Congenital hypopituitarism in two brothers with a duplication of the ‘acrogigantism gene’ GPR101: clinical findings and review of the literature

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Abstract

Purpose Congenital hypopituitarism (CH) can cause significant morbidity or even mortality. In the majority of patients, the etiology of CH is unknown. Understanding the etiology of CH is important for anticipation of clinical problems and for genetic counselling. Our previous studies showed that only a small proportion of cases have mutations in the known ‘CH genes’. In the current project, we present the results of SNP array based copy number variant analysis in a family with unexplained congenital hypopituitarism.

Methods DNA samples of two affected brothers with idiopathic CH and their mother were simultaneously analyzed by SNP arrays for copy number variant analysis and Whole Exome Sequencing (WES) for mutation screening. DNA of the father was not available.

Results We found a 6 Mb duplication including GPR101 and SOX3 on the X-chromosome (Xq26.2-q27.1) in the two siblings and their mother, leading to 2 copies of this region in the affected boys and 3 copies in the mother. Duplications of GPR101 are associated with X-linked acrogigantism (the phenotypic ‘opposite’ of the affected brothers), whereas alterations in SOX3 are associated with X-linked hypopituitarism.

Conclusion In our patients with hypopituitarism we found a 6 Mb duplication which includes GPR101, a gene associated with X-linked gigantism, and SOX3, a gene involved in early pituitary organogenesis that is associated with variable degrees of hypopituitarism. Our findings show that in duplications containing both GPR101 and SOX3, the growth hormone deficiency phenotype is dominant. This suggests that, if GPR101 is duplicated, it might not be expressed phenotypically when early patterning of the embryonic pituitary is affected due to SOX3 duplication. These results, together with the review of the literature, shed a new light on the role of GPR101 and SOX3 in pituitary function.

Keywords Pituitary gland · Transcription factors · Gene duplication · Acromegaly · G-protein coupled receptor

Abbreviations

ACTH Adrenocorticotropic hormone

ARHGEF6 Rho guanine nucleotide exchange factor 6

AVP Vasopressin

CD40LG CD40 ligand

CH Congenital hypopituitarism

PHD Pituitary hormone deficiency

IGHD Isolated growth hormone deficiency

CPHD Combined pituitary hormone deficiency

FSH Follicle stimulating hormone

GH Growth hormone

GH1 Growth hormone 1 gene

GHD Growth hormone deficiency

GHRH(R) Growth hormone releasing hormone (receptor)

GLI2 Glioma-associated oncogene family zinc finger 2

GPCR G protein coupled receptor

GPR101 G protein-coupled receptor 101

HESX1 HESX homeobox 1
Introduction

Normal development and function of the pituitary gland is crucial for several important physiological processes in the human body, such as growth, reproduction, lactation, response to stress, blood pressure, energy management and metabolism [1, 2]. Congenital hypopituitarism (CH) is a rare disorder with an estimated incidence of 1:3000–1:4000 live births. It is characterized by the diminished production or secretion of one or more of the pituitary hormones [3, 4].

Growth hormone deficiency (GHD) is the most common form of hypopituitarism. Both children and adults with GHD may present with short stature, increased fat mass and decreased lean body mass, delayed skeletal maturation, truncal obesity, abnormal glucose and lipid metabolism and an increased risk of cardiovascular disease [3, 4]. GHD can either be isolated (IGHD) or combined with other pituitary hormone deficiencies (CPHD). CPHD is defined as any combination of two or more pituitary hormone deficiencies, whereas in panhypopituitarism all pituitary hormones are deficient [5].

