Psychomotor Delay in a Child with FGFR3 G380R Pathogenic Mutation Causing Achondroplasia

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Introduction

Achondroplasia (ACH) is a hereditary disorder of dwarfism that is caused by the aberrant proliferation and differentiation of chondrocyte growth plates. The common findings of macrocephaly and facial anomalies accompany dwarfism in these patients. Fibroblast growth factor receptor 3 (FGFR3) gene mutations are common causes of achondroplasia. The current study presents a case of 2-year-old male child patient presenting with phenotypic characteristics of ACH. The interesting finding of the case is the presence of psychomotor delay that is not very common in these patients. Clinical exome sequencing analyzing 4,813 disease causing genes revealed a de novo c.1138G>A mutation within the FGFR3 gene. In conclusion, the mutation confirms the clinical diagnosis of ACH, and it seems to be causing the psychomotor delay in this patient.

Abstract

Achondroplasia (ACH) is a hereditary disorder of dwarfism that is caused by the aberrant proliferation and differentiation of chondrocyte growth plates. The common findings of macrocephaly and facial anomalies accompany dwarfism in these patients. Fibroblast growth factor receptor 3 (FGFR3) gene mutations are common causes of achondroplasia. The current study presents a case of 2-year-old male child patient presenting with phenotypic characteristics of ACH. The interesting finding of the case is the presence of psychomotor delay that is not very common in these patients. Clinical exome sequencing analyzing 4,813 disease causing genes revealed a de novo c.1138G>A mutation within the FGFR3 gene. In conclusion, the mutation confirms the clinical diagnosis of ACH, and it seems to be causing the psychomotor delay in this patient.

Keywords

► achondroplasia
► FGFR3 mutations
► psychomotor delay

Academically, this study suggests that the use of exome sequencing in the diagnosis of ACH could be beneficial. Further research is needed to understand the role of psychomotor delay in ACH patients and to explore potential therapeutic options.
Case Report

A 2-year-old male child patient was presented to pediatric endocrinology clinic at the Bursa Uludag University Hospital. He was born via caesarean delivery at 39 weeks of gestation as the second birth of the third pregnancy of a 33-year-old female (Fig. 1). His weight, height, and head circumference were 3340 g, 49 cm, and 35 cm, respectively. The femur shortness of the patient was reported at the 28th week of the gestational period. In the following weeks of the gestation, he was reported to have an increased head circumference. After the delivery, he was admitted to intensive care for 10 days due to respiratory distress. At the 17-month checkup, he weighed 6.5 kg (<3p), 65 cm (<3p), and head circumference of 49 cm (50–75p). Physical examination revealed macrocephaly, mild narrow thorax, long body, flatted nose, simian line on the left hand, shortness on the tips of the fingers, and shortness of rhizome in the limbs (Fig. 2). Furthermore, hypotonicity was also reported. Even though, he could control his head, pick up and hold the objects with his thumb and index fingers, turn sideways and crawl backwards; he could not sit without support. His speech was impaired, in such he could only communicate via single words, rather than sentences. Radiologic investigation showed a compression of the interpedicular distance toward the distal end, expansion of the discs and pelvis penetration and short extremities. Cranial MRI showed frontal bossing of the cranium. In the follow-up checkups, he was reported to have delayed neurologic development. At the age of 3.5 years, he weighed 9.8 kg with 74 cm in height, hypotonicity, impairment of walking, distinct hypersensibility, and gibbus deformity. Although these findings were in accordance with ACH phenotype, due to the absence of cervicomedullary compression and hydrocephaly, these findings could also be associated with another skeletal dysplasia. Therefore, genetic testing was offered to the parents of the patient.

Genetic Diagnosis

Informed consent was obtained from the patient’s parents, and whole blood was withdrawn from the patient as well as the parents for genetic analysis. DNA extraction was performed (DNeasy Blood and Tissue Kit, Qiagen, UK) and clinical exome sequencing of 4,813 genes was performed using TruSight One Sequencing Panel (Illumina, UK) on MiSeq platform.

