Ectopic Posterior Pituitary, Polydactyly, Midfacial Hypoplasia and Multiple Pituitary Hormone Deficiency due to a Novel Heterozygous IVS11-2A>C(c.1957-2A>C) Mutation in the GLI2 Gene

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What is already known on this topic?

Patients with GLI2 mutation usually present with multiple pituitary hormone deficiency (MPHD) accompanied by ectopic posterior pituitary, polydactyly and midfacial hypoplasia. Heterozygous mutations in GLI2 cause a wide range of clinical phenotypes ranging from asymptomatic cases to more severe clinical phenotypes including Culler-Jones syndrome and holoprosencephaly (HPE) or HPE-like syndrome.

What this study adds?

A patient is reported with a novel heterozygous IVS11-2A>C(c.1957-2A>C) mutation in the GLI2 gene which expands the mutation database. Extremely distinct phenotypical expression and incomplete penetrance of heterozygous GLI2 mutations may cause MPHD to skip a generation and thus delay or missed diagnosis of these life-threatening hormonal disorders. The response to growth hormone (GH) replacement may be excellent. It is suggested that a trial of GH therapy in cases of GLI2 mutation with GH deficiency may be beneficial.

Abstract

A novel heterozygous IVS11-2A>C(c.1957-2A>C) mutation in the GLI2 gene is reported. There was an extremely distinct phenotypical expression in two siblings and their father. The index case was a boy who developed cholestasis and hypoglycaemia in the neonatal period. He had bilateral postaxial polydactyly, mid-facial hypoplasia, high palatal arch, microopenis, and bilateral cryptorchidism. Laboratory examination revealed a diagnosis of multiple pituitary hormone deficiency. There was severe anterior pituitary hypoplasia, absent pituitary stalk and ectopic posterior pituitary on magnetic resonance imaging which suggested pituitary stalk interruption syndrome with no other midline structural abnormality. Molecular genetic analysis revealed a novel heterozygous splicing IVS11-2A>C(c.1957-2A>C) mutation detected in the GLI2 gene. His father and a six-year-old brother with the identical mutation also had unilateral postaxial polydactyly and mid-facial hypoplasia although there was no pituitary hormone deficiency. This novel heterozygous GLI2 mutation detected appears to present with an extremely variable clinical phenotype, even in related individuals with an identical mutation, suggesting incomplete penetrance of this GLI2 mutation.

Keywords: Growth hormone deficiency, polydactyly, GLI2 mutations, multiple pituitary hormone deficiency

Introduction

The sonic hedgehog (SHH) signalling pathway regulates differentiation, proliferation, tissue polarity, stem cell population, and carcinogenesis of the notochord and floor plate in the developing spinal cord (1,2). The SHH signalling pathway is mediated by three related zinc-finger transcription factors (GLI1, GLI2, and GLI3) which are members of the GLI-Kruppel family. GLI2 is an activating zinc-finger transcription factor which plays a crucial role in the development of the diencephalon and distal extremities.
during embryogenesis. It is encoded by the GLI2 gene, a large polymorphic gene, that is mapped to 2q14.2. Therefore, it is very likely that analysis will show variants of uncertain significance (VUS). Homozygous deletion of both GLI1 and GLI2 results in complete absence of the pituitary gland (3). Heterozygous mutations of the GLI2 gene cause a variety of clinical phenotypes, ranging from asymptomatic cases to more severe clinical phenotypes including Culler-Jones syndrome and holoprosencephaly (HPE) or HPE-like syndrome. Culler-Jones syndrome is a clinical spectrum of multiple pituitary hormone deficiency (MPHD), ectopic posterior pituitary, and postaxial polydactyly with or without midline defects and developmental delay (3). HPE presents with a more severe clinical spectrum with additional midline structural abnormality and forebrain cleavage defects. To date, about 25 different pathogenic GLI2 mutations have been identified (4). Heterozygous GLI2 mutations can be inherited in an autosomal dominant fashion or de novo (51% maternal, 40% paternal, and 9% de novo) (5). Herein, we report a novel heterozygous IVS11-2A>C(c.1957-2A>C) mutation in the GLI2 gene in two siblings and their father from a non-consanguineous marriage, suggesting an extremely distinct phenotypical expression and incomplete penetrance.

