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TWO DIFFERENT MUTATIONS OF GLI3 GENE IN TWO DIFFERENT SYNDROMES

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Summary: *Two different mutations of GLI3 gene in two different syndromes:* Polydactyly is among common extremity abnormalities. Mutations of *GLI3* gene have been reported commonly in Greig Cephalopolysyndactyly Syndrome (GCPS) and Pallister-Hall Syndrome (PHS). We have determined two different mutations of *GLI3* gene in two different cases, one of which is with GCPS and the other one is with PHS. A deletion mutation was detected in the proband with GCPS and his mother. Otherwise, we found that, unlike the previously reported, the mutation c.2437C>T, p.Q813X which was detected in the *GLI3* gene caused typical PHS. We are in thought of that our cases will contribute to understanding of phenotypic variability leading to *GLI3* mutations.

Key-words: *GLI3* Gene – Greig Cephalopolysyndactyly Syndrome – Pallister-Hall Syndrome – Polydactyly.

INTRODUCTION

Polydactyly is a common congenital hand/foot malformation. It may occur as isolated or as part of a syndrome. If polydactyly is unilateral, it is usually sporadic, and if it is bilateral, it is generally familial type. There are different classifications for polydactyly. According to commonly-used Temtamy-McKusick Classification (6), it is classified as pre-axial, post-axial and complex type. *GLI3* gene encodes the zinc finger transcription factor. Mutations in this gene lead to different clinical phenotypes: Greig cephalopolysyndactyly Syndrome (GCPS), Pallister-Hall Syndrome (PHS), Acro-Callosal Syndrome, Post-axial polydactyly type A/B and pre-axial polydactyly type IV.

GCPS is a rare autosomal dominant disease characterized by polysyndactyly, craniofacial malformations and hypertelorism. PHS is another autosomal dominant disease and its clinical features include hypothalamic hamartoma, post-axial polydactyly, bifid epiglottis and anal abnormalities.

Most of the known *GLI3* mutations cause loss of function. *GLI3* gene mutations leading to GCPS are diverse such as chromosomal rearrangements, deletions/duplications, missense and splicing mutations.

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Apart from these, truncating mutations located between nucleotide (nt) 1-1997 and nt 3482-4740 of the *GLI3* gene lead to GCPS. Mutations of the *GLI3* gene which involve the region between nt 1998-3481 of the gene lead primarily to PHS (3, 4).
We have reported two cases with typical PHS and GCPS in which different *GLI3* mutations have been determined.

CASE REPORT

Case 1 is a 6 year-old male patient. He was born as the second child of the family. Mother is 31 years old, father is 33 years old. His parents are consanguineous. In examination of the patient, macrocephaly (head circumference >97th percentile), hypertelorism, down-slanting palpebral fissures, broad nasal root were determined (Fig 1a and 1b). He had mild mental retardation. In examination of extremities, whereas bilateral post-axial polydactyly were observed on hands, bilateral pre-axial polydactyly were observed on feet. In addition, syndactyly was determined between 1st-2nd toes and 3rd-4th toes on right foot and 2nd-3rd toes on left foot (Fig. 1c and 1d). Renal USG and echocardiogram findings

Figure 1:
Photographs of the patient with Greig cephalopolysyndactyly syndrome in front (*a*) and lateral (*b*) views. Note bilateral post-axial polydactyly on hands (*c*), bilateral pre-axial polydactyly on feet (*d*).

were normal. Parents of the patient refused cranial MRI to be performed. In examination of his mother, post-axial polydactyly was determined on left foot. Pedigree of the family was drawn. Variable degrees of polydactyly were determined in mother and mother's relatives (Fig. 2). For genetic analysis of patient's parents, informed consent was signed. Karyotype of the patient was interpreted as 46,XY. *GLI3* Gene Sequencing Analysis was performed for the patient and his parents. A deletion mutation c.1880_1881delAT p.His627ArgfsTer48 was detected in the proband and his mother (GenBank accession number NM_000168.5) (Fig. 3a). In consequence of clinical and genetic analysis of the patient, GCPS was diagnosed and genetic counseling was given to the patient's parents about the result of the genetic analysis.

