Lynch SA. *et al.* (2003): Mutations in *SOX2* cause anophthalmia. *Nature Genetics;* 33: 461–463.

80. Ragge NK., Lorenz B., Schneider A. *et al.* (2005): SOX2 anophthalmia syndrome. *American Journal of Medical Genetics. Part A;* 135A: 1–7.

81. Hagstrom SA., Pauer GJT., Reid J. *et al.* (2005): *SOX2* mutation causes anophthalmia, hearing loss, and brain anomalies. *American Journal of Medical Genetics. Part A;* 138A: 95–98.

82. Zenteno JC., Gascon-Guzman G., Tovilla-Canales JL. (2005): Bilateral anophthalmia and brain malformations caused by a 20-bp deletion in the *SOX2* gene. *Clinical Genetics;* 68: 564–566.

83. Kelberman D., Rizzoti K., Avilion A. *et al.* (2006): Mutations within *Sox2*/*SOX2* are associated with abnormalities in the hypothalamo–pituitary–gonadal axis in mice and humans. *Journal of Clinical Investigation;* 116: 2442–2455.

84. Sato N., Kamachi Y., Kondoh H. *et al.* (2007): Hypogonadotropic hypogonadism in an adult female with a heterozygous hypomorphic mutation of *SOX2*. *European Journal of Endocrinology;* 156: 167–171.

85. Bach I., Rhodes SJ., Pearse RV. *et al.* (1995): P-Lim, a LIM homeodomain factor, is expressed during pituitary organ and cell commitment and synergizes with Pit-1. *PNAS;* 92: 2720–2724.

86. Zhadanov AB., Bertuzzi S., Taira M. *et al.* (1995): Expression pattern of the murine Lim class homeobox gene *LHX3* in subsets of neural and neuroendocrine tissues. *Developmental Dynamics;* 202: 354–364.

87. Netchine I., Sobrier ML., Krude H. *et al.* (2000): Mutations in *LHX3* result in a new syndrome revealed by combined pituitary hormone deficiency. *Nature Genetics;* 25: 182–186.

88. Sloop KW., Parker GE., Hanna KR. *et al.* (2001): *LHX3* transcription factor mutations associated with combined pituitary hormone deficiency impair the activation of pituitary target genes. *Gene;* 265: 61–69.

89. Bhangoo AP., Hunter CS., Savage JJ. *et al.* (2006): A novel *LHX3* mutation presenting as combined pituitary hormonal deficiency. *Journal of Clinical Endocrinology and Metabolism;* 91: 747–753.

90. Sobrier ML., Attie-Bitach T., Netchine I. *et al.* (2004): Pathophysiology of syndromic combined pituitary hormone deficiency due to a *LHX3* defect in light of *LHX3* and *LHX4* expression during early human development. *Gene Expression Patterns;* 5: 279–284.

91. Pfaeffle RW., Savage JJ., Hunter CS. *et al.* (2007): Four novel mutations of the *LHX3* gene cause combined pituitary hormone deficiencies with or without limited neck rotation. *J of Clin Endocrinol and Metab;* 92: 1909–1919.

92. Machinis K., Pantel J., Netchine I. *et al.* (2001): Syndromic short stature in patients with a germline mutation in the LIM homeobox *LHX4*. *American Journal of Human Genetics;* 69: 961–968.

93. Lamolet B., Pulichino A., Lamonerie T. *et al.* (2001): A pituitary cell-restricted T box factor, Tpit, activates POMC transcription in cooperation with Pitx homeoproteins. *Cell;* 104: 849–859.

94. Liu J., Lin C., Gleiberman A. *et al.* (2001): Tbx19, a tissue-selective regulator of *POMC* gene expression. *PNAS;* 98: 8674–8679.

95. Pulichino AM., Vallette-Kasic S., Tsai JP. *et al*. (2003): Tpit determines alternate fates during pituitary cell differentiation. *Genes and Development;* 17: 738–747.