Results

Clinical exome sequencing analysis revealed c.1138G>A mutation within the FGFR3 gene (Fig. 3). This missense mutation led to substitution of glycine with arginine at position 380 (p.G380R) within the FGFR3 protein. The mutation was heterozygous, and it was confirmed by Sanger Sequencing on CEq. 8800 system (Beckman Coulter). The parents’ genetic testing showed no mutation within exon 10 of FGFR3 gene, and therefore it was concluded that this mutation was de novo.

Discussion

ACH is the most common form of skeletal dysplasia that leads to short-limb dwarfism in humans. The main clinical manifestation is macrocephaly with prominent forehead, flat nasal bridge, and short upper arms and legs. More than 90% of the ACH patients were shown to have a mutation at nucleotide position 1138 on FGFR3 gene, located on 4p16.3. This gene has shown to have crucial roles in the development of the skeleton. The gene is approximately 15kb and compromizes 10 introns and 19 exons. All of these exons encode the TM domain of the gene. Receptor tyrosine kinase FGFR3 has 806 amino acid residues and three domains, including an intracellular region, a TM domain, and an extracellular...
region. FGF has the ability to bind to acetylated proteins on cells. This attachment stimulates the receptor dimerization and tyrosine kinase transautophosphorylation.8

In the current study, the genetic diagnosis of a male patient with the clinical manifestation suggestive of ACH, with the exception of cervicomedullary compression and hydrocephaly, is presented. The interesting side of this case is the presence of psychomotor delay, which is not very common in ACH patients. The clinical exome sequencing results revealed FGFR3 c.1138G>A pathogenic variation, which is a widespread deleterious variation detected in ACH patients. Mutations within the FGFR3 gene lead to dimerization of cell membrane proteins. Thus, the downregulatory effects may suppress the proliferation and differentiation of cartilage through activating intracellular signaling pathways.9 This mutation within the FGFR3 gene is the only finding that could lead to the psychomotor delay in this child with achondroplasia. A scarce number of ACH cases have been reported with neurologic and/or psychomotor delays.10–13 However, to our knowledge, none of these have associated the FGFR3 gene c.1138G>A (p.G380R) pathogenic variation in the ACH patients with psychomotor delay. Thus, this is the first report to associate the detected mutation with the psychomotor deficits. It has been shown previously via computer modeling of this mutation that G380R mutation causes a rotation within the only TM domain dimer of the FGFR3.14 The contact between two helices was mediated by different amino acids in the mutant dimer compared with the wild type. Previously investigated models using the program CHI revealed the interaction between Arg-380 and three aromatic residues (Phe-384 on the same helix; and Tyr-379, Phe-383 on the neighboring helix).14 The rotation of the TM dimer interface was associated with variations of the kinase activity. The positions of the catalytic domain positions were suggested to be determined by the RTK TM dimer structure. The phosphorylation capacity was also proposed to be directed by the RTK TM dimer structure. Thus, there can be an increase in the phosphorylation, due to the mutation that is caused by the change in the RTK TM dimer structure. Therefore, it has been suggested that the G380R mutation leading to TM dimer rotation causes the catalytic domains to rotate with respect to each other. This rotation of the catalytic domains was proposed to cause higher phosphorylation capacity of the unliganded G380R dimer.14 Thus, it is a possibility that these structural changes lead to the clinical manifestation of this patient with psychomotor delay, which is not widely observed in the ACH patients.

In conclusion, the detected FGFR3 c.1138G>A pathogenic variation is the most common cause of ACH. Thus, this mutation detected by sequencing the exons and exon-flanking regions of genes involved in clinical phenotypes is the most likely cause of the neurological manifestation, including the psychomotor delay of the patient with ACH phenotype.

Conflict of Interest None declared.

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