**Case Report**

**Index Case**

The proband was a male patient who was born after 40 weeks uneventful gestation via spontaneous vaginal delivery, with a birth weight of 3700 gr. The parents were not consanguineous. Family history revealed that one of his brothers, his father and paternal grandfather had polydactyly and atypical facial appearance with no known hormonal disorders. He had postaxial polydactyly, mid-facial hypoplasia, high palatal arch, micropenis and bilateral cryptorchidism. At the age of two months, he developed facial hypoplasia, high palatal arch, micropenis and bilateral cryptorchidism. At the age of one year, and GH replacement therapy was commenced at another paediatric endocrine centre. The patient was admitted to our hospital for the first time when he was 2.1 years old. He had been on GH replacement therapy for one year. His weight was 9 kg [-3.3 standard deviation score (SDS)] and height was 69 cm (-5.4 SDS). During follow up at our clinic response to the GH therapy was excellent (see Figure 1). At his most recent follow-up visit when he was 10-years-old, his height was 133.5 cm (-0.46 SDS), weight was 28.7 kg (-0.51 SDS), body mass index was

| Index case (two months) | Father (38 years) | Brother (six years) | Lab normal for index case |
|-------------------------|------------------|---------------------|--------------------------|
| Na (mEq/L) | 140 | 138 | 137 | 135-145 |
| K (mEq/L) | 4.5 | 4.2 | 3.9 | 3.5-5.5 |
| Glu (mg/dL) | 17 | 97 | 85 | 60-100 |
| ALT (IU/L) | 24 | 38 | 44 | 0-40 |
| AST (IU/L) | 34 | 31 | 43 | 0-40 |
| GGT (IU/L) | 501 | 10 | 61 |
| Total bilirubin (mg/dL) | 6.4 | 1.1 | 0.8 | 0-1.2 |
| Direct bilirubin (mg/dL) | 4.8 | 0.3 | 0.2 | 0-0.3 |
| LDH (IU/L) | 309 | 181 | 192 | 180-430 |
| Calcium (mg/dL) | 9.6 | 9.2 | 9.5 | 8.8-10.8 |
| Phosphorus (mg/dL) | 5.3 | 4.1 | 3.9 | 3.5-5.5 |
| ALP (IU/L) | 940 | 110 | 147 | 150-1076 |
| Cortisol* (µg/dL) | 1 | 7.2 | 7.2 | 5-25 |
| GH* (ng/mL) | 0.059 | N/A | N/A | - |
| Insulin (mIU/mL)* | <2 | N/A | N/A | - |
| FT4 (ng/dL) | 0.4 | 1 | 1.25 | 0.8-1.9 |
| TSH (IU/L) | 0.84 | 2.3 | 2.16 | 0.4-8.6 |
| Prolactin (ng/mL) | 1.99 | 7 | 14.5 | 3-11 |
| FSH** (mIU/mL) | 0.05 | 8 | 0.54 | 0.7-11.4 |
| LH** (mIU/mL) | 0.1 | 5.2 | 0.06 | 0.8-7.6 |
| Testosterone** (ng/dL) | <20 | 450 | N/A | 12-21 |
| IGF1 (ng/mL) | <25 | 467 | 138 | 15-109 |

* Growth hormone (GH), cortisol and insulin were measured from critical blood samples which revealed a diagnosis of congenital MPHD (Table 1). Hypoglycaemia and cholestasis resolved with replacement of hydrocortisone and sodium L-thyroxine (L-T4). He had severe anterior pituitary hypoplasia, absent pituitary stalk and ectopic posterior pituitary with no other midline structural abnormality on pituitary magnetic resonance imaging (MRI). A surgical orchidopexy was performed. Diagnosis of GH deficiency was confirmed at the age of one year, and GH replacement therapy was commenced at another paediatric endocrine centre.