The vast majority of GHD cases are idiopathic. Up to 30% of cases are familial, which suggests a genetic etiology [6, 7]. As a result of dedicated genetic studies, such as the Dutch HYPOPIT study, our knowledge about the genetic etiology of GHD has drastically improved. Frequent causes of IGHD are mutations in the Growth Hormone 1 (GH1) gene and the Growth Hormone Releasing Hormone Receptor (GHRHR) gene [4, 7]. In Dutch CPHD patients we have previously studied several known disease related genes encoding pituitary transcription factors, such as PROP1 [MIM 601,538], HESX1 (MIM 601802), POU1F1 (MIM 173110), LHX3 (MIM 600577), LHX4 (MIM 602146), OTX2 (MIM 600037), SHH (MIM 600725), HHIP (MIM 606178) and GLI2 (MIM 165230). However, we found a genetic explanation in only 10% of the patients, leaving the majority of cases unsolved [8–12]. When candidate gene analysis has turned out negative, array based copy number variation analysis and Next Generation Sequencing (NGS) is a next step. In this study we present the surprising results of NGS in two brothers with idiopathic CH.

Material and methods

Genetic analysis

DNA isolation

Genomic DNA of the two brothers and their mother was extracted from peripheral whole blood samples according to standard procedures. The samples were subsequently analyzed by SNP array and Whole Exome Sequencing (WES).

Copy number variant analysis by SNP array

DNA was hybridized to Illumina Human CytoSNP850K SNP arrays according to standard protocol. Copy number analysis was performed using Nexus 8.0 from BioDiscovery.

WES

Genomic DNA was fragmented into 200–400 base pairs (bp) fragments using Covaris Adaptive Focused Acoustics shearing according to the manufacturer’s instructions (Covaris, Inc., Woburn, MA). Illumina TruSeq DNA Library preparation (Illumina, Inc., San Diego, CA) was performed on a Caliper Sciclone NGS workstation (Caliper Life Sciences, Hopkinton, MA), followed by exome capture using the Nimblegen SeqCap EZ V2 kit (Roche Nimblegen, Inc., Madison, WI). This capture targets 44 Mb of exonic regions covering 30,246 coding genes, 329,028 exons and 710 miRNAs. Paired-end 2 × 100 bp sequencing was performed at 6 samples per lane on Illumina HiSeq2000 sequencer using Illumina TruSeq V3, resulting in 6 Gb of sequencing data.

Literature search

In order to explain the phenotype of the two brothers, we performed an extensive literature search of all genes included in the duplicated region using OMIM, NCBI, MGI and Pubmed online databases. PubMed search was carried out using the names of all duplicated genes,
combined with the terms ['hypopituitarism' OR 'growth retardation' OR 'growth hormone deficiency' OR 'growth hormone' OR 'combined pituitary hormone deficiency'] AND 'congenital'.

Results

Clinical data

The index case, an Italian male with idiopathic CH, presented with growth retardation late in life, with a height SDS of—2.1 at the age of 16 years. BMI was normal. The GH peak during a GH stimulation test was 2.16 µg/L (ref > 6.66 µg/L). Apart from GHD, he was diagnosed with central hypothyroidism, hypogonadism and hypocortisolism. Magnetic resonance imaging (MRI) revealed anterior pituitary hypoplasia (APH) and an ectopic posterior pituitary (EPP). His brother also had growth retardation. Despite the fact that he did not present until the age of 21 years, he had always been small (height—3 SDS). The GH peak during his GH test was 1.86 µg/L. Although the original laboratory values and MRI images of both brothers were not available, the medical files reported that all pituitary hormone concentrations as well as IGF-I and IGFBP3 were low. Both brothers had normal cognition and no other birth defects. The unaffected mother had no pituitary hormone deficiencies and a height of 153.5 cm (−1.5 SDS). Clinical data of the father were not available.

Genetic analysis

SNP array data analysis revealed a 6 Mb duplication of chromosome Xq26.2-q27.1 in all 3 subjects. Figure 1 shows the 6 Mb duplication that results in two copies of part of the X-chromosome in the affected brothers and 3 copies in the mother. The duplicated region (chrX: 133,553,751–139,613,851; build 37) contains 70 genes (Fig. 2a). Table 1 shows the phenotypes associated with defects in these genes. The duplicated region includes GPR101 (MIM 300393), a gene previously described in patients with X-linked acrogigantism (X-LAG) and acromegaly, which is the opposite clinical phenotype of our patients.

The duplication also includes SOX3 (MIM 313430), a gene associated with variable degrees of X-linked hypopituitarism and GHD, sometimes combined with intellectual disability (ID). Additional information of all genes located in the duplicated region is documented in Supplementary Table 1. WES data of the brothers and their mother returned negative.