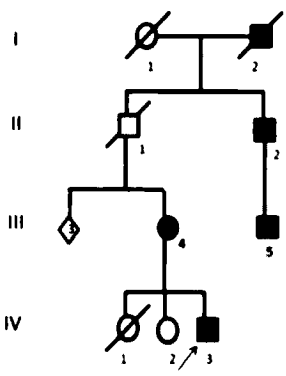
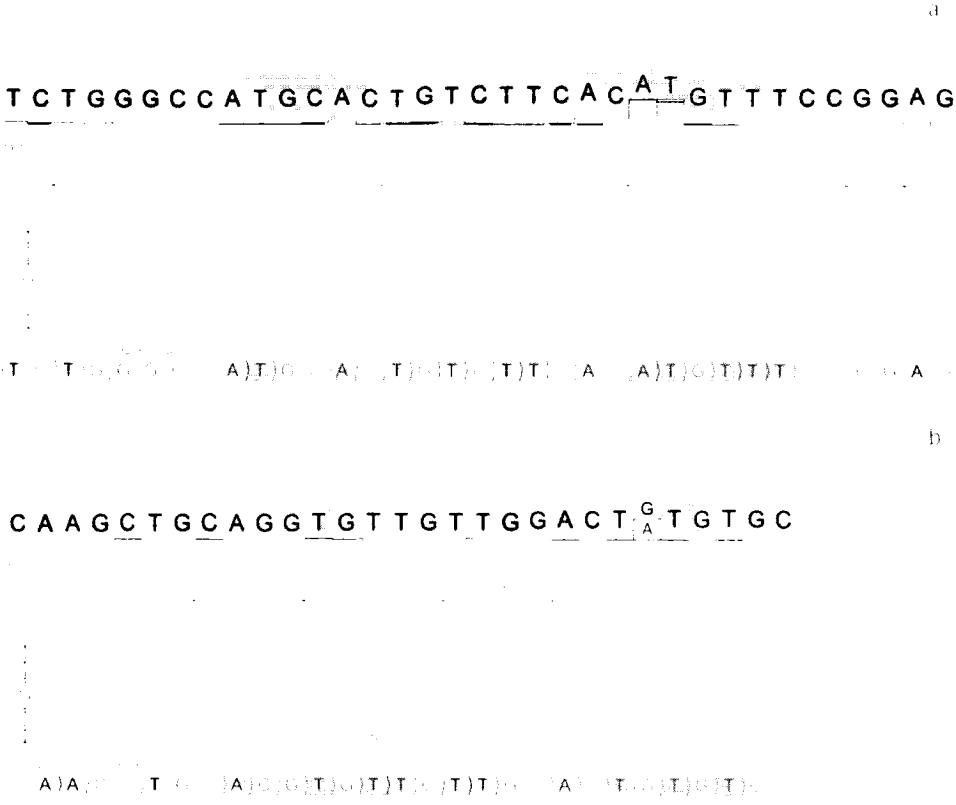


Figure 2: Pedigree of the patient with Greig cephalopolysyndactyly syndrome. Affected family members are identified by filled symbols; c.1880_1881delAT p.His627ArgfsTer48 in III-4 and IV-3.

Figure 3: Sequences showing a deletion mutation c.1880_1881delAT p.His627ArgfsTer48 (*a*) and a heterozygous mutation c.2437C>T, p.Q813X (b) in GLI3 gene (*b*).



Case 2 is a 16 year-old male patient. There was no consanguinity between mother and father. He was the only living child of the family. In prenatal USG, polyhydramnios was detected in the 6th month. The patient who was delivered by Cesarean Section on time was followed-up in neonatal intensive care unit due to meconium aspiration. He underwent a colostomy operation due to anal atresia when he was 6 months old. In workup performed due to short stature, panhypopitutiarism was determined and in cranial MRI hypophysial hamartoma was diagnosed. Patient is still receiving growth hormone replacement therapy. In examination of the patient, length <3th percentile, weight <25th percentile, highly-arched palate, gynecomastia, micropenis and anal atresia were determined (Fig. 4a and 4b). In examination of extremities, operated post-axial polydactyly (post minimi), syndactyly on 4th-5th fingers and short 4th and 5th metacarpal bones were observed on the right hand. In addition, syndactyly on 2nd-3rd toes and hypoplastic nails were determined on feet and malposition and short 4th-5th metatarsal bones were determined on right foot (Fig. 4c and 4d). We did not achieve his X-rays so he was not evaluated in terms of central polydactyly. In the pedigree,