**Table 1. Biochemical and hormonal characteristics of the index case and affected relatives**
16.1 kg/m\(^2\) (-0.4 SDS). He had no signs of puberty. He had bilateral postaxial polydactyly, mid-facial hypoplasia, high palatal arch and moderate developmental delay. He was on L-T4 (2.6 µg/kg/day), GH (with a dose of 0.033 mg/kg/day), hydrocortisone and antiepileptic therapy for focal epileptic seizures.

The patient’s brother was six-years old with a weight of 20.7 kg (-0.01 SDS), and height was 116.2 cm (0.01 SDS). He had normal sized, pre-pubertal testes with no history of undescended testis. He had left postaxial polydactyly and mid-facial hypoplasia with no pituitary hormone deficiency. The patient’s father was 38-years-old and his adult height was 166 cm. He also had left postaxial polydactyly and mid-facial hypoplasia with no pituitary hormone deficiency (Table 1). Cranial MRI was not performed in the father and sibling as they had no evidence of pituitary dysfunction.

**Molecular Genetic Analysis**

Genomic DNA was extracted according to the manufacturer’s standard procedure using the QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany). All coding exons of the \textit{GLI2} gene and their flanking splice site junctions were amplified using in-house designed PCR primers (available upon request). These were subsequently sequenced by the MiSeq next-generation sequencing (NGS) platform (Illumina Inc., San Diego, CA, USA). The libraries were prepared with the NexteraXT kit (Illumina Inc., San Diego, CA, USA), according to the manufacturer’s instructions. Next-generation sequencing was carried on MiSeq (Illumina Inc., San Diego, CA, USA). Sequences were aligned to the hg19 genome within MiSeq Reporter software (Illumina Inc., San Diego, CA, USA). The data were visualized with IGV 2.3 (Broad Institute; http://exac.broadinstitute.org) software. Sanger sequencing analysis was performed for confirmation of the variant detected at NGS analysis.

\textit{In silico} prediction tools (MutationTaster and Human splicing finder) were used for evaluation of the novel unpublished variant. The variant was classified based on the 2015 American College of Medical Genetics and Genomics and Association for Molecular Pathology guidelines (6).

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Local Ethical Committee. Written informed consent was obtained from the participants and their legal guardians.

A novel heterozygous IVS11-2A>C (c.1957-2A>C) mutation in intron 11 of the \textit{GLI2} gene was identified in the proband (Figure 2). His father and six-year-old brother, who both had postaxial polydactyly and facial dysmorphism with no hormonal deficiency, were also heterozygous for the identical mutation. The unaffected mother and sister had normal alleles. This variant was listed neither in the 1000 genomes

![Figure 1. Facial dysmorphism and polydactyly in the index case, brother and father (a-f). Good response to recombinant human growth hormone therapy in the index case (g)](image)
nor in the ExAC database (http://browser.1000genomes.org/index.html, http://exac.broadinstitute.org/, respectively). This mutation in GLI2 disrupted the intron 1 acceptor splice-site and this was predicted to result in aberrant splicing, and thus synthesis of a truncated protein.

Discussion

Herein, a patient is presented with congenital MPHD, midfacial hypoplasia, bilateral postaxial polydactyly, anterior pituitary hypoplasia and ectopic posterior pituitary due to a novel heterozygous splicing mutation IVS1-2A>C(c.1957-2A>C) in the GLI2 gene. Clinical features were similar to Culler-Jones syndrome. Although his father and brother with the identical heterozygous mutation had similar physical dysmorphisms, including postaxial polydactyly and mild facial hypoplasia, they had no hormonal deficiency (Table 2).