Discussion

We performed SNP array analysis and WES in a family with unexplained hypopituitarism. SNP array data revealed a 6 Mb duplication of Chromosome X at position Xq26.2-q27.1. The duplication included GPR101, a single exon gene that has been associated with X-LAG and acromegaly. GPR101 encodes an Orphan G-protein Coupled Receptor (GPCR) that is strongly expressed in the hypothalamus in rodents [13–15]. In humans, high expression of GPR101 is seen during fetal development of the pituitary gland while expression is low in the adult pituitary, suggesting that GPR101 is predominantly active during proliferation and maturation of the pituitary. Overexpression of GPR101 leads to increased Growth Hormone-Releasing Hormone (GHRH) expression, which causes hyperplasia of the pituitary and leads to increased GH and IGF-I concentrations [14].

Xq26.3 (micro) duplications including GPR101 have been described in patients with X-linked acro-gigantism (X-LAG). X-LAG is characterized by early age pediatric-onset gigantism associated with mixed GH-PRL secreting pituitary adenomas, or hyperplasia that leads to GH and IGF-I overexpression resulting in gigantism [14, 16–19]. In 2014, the smallest region of overlap (SRO) was reported,
which was shared by all X-LAG patients, and which contains four genes: CD40LG (MIM 300386), ARHGEF6 (MIM 300267), RBMX (MIM 300199) and GPR101 (MIM 300393). Of these four genes, only GPR101 was overexpressed in pituitary samples of X-LAG patients [16]. Two years later, a smaller duplication including GPR101 only was reported in a patient with X-LAG, thereby supporting the causative role of GPR101 [16]. In addition, GPR101 variants have been identified in pituitary adenoma samples of patients with sporadic acromegaly [16].

The duplication of an acrogigantism gene in the two boys with the phenotypic opposite (hypopituitarism) was unexpected. However, the duplication also included SOX3, also a single exon gene, which has been associated with variable degrees of hypopituitarism. SOX3 belongs to the SOX (SRY-related high mobility group-box) family of transcription factors that is expressed in neuro-epithelial progenitor and stem cells in the earliest stages of embryogenesis [20–23]. SOX3 protein is required for normal development of the brain, pituitary and face in mice and humans. Correct gene dosage of SOX3 is critical for the development of the hypothalmo-pituitary axis and for cognitive development [24–26].

Duplications including SOX3 have been associated with variable clinical phenotypes, including X-linked intellectual disability (ID), GHD, X-linked hypopituitarism (XH), SRY-negative 46,XX disorders of sex development (DSD) and neural tube defects (NTD) [27–33]. The severity of the phenotype is not dependent on the size of the duplication. Hypopituitarism is the most frequently reported phenotype among males with SOX3 duplication, followed by GHD. Most of the reported cases were of familial origin with transmission of the duplicated region from mother to son. Transmission to females often resulted in a NTD phenotype, and in most cases elective termination of pregnancies. However females with SOX3 duplications can also have a normal phenotype, which is probably due

![SNP array results of the two brothers and their mother. LogR ratios and B-allele frequencies (BAF) are indicated. Duplications are shown between vertical bars for a the mother, b and c the affected brothers](image1)

![Overview of 70 genes included in the duplicated region. a All duplications and deletions found in the literature involving GPR101 and SOX3](image2)
to non-random X-inactivation of the affected X chromosome. Normal X-inactivation is a random process which is thought to have arisen during the differentiation of mammalian sex chromosomes to achieve an equal dosage of X chromosome genes in females and males (as males only possess a single copy of the X chromosome). Non-random X inactivation might explain the presence or absence of a X-LAG phenotype. In females with GPR101 duplications, non-random inactivation of the affected allele can lead to a normal phenotype. When inactivation of the affected X does not occur at a high rate, leaving expression of the affected copy, females with GPR101 duplications do have the X-LAG phenotype. This mechanism is likely also true for females with SOX3 duplications. These females often have a normal phenotype, due to the non-random inactivation of the affected allele. Only few females with SOX3
Table 2  Endocrine phenotypes of SOX3 duplications