96. Pulichino AM., Vallette-Kasic S., Couture C. *et al.* (2003): Human and mouse *TPIT* gene mutations cause early onset pituitary ACTH deficiency. *Genes and Development;* 17: 711–716.

97. Vallette-Kasic S., Brue T., Pulichino AM. *et al*. (2005): Congenital isolated adrenocortico-tropin deficiency: an underestimated cause of neonatal death, explained by *TPIT* gene muta-tions. *Journal of Clinical Endocrinology and Metabolism;* 90: 1323–1331.

98. Metherell LA., Savage MO., Dattani M. *et al*. (2004): *TPIT* mutations are associated with early-onset, but not late-onset isolated ACTH deficiency. *Eur J of Endocrinol;* 151: 463–465.

99. Weintrob N., Drouin J., Vallette-Kasic S. *et al.* (2006): Low estriol levels in the maternal triple-marker screen as a predictor of isolated adrenocorticotropic hormone deficiency caused by a new mutation in the *TPIT* gene. *Pediatrics;* 117: e322–e327.

100. Wu W., Cogan JD., Pfaffle RW. *et al.* (1998): Mutations in *PROP1* cause familial combined pituitary hormone deficiency. *Nature Genetics;* 18: 147–149.

101. Deladoey J., Fluck C., Buyukgebiz A. *et al.* (1999): 'Hot spot' in the *PROP1* gene responsible for combined pituitary hormone deficiency. *Journal of Clinical Endocrinology and Metabolism;* 84: 1645–1650.

102. Cogan JD., Wu W., Phillips JA. *et al.* (1998): The PROP1 2-base pair deletion is a common cause of combined pituitary hormone deficiency. *Journal of Clinical Endocrinology and Metabolism;* 83: 3346–3349.

103. Turton JPG., Mehta A., Raza J. *et al.* (2005): Mutations within the transcription factor *PROP1* are rare in a cohort of patients with sporadic combined pituitary hormone deficiency (CPHD). *Clinical Endocrinology;* 63: 10–18.

104. Duquesnoy P., Roy A., Dastot F. *et al*. (1998): Human *Prop-1*: cloning, mapping, genomic structure. Mutations in familial combined pituitary hormone deficiency. *FEBS Letters;* 437: 216–220.

105. Lebl J., Vosahlo J., Pfaeffle RW. (2005): Auxological and endocrine phenotype in a population-based cohort of patients with *PROP1* gene defects. *European Journal of Endocrinology;* 153: 389–396.

106. Cogan JD., Wu W., Phillips JA III. *et al.* (1998): The PROP1 2-base pair deletion is a common cause of combined pituitary hormone deficiency. *J of Clin Endocrin and Metabol;* 83: 3346–3349.

107. Reynaud R., Barlier A., Vallette-Kasic S. *et al.* (2005): An uncommon phenotype with familial central hypogonadism caused by a novel *PROP1* gene mutant truncated in the transactivation domain. *Journal of Clinical Endocrinology and Metabolism;* 90: 4880–4887.

108. Arroyo A., Pernasetti F., Vasilyev VV. *et al.* (2002): A unique case of combined pituitary hormone deficiency caused by a *PROP1* gene mutation (R120C) associated with normal height and absent puberty. *Clinical Endocrinology;* 57: 283–291.

109. Fluck C., Deladoey J., Rutishauser K. *et al.* (1998): Phenotypic variability in familial combined pituitary hormone deficiency caused by a *PROP1* gene mutation resulting in the substitution of Arg-Cys at codon 120 (R120C). *Journal of Clinical Endocrinology and Metabolism;* 83: 3727–3734.

110. Vallette-Kasic S., Barlier A., Teinturier C. *et al.* (2001): *PROP1* gene screening in patients with multiple pituitary hormone deficiency reveals two sites of hypermutability and a high incidence of corticotroph deficiency. *Journal of Clinical Endocrinology and Metabolism;* 86: 4529–4535.