The heterozygous IVS1-2A>C(c.1957-2A>C) mutation is predicted to cause a splicing defect that would result in aberrantly spliced transcripts, and thus the synthesis of a truncated protein. GLI2 mutations leading to a truncated protein usually cause panhypopituitarism, polydactyly and midfacial hypoplasia, which were present in our index case. Interestingly, pituitary dysfunction was not detected in the proband’s father and brother, both of whom had the identical mutation, suggesting incomplete penetrance and variable expressivity (3,5,7,8). Distinct clinical phenotypes in subjects with identical heterozygous GLI2 mutations have previously been reported and suggested as evidence for incomplete penetrance and variable expressivity (3,9). The variable expression of the GLI2 gene mutations has been attributed to the combination of genetic, environmental and epigenetic factors or contribution of the other genes involved in the SHH pathway, which include SHH, ZIC2, SIX3, PTCH1, GLI3 and TGIF genes (5,9,10,11).

The largest cohort with GLI2 variants was reported by Bear et al (5) where a GLI2 variant was detected in 112 of 400 patients with HPE spectrum, endocrine disorders or craniofacial anomaly. Of these 112, 43 were found to have a truncating mutation (frameshift, nonsense, or large deletion) and 69 were reported to have a VUS (5). The clinical characteristics of cases with GLI2 mutations reported so far are shown in Table 3 (Supplementary file).

The clinical spectrum of mutations in GLI2 may vary from asymptomatic individuals to polydactyly, functional

| Symptoms                        | Index case          | Father             | Brother            | Culler-Jones syndrome |
|---------------------------------|---------------------|--------------------|--------------------|-----------------------|
| Mutation                        | IVS1-2A>C (c.1957-2A>C) | IVS1-2A>C (c.1957-2A>C) | IVS1-2A>C (c.1957-2A>C) | -                     |
| Inheritance pattern             | Heterozygous        | Heterozygous       | Heterozygous       | Heterozygous          |
| Polydactyly                     | +                   | +                  | +                  | +/-                   |
| Forebrain cleavage defect       | -                   | -                  | -                  | -                     |
| Anomalous pituitary hypoplasia   | +                   | N/A                | N/A                | +/-                   |
| Posterior pituitary abnormality  | Ectopic posterior pituitary | N/A                | N/A                | Ectopic posterior pituitary |
| Pituitary stalk                  | Interrupted         | N/A                | N/A                | +/-                   |
| GH deficiency                   | +                   | -                  | -                  | +/-                   |
| TSH deficiency                   | +                   | -                  | -                  | +/-                   |
| ACTH deficiency                  | +                   | -                  | -                  | +/-                   |
| Gonadotropin deficiency         | +                   | -                  | -                  | +/-                   |
| Prolactin deficiency            | +                   | -                  | -                  | +/-                   |
| ADH deficiency                   | -                   | -                  | -                  | +/-                   |
| Genitourinary system abnormality| Micropenis, cryptorchidism | -                  | -                  | +/-                   |
| Developmental delay             | +                   | -                  | -                  | +/-                   |

GH: Growth hormone, TSH: thyroid stimulating hormone, ACTH: adrenocorticotropic hormone, N/A: not available
and structural abnormality in the pituitary gland, facial dysmorphism, Culler-Jones syndrome, HPE-like syndrome, and frank HPE (4,8). In addition, renal problems such as renal hypoplasia/dysplasia, urethral stricture and cardiac problems such as ASD/VSD have been reported in patients with GLI2 mutations (4,8). HPE is the most common anterior brain anomaly and HPE is characterized by incomplete separation of cerebral hemispheres and underdeveloped midbrain structures. However, the mutations in GLI2 are rarely associated with an HPE phenotype (7,12). Indeed, in the study of Bear et al (5) only three of the 112 (2.7%) patients with GLI2 mutations, had HPE (13). Also, neuroanatomical anomalies, such as agenesis of the corpus callosum, abnormal cerebral periventricular venous system and abnormal gyri have been reported in patients with GLI2 mutations (8,14,15,16,17). In contrast to the literature, our patient had severe anterior pituitary hypoplasia, MPHD, and ectopic posterior pituitary with no features of HPE or HPE like syndrome. Pituitary stalk interruption syndrome (PSIS) is a congenital anomaly of the pituitary gland characterized by small or absent anterior pituitary lobe, interrupted or absent pituitary stalk, and ectopic posterior pituitary lobe (18). PSIS may be associated with isolated or syndromic features (18). Mutations in genes encoding transcription factors in signalling pathways, especially GLI2 variants, have been reported in PSIS, which is consistent with our case (18,19).