| Refs | Case | Sex | Growth | Gonads | Hormone deficiencies | Neonatal | MRI |
|------|------|-----|--------|--------|----------------------|----------|-----|
| [38] | F1   | F   | NA     | NA     | NA                   | Chiari II malformation |      |
| [38] | F2   | F   | NA     | NA     | NA                   | Chiari II malformation, voluminous AP, absent PP |      |
| [39] | F3   | F   | NA     | NA     | NA                   | Chiari II malformation |      |
| [39] | IV   | ?   | Hydrocephalus |        |                      | Hydrocephalus |      |
| [40] | III.2| F   | SS/GR  |        |                      | Hydrocephalus |      |
| [40] | II.2 | F   | SS/GR  |        |                      | Hydrocephalus |      |
| [40] | III.4| F   | SS/GR  |        |                      | Hydrocephalus |      |
| [32] | I    | M   | FTT    | Micropenis, hypoplastic scrotum | GH, LH/FSH, TSH, ACTH, Jaundice, hypoglycemia | APH, EPP |      |
| [32] | II   | M   | SS/GR  | Micropenis and STV | GH, ACTH, TSH, LH/FSH, Hypoglycemia | ACC, hydrocephalus |      |
| [32] | III  | M   | SS/GR  | Slender phallus and STV | LH/FSH, Thin CC, hydrocephalus |      |
| [32] | IV   | M   | SS/GR  | Micropenis and STV, hypogonadism, pubertal delay | GH, LH/FSH, Partial ACC, absent SP, heterotopic grey matter |      |
| [32] | V    | M   | SS/GR  | Micropenis, cryptorchidism, ovarian tissue and primary follicles | LH/FSH, Testosterone, AMH |      |
| [21] | M    |     |        | Neuroglycopenia | mild GH |      |
| [41] | M    |     |        | Neuroglycopenia | mild GH |      |
| [39] | F2   | M   |        |        |                      | CVP, shallow pituitary fossa | Thin CC, poorly developed pituitary gland and stalk |
| [39] | F3   | M   |        |        |                      | Thin CC, poorly developed pituitary gland and stalk |      |
| [44] | C1   | M   | SS/GR  | Microphallus and undescended testes | Hypopituitarism, GH, testosterone, Hypoglycemia, Jaundice | CVP, shallow pituitary fossa |      |
| [44] | C2   | M   |        |        |                      | Thin CC, poorly developed pituitary gland and stalk |      |
| [44] | C3   | M   |        | Microphallus, small penis, undescended testis, underdeveloped scrotum | All including diabetes insipidus, Hypoglycemia | Absent pituitary gland and stalk |      |
| [44] | C4   | M   |        |        |                      | Hypoglycemia, APH, hypoplastic pituitary stalk |      |
| [37] | M    |     |        |         | GH | Temporal brain atrophy |      |
| [39] | III.7| M   | Growth delay | Undescended testicle, pubertal delay | GH, LH/FSH |      |
| [39] | III.1| M   | SS     | Small testicles | GH, LH/FSH | Temporal brain atrophy |      |
| [45] | M    |     |        |        |                      | Temporal brain atrophy |      |
| [46] | M    |     |        |        |                      | Temporal brain atrophy |      |
| [47] | A    | M   | SRY, 46, XX negative |        |                      | APH, undescended PP, absent infundibulum |      |
| [24] | 2    | M   |        |        | GH, TSH, ACTH, LH/FSH | APH, undescended hypoplastic infundibulum |      |
| [24] | I    | M   |        |        | GH | APH, undescended hypoplastic infundibulum |      |
| [28] | A II.1| M  |        |        | GH, TSH | APH, undescended hypoplastic infundibulum |      |
Apart from SOX3 duplications, SOX3 single nucleotide substitutions (three point variants and one polymorphism) have also been described. Two variants (p.S150Y and p.142T), predicted as pathogenic, were found in patients with pituitary anomalies with GHD or hypopituitarism [24, 34–36]. Several insertions and deletions found in the first poly-alanine tract of SOX3 have been described in patients with short stature with IGHD, with and without cognitive impairment [5, 24, 25, 33].

