A Novel NOTCH2 Mutation Identified in a Korean Family with Hajdu–Cheney Syndrome Showing Phenotypic Diversity

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Abstract. Hajdu–Cheney syndrome (HCS) and serpentine fibula–polycystic kidney syndrome (SFPKS) share many similarities, including craniofacial abnormalities, bony deformities, and renal involvement. Because mutations in exon 34 of NOTCH2 have been identified recently in both HCS and SFPKS patients, it has been suggested that these two syndromes be classed as the same disorder. A 3-year-old boy presented with polycystic kidneys and club feet detected during the fetal period; however, acroosteolysis and curved fibulae were not observed. His mother showed osteoporosis and had a history of compression fractures in the spine without renal anomalies. Although the same novel mutation in NOTCH2 was found in both the mother and her son, these patients displayed different clinical manifestations. In this report, we present a familial case of HCS in a boy and his mother that was suspected on physical examination and radiological findings. We speculate that HCS and SFPKS are a single disease entity with a wide spectrum of clinical manifestations associated with truncating mutations in exon 34 of NOTCH2.

Keywords: Hajdu–Cheney syndrome, Serpentine fibula-polycystic kidney syndrome, Osteoporosis, Acroosteolysis, NOTCH2.

Introduction

Hajdu–Cheney syndrome (HCS, OMIM#102500) is a rare, autosomal-dominant genetic disorder characterized mainly by bony abnormalities and prominent radiographic findings, including osteoporosis associated with recurrent fractures, abnormal dentition, acroosteolysis, wormian bones, and platybasia. Craniofacial anomalies are usually observed, and there can be involvement of other organs, especially the kidneys and heart, in some patients [1]. Serpentine fibula–polycystic kidney syndrome (SFPKS), usually distinguished by the presence of renal cysts and s-shaped fibulae, shares common clinical manifestations with HCS. Thus, it has been hypothesized that the two diseases are in fact a single disease entity with a wide spectrum of clinical manifestations [2].

In 2011, truncating mutations in exon 34 of the neurogenic locus Notch homolog protein 2 gene (NOTCH2), located on chromosome 1, were identified in families and sporadic patients with HCS and SFPKS from whole-exome sequencing. NOTCH2 is the only known disease-causing gene for HCS and SFPKS, and all identified mutations are located in exon 34 [3]. HCS and SFPKS are quite rare diseases, and their exact prevalence is unknown. To date, approximately 37 mutations in 65 HCS and SFPKS patients have been reported [3-9]. Considering that the same mutation was reported both in patients showing SFPKS and HCS phenotypes [5, 9], variable expression and phenotypic diversity of the disease are possible.

Here, we present a familial case of HCS involving a mother and her son, who display different clinical manifestations despite having the same novel mutation in exon 34 of NOTCH2.
Case Report

**Patient 1 (son).** A 3-year-old boy who met normal developmental milestones was referred to a clinical geneticist for his coarse face and hypertrichosis noted during admission for community-acquired pneumonia. He was born at 38 plus 3 weeks of gestation with a birth weight of 3.2 kg (25th–50th percentile) and was delivered by Cesarean section due to breech presentation. He was his parents’ first child, and there was no family history of renal cysts. As multiple cysts in both kidneys were persistently observed by fetal ultrasonography, kidney ultrasonography was performed immediately after birth. Multiple renal cysts were identified mainly in the cortex, and he was referred to our hospital at the age of 7 months because the size and extent of the cysts had increased by the following examination. Coarse face, high arched palate, club feet, and bilateral cryptorchidism were noted on physical examination. Therefore, chromosome analysis and urine glycosaminoglycan (GAG) analysis for mucopolysaccharidosis screening were performed. The karyotype was 46, XY, and urine GAG was negative. During the follow up, bilateral orchiopexy was performed at the age of 10 months. At the age of 2.5 years, deformities of both elbows and feet were suspected, and bilateral hypoplastic proximal radii with dislocation of the radial head and metatarsus adductus of both feet were detected by skeletal radiographs.

At the age of 3.0 years, his height was 93.8 cm (25th–50th percentile), weight was 15.8 kg (75th percentile), and head circumference was 50.8 cm (75th percentile). He had a coarse face with

![Figure 1. A. Facial photographs of patient 1 (son) showing thick eyebrows, a long philtrum, microretrognathia, and low-set ears. B. Simple radiographs of patient 1 showing multiple wormian bones on the skull and bilateral hypoplastic proximal radii with dislocation of the radial head. C. Multiple cortical cysts in both kidneys are observed on ultrasonographic images. D. Osteopenia and multiple spinal compression fractures are noted on the spine radiograph of patient 2 (mother).]
low-set ears, bushy eyebrows, synophrys, wide nose, flat nasal bridge, long philtrum, thin upper lip, high arched palate, and midfacial hypoplasia. Neither his fingers nor toes were short. Hypoplastic maxillary sinuses and multiple wormian bones were noted on skull radiographs (Figures 1A and B). However, no osteopenia, acroosteolysis, or brachydactyly of either hands or feet was observed. In his most recent kidney ultrasonography, the number of renal cysts had not increased and the overall size of each cyst had decreased (Figure 1C).