Pituitary dysfunction due to GLI2 mutations may vary from idiopathic GH deficiency to MPHD, with or without ADH deficiency (3,5). Our index case had biochemical and hormonal features of complete anterior pituitary hormone deficiency including GH, thyroid-stimulating hormone,
| Reference | Proband’s age/gender | Consanguinity | Pituitary imaging                          | Polydactyly | Pituitary insufficiency | Intellectual disability | Other clinical findings | Mutation |
|-----------|----------------------|---------------|--------------------------------------------|-------------|------------------------|------------------------|------------------------|----------|
| Present case | 10-year-old/male | No            | Ectopic posterior pituitary, anterior pituitary hypoplasia, absent of pituitary stalk | Bilateral post-axial polydactyly | ACTH, GH, TSH, FSH, LH, PRL | Yes | Facial dysmorphism | Paternal c.1957-2A > C |
| Babu et al (19) | 4.9-year-old/female | | Hypoplasia of the pituitary gland | No | GH | No | No | Maternal p.Pro386Leu |
| 2-year-old/female | | | Anterior pituitary hypoplasia | Post-axial polydactyly | GH, TSH and ACTH | No | Cranio-facial abnormalities, bilateral renal hypoplasia | Maternal p.Tyr575His |
| 3.5-year-old/male | | | Normal | No | GH, TSH and ACTH | No | No | p.Ala593Val |
| 3-year-old/male | | | Anterior pituitary hypoplasia | No | ACTH, GH, TSH, FSH, LH, PRL | No | No | De novo p.Arg1226X |
| 16.6-year-old/female | | | stalk interruption syndrome with ectopy of the neurohypophysis and hypoplasia of the anterior pituitary | No | GH, TSH and ACTH | Yes | Congenital heart disease renal hypoplasia with bladder - ureteral reflux, labiopalatoschisis, mental retardation, deafness and visual impairment | De novo p.Val1111Gfs*19 |
| Kordaß et al (8) | 25-year-old/female | No | Abnormal temporal myelinization | No | No | No | | Paternal heterozygous deletion 2q14.2q14.3 |
| Shirakawa et al (4) | 15-year-old/male | No | Ectopic posterior lobe | Bilateral finger and toes | GH | Yes | Renal hypoplasia/ dysplasia, ASD ureteral stricture/renal failure, midfacial hypoplasia | De novo heterozygous frameshift c.3569delg |
| Martín-Rivada et al (21) | 12-year old/male | No | Absence of pituitary stalk and posterior pituitary | Bilateral postaxial | GH, TSH, ACTH, FSH, LH | Yes | Bilateral labial cleft, facial dysmorphism, bilateral cryptorchidism, micropenis | De novo c.2125del |
| Valenza et al (11) | 6-year-old/female | N/A | Anterior pituitary agenesis | Bilaterally postaxial | Panhypopituitarism | N/A | Facial dysmorphism, prominent forehead, 2-3 finger syndactyly single median maxillary incisor choanal atresia | Paternal c.3495del |