Although rare, large duplications and deletions including both GPR101 and SOX3 have previously been reported [28, 30, 31, 37]. A Xq26.1–q27.3 duplication was reported in 2 male patients with hypopituitarism only [28], whereas a deletion of this region was reported in a male patient with panhypopituitarism who also had ID, spina bifida (NTD), and growth retardation [30]. Another Xq26.3–q27.3 duplication was reported in a male patient with severe growth retardation, ocular abnormalities, hypotonia, seizures and developmental delay [37]. Hamel et al. reported the largest duplication (Xq24–q27.3) containing GPR101 and SOX3 in a male patient with ID, GHD and growth retardation [31]. These data support our current finding that, in duplications containing both GPR101 and SOX3, the GHD phenotype is dominant. This is probably explained by the timing of GPR101 and SOX3 expression. SOX proteins are crucial for the patterning and morphogenetic processes occurring in the early embryo. During early embryogenesis, cells are organized by tissue patterning. This means that induction of fate-determining genes is spatially controlled to generate patterns for cell differentiation and maturation.

GPR101 is predominantly active during maturation of the pituitary [14], whereas SOX3 is affected, and patterning is thus already disturbed, the later possible effects of GPR101 overexpression in the pituitary might be overruled. We cannot disregard the possibility that dysregulation of other genes in this duplicated region might contribute to the suppression of GPR101.

### Table 2 (continued)

| Refs | Case | Sex | Growth | Gonads | Hormone deficiencies | Neonatal | MRI |
|------|------|-----|--------|--------|----------------------|----------|-----|
| [28] | A II.2 | M | | | GH | | |
| [28] | B II.1 | M | | | GH, TSH | | |
| [28] | B II.2 | M | | | GH, TSH | | |
| [48] | M | Cryptorchidism with a small penis, hypogonadism | | | Hypoglycaemia Microcephaly | | |
| [30] | M | | | | Pan-hypopituitarism | | |
| [29] | 1 | M | | | GH | | |
| [29] | 2 | M | | | GH | | |
| [29] | 3 | M | | | GH | | |
| [27] | IV | M | | | GH, NA | | |
| [27] | IV.4 | M | | | GH | | |
| [27] | IV.5 | M | | | GH | | |
| [27] | IL.5 | M | | | Hypogonadal GH, TSH, PRL | | |
| [27] | III.3 | M | | | GH, TSH, PRL | | |
| [27] | III.9 | M | | | Hypogonadal GH, TSH, PRL | | |
| [31] | III.9 | M | | | Mild gynaecomastia GH | | |
| [31] | II.6 | M | | | NA | | |
| [31] | II.7 | M | | | NA | | |
| [31] | II.8 | M | SS | | All pituitary hormones APH, EPP | | |
| [31] | III.3 | M | GR | | All pituitary hormones | | |
| [31] | III.6 | M | SS | | All pituitary hormones | | |
| [31] | III.7 | M | SS | | All pituitary hormones | | |
| [31] | IV.6 | M | SS | | All pituitary hormones | | |
| Present case | M | SS/GR | | | APH, EPP | | |
| Present case | M | SS/GR | | | All pituitary hormones | | |

**Abbreviations:** AP anterior pituitary, APH anterior pituitary hypoplasia, EPP ectopic posterior pituitary, EP ectopic pituitary, NA not assessed, ACC agenesis corpus callosum, CC corpus callosum, SP septum pellucidum, FTT failure to thrive, STV small testicle volume, SS/GR short stature or growth retardation
Table 3  Non-endocrine phenotypes of SOX3 duplications