111. Mendonca BB., Osorio MG., Latronico AC. *et al.* (1999): Longitudinal hormonal and pituitary imaging changes in two females with combined pituitary hormone deficiency due to deletion of A301,G302 in the *PROP1* gene. *Journal of Clinical Endocrinology and Metabolism;* 84: 942–945.

112. Asteria C., Oliveira JH., Abucham J. *et al.* (2000): Central hypocortisolism as part of combined pituitary hormone deficiency due to mutations of *PROP-1* gene. *European Journal of Endocrinology;* 143: 347–352.

113. Pernasetti F., Toledo SP., Vasilyev VV. *et al.* (2000): Impaired adrenocorticotropin–adrenal axis in combined pituitary hormone deficiency caused by a two-base pair deletion (301-302delAG) in the prophet of *Pit-1* gene. *Journal of Clinical Endocrinology and Metabolism;* 85: 390–397.

114. Riepe FG., Partsch CJ., Blankenstein O. *et al.* (2001): Longitudinal imaging reveals pituitary enlargement preceding hypoplasia in two brothers with combined pituitary hormone deficiency attributable to *PROP1* mutation. *Journal of Clinical Endocrinology and Metabolism;* 86: 4353–4357.

115. Bottner A., Keller E., Kratzsch J. *et al.* (2004): *PROP1* mutations cause progressive deterioration of anterior pituitary function including adrenal insufficiency: a longitudinal analysis. *Journal of Clinical Endocrinology and Metabolism;* 89: 5256–5265.

116. Agarwal G., Bhatia V., Cook S. *et al*. (2000): Adrenocorticotropin deficiency in combined pituitary hormone deficiency patients homozygous for a novel *PROP1* deletion. *Journal of Clinical Endocrinology and Metabolism;* 85: 4556–4561.

117. Fofanova O., Takamura N., Kinoshita E. *et al.* (2000): MR imaging of the pituitary gland in children and young adults with congenital combined pituitary hormone deficiency associated with *PROP1* mutations. *American Journal of Roentgenology;* 174: 555–559.

118. Voutetakis A., Argyropoulou M., Sertedaki A. *et al.* (2004): Pituitary magnetic resonance imaging in 15 patients with *Prop1* gene mutations: pituitary enlargement may originate from the intermediate lobe. *Journal of Clinical Endocrinology and Metabolism;* 89: 2200–2206.

119. Andersen B., Rosenfeld MG. (2001): POU domain factors in the neuroendocrine system: lessons from developmental biology provide insights into human disease. *Endocrine Reviews;* 22: 2–35.

120. Cohen LE., Wondisford FE., Salvatoni A. *et al.* (1995): A 'hot spot' in the *Pit-1* gene responsible for combined pituitary hormone deficiency: clinical and molecular correlates. *Journal of Clinical Endocrinology and Metabolism;* 80: 679–684.

121. Cohen LE., Radovick S. (2002): Molecular basis of combined pituitary hormone deficiencies. *Endocrine Reviews;* 23: 431–442.

122. Pfaffle RW., DiMattia GE., Parks JS. *et al*. (1992): Mutation of the POU-specific domain of Pit-1 and hypopituitarism without pituitary hypoplasia. *Science;* 257: 1118–1121.

123. Pfaffle RW., Martinez R., Kim C. *et al.* (1997): GH and TSH deficiency. *Experimental and Clinical Endocrinology and Diabetes;* 105: (Suppl 4) 1–5.

124. Turton JPG., Reynaud R., Mehta A. *et al.* (2005): Novel mutations within the *POU1F1* gene associated with variable combined pituitary hormone deficiency. *Journal of Clinical Endocrinology and Metabolism;* 90: 4762–4770.

125. Abuzzahab ML., Schneider A., Goddard A. *et al.* (2003): IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. *N Engl J Med;* 349: 2211–2222.