Table 3 (Supplementary file). Clinical and genetic characteristics of cases with mutations in GLI2 gene.
| Reference                | Proband's age/gender | Consanguinity | Pituitary imaging                                                                 | Polydactyly | Pituitary insufficiency | Intellectual disability | Other clinical findings                                                                 | Mutation                          |
|--------------------------|----------------------|---------------|----------------------------------------------------------------------------------|-------------|------------------------|-------------------------|------------------------------------------------------------------------------------------|-----------------------------------|
| Juanes et al (23)        | 4-year-old/ female   | No            | Ectopic posterior lobe, absent pituitary stalk                                    | No          | GH                     | Yes mild                | Right cleft lip and palate, facial dysmorphism, hypoplastic nostrils, hypotelorism, mild facial asymmetry | p.arg231gln heterozygous missense |
|                          | 14-year-old/ male    | No            | Posterior pituitary lobe and stalk were absent                                    | No          | GH, TSH, ACTH, FSH, LH | No                      | N/A                                                                                       | p.arg226leu heterozygous missense |
| Kevelam et al (10)       | 9-year-old/ female   | No            | Ectopic neurohypophysis                                                           | No          | GH, TSH                | No                      | Bilateral cleft lip and palate left isomerism mild midface hypoplasia                      | Paternal heterozygous 2q14.2 deletion |
| França et al (3)         | 7-year-old / female  | No            | Ectopic posterior pituitary lobe, asymmetric brain hemispheres                    | Bilateral postaxial | GH, TSH, ACTH, PRL, FSH, LH | Yes | Seizures vesicouretral reflux                                                                 | Maternal heterozygous frameshift c.2362_2368del |
|                          | 4.5-year-old/ male   | No            | Ectopic posterior pituitary lobe                                                  | No          | GH, ACTH               | No                      | Cleft lip and palate, flat nasal brige unilateral cryptorchidism                           | Paternal heterozygous frameshift c.2081_2084del |
|                          | 8-month-old/ male    | No            | Posterior pituitary lobe, not visible hypoplastic anterior pituitary             | No          | GH, ACTH, TSH, ADH     | Yes | Seizures                                                                                   | Maternal heterozygous c.1138g>t |
| Kremer Hovinga et al (9) | 12-year-old/ male    |               | Ectopic posterior pituitary lobe                                                  | Bilateral postaxial | Panhypopituitarism | N/A | Hypotelorism, single median incisor mid urethral stenosis-urethral valves cryptorchidism ribbed palatum durum | Paternal heterozygous c.5676c>t nosense |
| Bertolacini et al (7)    | 4-year-old/ male     | N/A           | Normal                                                                            | No          | N/A                    | No                      | High forehead, flat facial profile, facial dysmorphism, right cleft lip                     | Heterozygous c.805 c>t 3' utr |
|                          | 3-month-old/ female  | N/A           | Normal                                                                            | Right preaxial | N/A                    | No                      | Bilateral cleft lip/palate, flat face, maxillary hypoplasia                                | Maternal heterozygous c.4663>c |
|                          | 28-year-old/ female  | N/A           | Normal                                                                            | Bilaterally postaxial | N/A                    | No                      | Hypotelorism, long and flat profile, mid line cleft, broad nasal tip, agenesis of pre-maxilla, long philtrum | Maternal heterozygous c.1530_1531 insc |
### Table 3 (Supplementary file). Continued