| Refs | Case | Sex | ID  | Myelum                  | Senses                  | Speech               | Musculo-skeletal Findings | Kidney               | Additional Findings |
|------|------|-----|-----|-------------------------|-------------------------|----------------------|---------------------------|-----------------------|---------------------|
| [39] | F IV | ?   | −   | Lumbosacral MMC          | −                       | Dystrophia            | Clubfeet, calf muscle atrophy, 3 sacral vertebrae | −                     |                     |
| [39] | F    | F   | −   | Lumbosacral MMC and myeloschisis | −                       | Dystrophia            |                           | −                     |                     |
| [40] | III.2 | F   | −   | Hearing impairment       | −                       | Dystrophia            |                           | −                     |                     |
| [40] | II.2  | F   | −   | Hearing impairment       | −                       | Dystrophia            |                           | −                     |                     |
| [40] | III.4 | F   | −   | Hearing impairment       | −                       | Dystrophia            |                           | −                     |                     |
| [31] | III.2 | F   | +   | MMC                      | −                       | Clubfeet, calf muscle atrophy, 3 sacral vertebrae | −                     | −                     |                     |
| [38] | F1   | F   | −   | MMC                      | −                       | Clubfeet, calf muscle atrophy, 3 sacral vertebrae | −                     | −                     |                     |
| [38] | F2   | F   | −   | Lumbosacral MMC          | −                       | Varus feet            |                           | −                     |                     |
| [38] | F3   | F   | −   | Lumbosacral MMC          | −                       | Bilateral kidney hypertrophy |                           | −                     |                     |
| [32] | I    | M   | ++  | Lumbral MMC (repaired after birth) | −                       | −                       |                           | −                     |                     |
| [32] | II   | M   | ++  | Lumbral MMC (repaired after birth) | −                       | −                       |                           | −                     |                     |
| [32] | III  | M   | −   | Lumbral MMC (repaired after birth) | −                       | −                       |                           | −                     |                     |
| [32] | IV   | M   | +   | Hyposmia, dysgeusia      | −                       | −                       |                           | −                     |                     |
| [21] | V    | M   | +   | Hyposmia, dysgeusia      | −                       | −                       |                           | −                     |                     |
| [42] | Index| M   | −   | Madelung deformity of the forearm, hypoplastic tibia and fibula, clubfeet | −                       | −                       |                           | −                     |                     |
| [43] | F2   | M   | −   | MMC                      | −                       | −                       |                           | −                     |                     |
| [43] | F3   | M   | −   | MMC                      | −                       | −                       |                           | −                     |                     |
| [44] | C1   | M   | −   | −                       | −                       | −                       | Raspy voice, language delay | −                     |                     |
| [44] | C2   | M   | −   | −                       | −                       | −                       | Raspy voice, language delay | −                     |                     |
| [44] | C3   | M   | +   | −                       | −                       | −                       | −                       | −                     |                     |
| [44] | C4   | M   | −   | −                       | −                       | −                       | −                       | −                     |                     |
| [39] | III.7| M   | +   | −                       | −                       | −                       | High pitched voice        | −                     |                     |
| [39] | III.1| M   | +   | −                       | −                       | −                       | −                       | −                     |                     |
| [37] | M    | +   | −   | Ocular dyspraxia         | −                       | −                       | −                       | −                     | Obesity             |
| [45] | M    | +   | −   | Ocular dyspraxia         | −                       | −                       | −                       | −                     | Behavior problems, minor facial anomalies |
In conclusion, we found a 6 Mb duplication of Xq26.2-q27.1 in two brothers with hypopituitarism, which included GPR101, a gene associated with the phenotypic opposite: X-linked acrogigantism. Additional analysis showed that the duplication also included SOX3, a gene involved in early pituitary organogenesis which is associated with variable degrees of hypopituitarism. Our findings, supported by the literature, show that in duplications containing both GPR101 and SOX3, the GHD phenotype is dominant. This suggests that GPR101 duplication is overruled when early patterning of the embryonic pituitary is affected due to SOX3 duplication. The fact that the mother (carrying the same duplication as the two boys) was unaffected, is probably due to non-random X inactivation. Our results, combined with our genotype–phenotype analysis, sheds a new light on the genetic background of both hypopituitarism and gigantism.