**Patient 2 (mother).** The boy's mother was 32 years old and her height was 158.0 cm (25th–50th percentile). She did not have kidney cysts or any apparent skeletal deformities, including brachydactyly, acroosteolysis, or fibulae bowing (Figure 1D), and denied any family history of kidney or skeletal diseases. However, she had a history of multiple spinal compression fractures that occurred at the age of 29 years, and extraction of two molar teeth, which became loose in her twenties. She also displayed facial dysmorphism similar to her son, including a round and coarse face, low nasal bridge, low-set ears, and micrognathia. Decreased bone mineral density was noted on dual energy x-ray absorptiometry (DEXA) scan, and she was diagnosed as having osteoporosis. Vitamin D and calcium supplementation were begun. Oral bisphosphonate treatment is under consideration according to the results of a follow-up DEXA examination.

**Molecular Genetic Analysis.** The boy and his mother were suspected of having familial HCS based on the medical history and findings of the physical examinations, and molecular genetic analysis for HCS was performed. Written informed consent was obtained from participants, and the Institutional Review Boards of Seoul National University Hospital approved this study. Sequencing analysis of exon 34 in NOTCH2 was performed using genomic DNA isolated from peripheral blood leukocytes. NOTCH2 exon 34 and exon–intron boundaries were amplified using a polymerase chain reaction, and direct sequencing was performed. A novel deletion mutation, c.6854delA (p.Q2285Rfs*2294), was detected in the son. His mother was found to carry the same mutant allele (Figure 2).

**Discussion**

HCS is clinically suspected from the appearance of a coarse face, short stature, abnormal dentition, synophrys, and other morphological peculiarities. About 83% of the HCS patients display acroosteolysis of the distal phalanges, and wormian bones and osteoporosis are common radiological findings [1]. SFPKS has usually been distinguished from HCS by the presence of renal cysts and s-shaped fibulae. However, clinical manifestations of HCS and SFPKS overlap, and mutations in NOTCH2 have been identified in both syndromes. Facial dysmorphism, short stature, normal intelligence, and radiological findings such as osteoporosis and wormian bones are commonly observed in both HCS and SFPKS. Whereas serpentine fibulae or polycystic kidneys can be present in HCS patients, acroosteolysis, abnormal dentition, or platybasia can conversely be noted in cases of SFPKS [2,3]. Therefore, HCS and SFPKS appear to be a single genetic disorder showing a wide spectrum of clinical manifestations.

**NOTCH2** is a member of the NOTCH family of single-pass type I transmembrane proteins. Four receptors (NOTCH1 to 4) are expressed in humans, and they play a role in a variety of developmental processes by controlling cell fate [10]. Mutations in **NOTCH2** are also associated with Alagille syndrome (AGS, OMIM#118450), a genetic disorder clinically defined by hepatic bile duct paucity, cholestasis, and cardiac, skeletal, and ophthalmologic...
manifestations. About 94%–96% of AGS cases are caused by mutations in JAG1, and 1%–2% of cases occur because of NOTCH2 mutations. In AGS, NOTCH2 interacts with its ligand JAG1, and NOTCH2 signaling is consequently reduced [11]. Mutations in the last coding exon of NOTCH2 exclusively cause HCS or SFPKS, which is clearly distinct from AGS. The proline-, glutamic acid-, serine-, and threonine-rich (PEST) domain of NOTCH2 is located very close to the C terminus of the receptor and is evolutionarily conserved. Truncating mutations in exon 34 of NOTCH2 remove the PEST domain and escape nonsense-mediated mRNA decay [5,8]. The NOTCH2 signal is eventually increased and affects the development of embryonic kidneys, bone remodeling, and skeletal genesis [10,12].

In this study, we describe a Korean HCS family of a mother and her son with a novel mutation in NOTCH2. Although the mother and son showed similar facial features suggesting HCS, and the identified mutation was cosegregated with HCS phenotypes, their clinical manifestations were different. The son had multiple renal cysts detected during the fetal period, but did not have acroosteolysis. The mother suffered from osteoporosis leading to multiple spinal compression fractures in her twenties without other skeletal or renal abnormalities. This discrepancy between the affected mother and her son could be explained by the phenotypic variability in HCS. Five reports were published previously, presenting 12 familial cases of HCS with NOTCH2 mutation and phenotypes that are well described in four cases [3,6-9]. The degree of skeletal deformities or organ involvement was different within the same family with an identical genetic mutation, as was found in our case. Patients did not have renal cysts, implying that our case is the first reported familial HCS case with NOTCH2 mutation presenting polycystic kidneys.

To date, more than 30 mutations of exon 34 in NOTCH2 associated with HCS or SFPKS have been reported [3]. Although only about 65 patients are known to be affected, the clinical manifestations are variable, ranging from cases of only craniofacial anomalies and skeletal abnormalities to those with multiple organ involvement, and there is no established genotype–phenotype correlation. There is a report of an HCS patient with a nonsense mutation, c.6853C>T (p.Q2285X) [6], which is located just one base pair away from our novel nonsense mutation (c.6854delA). That patient was a 25-year-old woman showing clinical characteristics similar to those in our patients, such as facial dysmorphology, short stature, patent ductus arteriosus, polycystic kidneys, and skeletal findings including acroosteolysis, osteoporosis, wormian bones, vertebral compression, and platybasia. Fibula bowing was absent in that patient, as it was in our patients.

In conclusion, we identified a novel NOTCH2 mutation in a family with HCS. The clinical manifestations and genetic data in our case and previously reported case series suggest that NOTCH2 mutation causes a disorder, named either HCS or SFPKS, with a wide spectrum of clinical manifestations. In particular, hearing deficits and skeletal manifestations including osteoporosis are common findings and can progress with age, so regular monitoring for development or progression of associated complications is necessary. Further studies are needed to thoroughly explain the pathogenesis of HCS or SFPKS, as well as the impact of mutations in exon 34 of NOTCH2 on tissue and organ development.

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