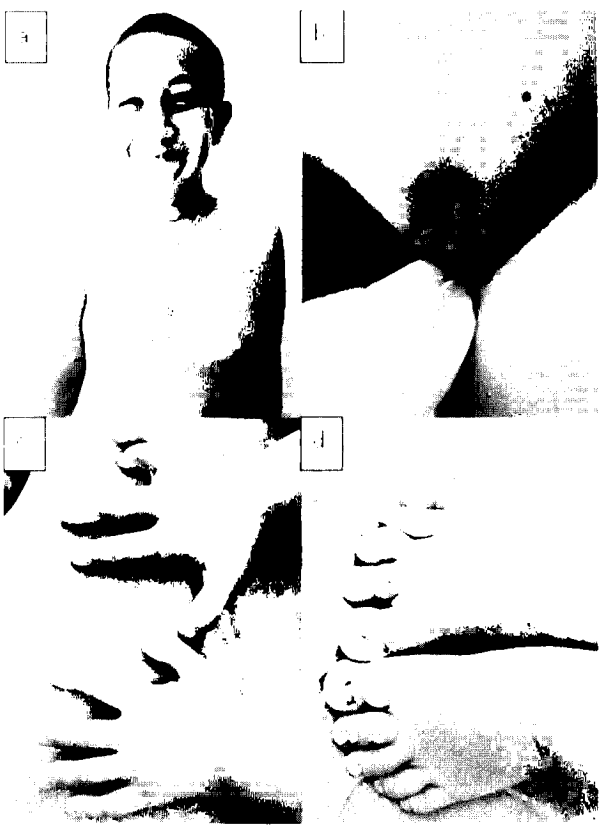


Figure 4:
Photographs of the patient with Pallister-Hall Syndrome.
Note gynecomastia (*a*), micropenis (*b*), syndactyly, short 4th and 5th metacarpal bones on right hand (*c*), syndactyly, hypoplastic nails and short 4th-5th metatarsal bones on right foot (*d*).

other family members seemed to be healthy. Informed consent for genetic analysis was signed to the parents of the patient. Karyotype of the patient was normal. Patient was diagnosed with PHS and *GLI3* Gene Sequencing Analysis was performed. A heterozygous mutation c.2437C>T, p.Q813X was detected in the proband (GenBank accession number NM_000168.5) (Fig. 3b). Genetic counseling was given to the patient's parents about the result of the genetic analysis.

DISCUSSION

GLI3 gene which encodes the zinc finger transcription factor is localized on chromosome 7p14.1. *GLI3* protein participates as both an activator and a depressor on sonic hedgehog pathway during skeletogenesis (1). This pathway regulates the identity and number of fingers with *GLI3* (2). Both GCPS and PHS are diseases characterized by hand/foot abnormalities. Whereas generally pre-axial polydactyly is observed in GCPS, post-axial polydactyly is observed in PHS. Severity and diversity of polydactyly and syndactyly is extremely large. Along with that it varies among individuals, it can vary in extremities of even the same individual. Sethi *et al.* has determined *GLI3* mutation in families with nonsyndromic polydactyly and syndactyly (5). Therefore, these authors supposed that *GLI3* mutation analysis should be performed for all cases with familial polysyndactyly, even if it is not syndromic. Both of our cases were syndromic cases and they have mutations in *GLI3* gene. Deletion mutation that we detected in case of GCPS is located in exon 13 of *GLI3* gene. This mutation leads to formation of a stop codon as a result of deletion AT. Johnston *et al.* has determined this mutation as sporadic (3). On the contrary, because the mother of our patient was carrying the same mutation our case was of familial type. Whereas only polydactyly was reported in the case taking place in previous study, both syndactyly and polydactyly are determined in our case.

Johnston *et al.* have defined the cases meeting at least one of the following criteria of PHS as sub-PHS: polydactyly, bifid epiglottis, and/or hypothalamic hamartoma (4). In that study, c.2437C>T, p.Q813X mutation in *GLI3* gene was reported in one case. This case was classified as sub-PHS. Our case was a typical PHS case, as it met all of PHS criteria. Termination codon is formed as a result of a single nucleotide substitution in codon 2437 and this mutation leads to premature termination of translation.

In conclusion; in both of our cases with typical GCPS and PHS we determined the mutations in *GLI3* gene. In cases of isolated or syndromic

polydactyly, clinical parameters of GCPS and PHS should be investigated and necessity of performing *GLI3* mutation analysis in these cases should be kept in mind.

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