Table 3 (continued)

| Refs | Case | Sex | ID | Myelum | Senses | Speech | Musculo-skeletal | Kidney | Additional findings |
|------|------|-----|----|--------|--------|--------|------------------|--------|---------------------|
| [46] | M    | −   |    |        |        |        |                  |        |                     |
| [47] | A    | M   | −   |        |        |        |                  |        |                     |
| [47] | C    | M   | −   |        |        |        |                  |        |                     |
| [24] | I    | M   | −   |        |        |        |                  |        |                     |
| [24] | 2    | M   | −   |        |        |        |                  |        |                     |
| [28] | A II.1 | M | −   |        |        |        |                  |        |                     |
| [28] | A II.2 | M | −   |        |        |        |                  |        |                     |
| [28] | B II.1 | M | −   |        |        |        |                  |        |                     |
| [28] | B II.2 | M | −   |        |        |        |                  |        |                     |
| [30] | M    | −   |    | Spina bifida |        |        |                  |        |                     |
| [48] | M    | +   |    |        |        |        |                  |        | Conductive hearing loss |

[29] 1 M +
[29] 2 M +
[29] 3 M +
[27] IV M +
[27] IV.4 M +
[27] IV.5 M +
[27] II.5 M +
[27] III.3 M +
[27] III.9 M +
[31] III.9 M +
[31] II.6 M +
[31] II.7 M +
[31] II.8 M +
[31] III.3 M +
[31] III.6 M +
[31] III.7 M +

[31] IV.6 M

Postaxial polydactyly of both hands

Present case M −
Present case M −

Truncal obesity and puffy face
| Refs | Sex | ID | Clinical findings | Affected pituitary hormones | MRI findings | SOX 3 mutation | Functional relevance |
|------|-----|----|-------------------|-----------------------------|-------------|----------------|---------------------|
| [34] |    | Mild ID | GH | Small AP; EPP | c.424C>A; p.142T | Predicted as disease-causing transcription activation |
| [34] |    | | GH | APH | c.424C>A; p.142T |               |
| [35] | M1 | Mild ID | GH, THD, LH/FSH | AP | c.449C>A; p.S150Y | Predicted as disease-causing |
| [35] | M2 | Mild ID | GH, THD, LH/FSH | DP | c.449C>A; p.S150Y |               |
| [35] | M3 | Mild ID | GH, LH/FSH | EP | c.449C>A; p.S150Y |               |
| [36] | M | Severe SS/GR | GH, LH and FSH | APH | c.14G>A; p.R5Q | No functional effect, benign likely benign |
| [24] |    |       | GH | Enlarged AP; NPP | p.243-248del6 | Transcription activation; Repress β-catenin |
| [37] | M | Normal intelligence | SS/GR | All | NA | p.A240-241ins7 | Loss of transcriptional activity; Reduced nuclear transport unable to repress β-catenin |
| [37] | M | Learning difficulties | SS/GR | GH | APH; EPP | p.A240-241ins7 | Loss of transcriptional activity; Reduced nuclear transport unable to repress β-catenin |
| [49] | M | Normal intelligence | SS/GR | GH | Normal AP; EPP | p.A240-241ins7 | Loss of transcriptional activity; Reduced nuclear transport unable to repress β-catenin |
| [49] | M | Normal intelligence | GH, TSH, LH/FSH, ACTH | APH; EPP | p.A240-241ins7 | Loss of transcriptional activity; Reduced nuclear transport unable to repress β-catenin |
| [16] | M | Normal intelligence | GH, TSH, LH/FSH, ACTH | APH; EPP, AHI |               |
| [16] | M | Normal intelligence | SS/GR | GH, TSH, LH/FSH, ACTH | APH; EPP, AHI |               |
| [33] | M | X-linked ID | SS/GR | GH | NA | p.A234-245ins11 | Transcription activation; Repress β-catenin |
| [33] | M | Severe ID | SS/GR | – | NA | p.214-248del9 |               |

PA polyalanine, ID intellectual disability, APH anterior pituitary hypoplasia, EPP ectopic posterior pituitary, AHI absent or hypoplastic infundibulum, AP absent pituitary gland, DP dysplastic pituitary gland, EP ectopic pituitary gland, NA not available (adapted from Tagaki et al. 2013)

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Compliance with ethical standards

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or
national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We obtained approval from the medical ethics committees of all participating hospitals.

Informed consent Informed consent was obtained from the individuals participating in this study and their parents if they were younger than 18 years.

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