126. Walenkamp MJ., Wit JM., (2006): Genetic disorders in the growth hormone – insulin-like growth factor-I axis. *Hormon Res;* 66: 221–230.

127. Kofoed EM., Hwa V., Little B. *et al.* (2003). Growth hormone insensivity associated with a STAT5b mutation. *N Engl J Med;* 349: 1139–1147.

128. Woods KA., Camacho-Hubner C., Barter D. *et al.* (1997): Insulin-like growth factor I gene deletion causing intrauterine growth retardation and severe short stature. *Acta Paediatr;* Suppl 423: 39–45.

129. Pirola L., Johnston AM., Van Obberghen E. (2004): Modulation of insulin action. *Diabetologia;* 47: 170–184.

130. Bachman KE., Argani P., Samuels Y. *et al.* (2004): The PIK3CA gene is mutated with high frequency in human breast cancers. *Cancer Biol. Ther;* 3: 772–775.

131. Campbell IG., Russell SE., Choong DY. *et al.* (2004): Mutation of the PIK3CA gene in ovarian and breast cancer. *Cancer Res;* 64: 7678–7681.

132. Morgensztem D, McLeod HL. (2005). PI3K1AktlmTOR, pathway as a target for cancer therapy. *Anticancer Drugs;* 16: 797–803.

133. Yee D. (2006): Targeting insulin-like growth factor pathways. *Br. J Cancer;* 94: 465–468.

134. Granville CA., Memmott RM., Gills JJ. *et al.* (2006): Handicapping the race to develop inhibitors of the phosphoinositide 3-0kinase/AkVmammalian target of rapamycin pathway. *Clin Cancer Res;* 12: 679–689.

Резиме

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

Јанчевска А.,[1,2] Гучев З. С.,[1,2] Тасиќ В.,[1,2] Поп-Јорданова Н.[1,2]

[1]Медицински Факултет, Скопје, Р. Македонија,
[2] Универзитетска клиника за детски болести, Скопје, Р. Македонија

Низок раст асоциран со дефицит 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 оската се опишани во последните десетина години. Генетските дефекти кои предизвикуваат изолиран дефицит на ХР, како и мултипни питуитарни дефицити се предмет на детална анализа. Откриени се и сигналните молекули и транскрипциските фактори кои влијаат на развојот на питуитарната жлезда, како и нивните функции. Кај животни и луѓе значењето на транскрипциските фактори HESX1, PROP1, POU1F1, LHX3, LHX4, TBX19, SOX2 и SOX3 е предмет на детално испитување. Генетските алтерации на овие транскрипциски фактори диктираат различни фенотипови: од изолиран хипопитуитаризам, до мултипни питуитарни хормонски дефицити со или без малформации (на пример септо-оптичка дисплазија или холопрозенцефалија). Од друга страна, децата родени мали за гестациската возраст (SGA) се хетерогена група каде што се посочени нови механизми на ретардација на растот и метаболни нарушувања. Бидејќи SGA се смета за главна причина

за низок раст кај 10% од возрасните, оваа голема група нуди можност за нови сознанија за механизмите на раст и метаболни нарушувања. Група на сигнални протеини се вклучени во пренаталната ретардација на растот: IRS-1, PDK1, AKT1, and S6K1. Денес, атрактивната модерна теорија тврди дека нарушената релација мајка-плацента-фетус резултира со активација на т.н. "thrifty phenotype" („штедлив фенотип“) од кој витален дел е и IGF системот. Овие механизми обезбедуваат постнатално преживување на кус рок во состојби со намален внес на храна. Но, постнатално, изобилната исхрана кај „штедливиот 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, мултипни питуитарни хормонални дефицити и SGA.

Клучни зборови: питуитарни генетски дефекти, IGF систем, питуитарни транскрипциски фактори, мали за гестациска возраст.

Corresponding Author:

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

E-mail: gucevz@gmail.com