| Reference          | Proband’s age/gender | Consanguinity | Pituitary imaging | Polydactyly | Pituitary insufficiency | Intellectual disability | Other clinical findings                                                                 | Mutation                                                                 |
|--------------------|----------------------|---------------|-------------------|-------------|------------------------|------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 3-month-old/ female | N/A                  | Semi-lobar HPE | Bilateral postaxial | N/A         | Yes                    | Yes                    | Microcephaly, large cleft lip/palate involving partially premaxilla                        | Maternal c.864_866delcc                                                   |
| 5-year-old/ male   | N/A                  | Normal        | No                | N/A         | No                     | Yes                    | Facial asymmetry, abnormal oedelled ears with skin tags, tessier cleft number 7 at right, abnormal temporomandibulary joint | c.1886g > a                                                              |
| 5-month-old        | N/A                  | Normal        | No                | N/A         | No                     | No                     | Facial asymmetry with hypoplastic left side left anophtalmia, abnormal modelled ears preauricular skin tag tessier cleft number 7 at left | De novo c.4558g > a                                                   |
| Antich et al (14)   | 8-month-old/ male    | No            | Corpus callosum agenesis | Yes        | N/A                    | Yes                    | Cleft lip and palate, facial dysmorphism, Low-set ears, microretrognathia, imperforate anus, VSD, hydronephrosis | De novo 2q14-q14 heterozygous                                           |
| Lucas et al (24)    | Newborn female       | N/A           | N/A               | No          | N/A                    | No                     | Cleft lip and palate, facial dysmorphism, hypertelorism, low set ears, premature cranial synostosis | De novo 2q14-q21 heterozygous                                           |
| Frydman et al (16)  | 2-year-old/ female   | No            | Corpus callosum agenesis | No         | N/A                    | Yes                    | Cleft lip and palate, persistent disease activity, microphthalmia, low set ears            | 2q14-q21 heterozygous                                                  |
| Davis et al (15)    | 29 month-old/female  | No            | Corpus callosum agenesis, dandywalker malformation | No         | N/A                    | Yes                    | Cleft lip and palate, facial dysmorphism poorly developed auricles, epicanthic fold, ASD, seizures, ovarian dysgenesis | De novo 2q13-q21 heterozygous                                           |
| Baker et al (25)    | 15-year-old/ male    | No            | N/A               | No          | N/A                    | Yes learning difficulties | Thoracoelombar kyphoscoliosis, pectus carinatum, facial dysmorphism mild aortic root dilatation | Paternal 2q14.1-22.1 heterozygous                                       |
adrenocorticotropic hormone (ACTH), prolactin, follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) (Table 1). The most common pituitary hormone deficiency is GHD (20). Although the response to rhGH replacement has been reported to be poor in some cases with GLI2 mutations, an excellent response to rhGH replacement was observed in our case and has been reported previously. This suggests that clinicians should consider a trial of rhGH therapy in cases with GLI2 mutation who have GHD (Figure 1) (3,8,21). In addition, hypoglycaemia, cholestasis, recurrent seizures and intellectual disability have been reported in patients with GLI2 mutations as a consequence of ACTH and GH deficiency (22). Hypoglycaemic episodes and cholestasis in our case resolved after replacement of hydrocortisone and with rhGH therapy. We also attributed the seizures and moderate developmental delay evident in our case to neonatal hypoglycaemic episodes due to ACTH and GH deficiency. While the presence of micropenis in our case may be attributed to GH deficiency, he also had cryptorchidism and inappropriately low FSH, LH and testosterone levels during mini-puberty, suggesting concomitant gonadotropin deficiency. Despite having an ectopic posterior pituitary on pituitary-imaging he had no diabetes insipidus at presentation and this has not developed to date during follow-up.

Conclusion

In conclusion, extra-pituitary findings may provide clues for the diagnosis of particular gene mutations including GLI2, HESX1, LHX4, SOX3, and OTX2 which are involved in the development and differentiation of the pituitary gland resulting in a variety of pituitary hormone deficiencies. In cases presenting with MPHD accompanied by ectopic posterior pituitary, polydactyly and midfacial hypoplasia, a diagnosis of GLI2 mutation should be considered. Furthermore, extremely distinct phenotypical expression and incomplete penetrance of heterozygous GLI2 mutations may be associated with MPHD skipping a generation and thus delay or missed diagnosis of these life-threatening hormonal disorders. In light of this genetic analysis of either asymptomatic or symptomatic relatives for GLI2 gene mutations and evaluation of carriers for panhypopituitarism is warranted.

Ethics

Informed Consent: The subject and his parents have given their written informed consent to publish their case, in accordance with the Declaration of Helsinki.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Meliha Demiral, Hüseyin Demirbilek, Mehmet Nuri Özbek, Design: Meliha Demiral, Hüseyin Demirbilek, Mehmet Nuri Özbek, Data Collection or Processing: Meliha Demiral, Hüseyin Demirbilek, Mehmet Nuri Özbek, Analysis or Interpretation: Meliha Demiral, Edip Ünal, Ceren Damla Durmaz, Serdar Ceylaner, Literature Search: Meliha Demiral, Edip Ünal, Writing: Meliha Demiral, Hüseyin Demirbilek, Mehmet Nuri Özbek.

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