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PTCH2 유전자 변이에 의한 Gorlin–Goltz 증후군 진단을 Whole Exome Sequencing을 통해 밝힌 한국인에서의 첫 증례

The First Korean Case of Gorlin–Goltz Syndrome Caused by a *PTCH2* Pathogenic Variant Identified via Whole Exome Sequencing

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Gorlin–Goltz syndrome, also known as basal cell nevus syndrome, is a condition that affects several body parts and increases the risk of developing various cancerous and noncancerous tumors. This syndrome is mostly caused by the pathogenic variants of the *PTCH1* and *SUFU* genes; however, it is rarely diagnosed due to limited prevalence. *PTCH2* has rarely been identified as a pathogenic variant in patients with the Gorlin–Goltz syndrome in China and Japan. Here, we report the case of a 30-year-old woman who was diagnosed with the Gorlin–Goltz syndrome—based on multiple calcifications on the body—who carried a frame shift pathogenic variant of the *PTCH2* gene (c.1172_1173del) identified via whole exome sequencing. The patient did not present the typical phenotypes of the Gorlin–Goltz syndrome, such as basal cell carcinoma, palmar/plantar pits, macrocephaly, and keratocystic odontogenic tumors. Based on these observations, we suggest that a pathogenic variant of *PTCH2* can manifest a milder phenotype of the Gorlin–Goltz syndrome.

Key Words: Gorlin–Goltz syndrome, *PTCH2, PTCH1*, Basal cell nevus syndrome

INTRODUCTION

Gorlin–Goltz syndrome, also known as the basal cell nevus syndrome, is an autosomal dominant inherited syndrome that predisposes the patient to the formation of basal cell carcinomas, odontogenic keratocysts, and skeletal anomalies. Pathogenic variants of several genes associated with the sonic hedgehog (SHH) signaling pathway, including *PTCH1*, have been identified in patients with the Gorlin–Goltz syndrome, and are presumed to cause the disease [1]. The genes responsible for this syndrome were found to be *PTCH1* and *SUFU* by homologs of the *Drosophila* patched gene [2, 3]. A *PTCH2* gene, close homolog of *PTCH1*, is found in vertebrates. Human *PTCH2* has 22 coding exons, which encode a protein of 1209 amino acid residues. A Chinese family and a Japanese girl have been previously reported to possess a pathogenic variant of the *PTCH2* gene [4, 5]. To the best of our knowledge, we report the first case of the Gorlin–Goltz syndrome associated with a frame-shift pathogenic variant of *PTCH2*, in Korea.

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CASE REPORT

A 30-year-old woman visited our genetic counseling center for

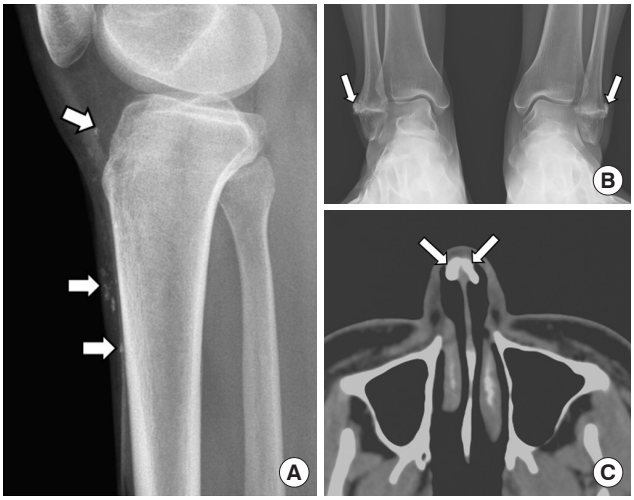

Fig. 1. (A) Lateral view of proximal lower leg plain radiograph shows multiple tiny calcified opacities at anterior subcutaneous layer. (B) Anterior–posterior view of both ankle plain radiographs reveals incomplete fused lateral malleolar growth plates and juxtacortical nodular calcific opacities at their lateral aspect. (C) Computed tomography scan with axial plane of maxillary sinus level indicates a nodular calcification at the nasal cartilage.

a pregnancy consultation as she was worried about having undiagnosed diseases. She had multiple calcifications on her nose, knee, and intermalleolar space for the past 10 years. For 10 years, she had consulted a doctor who eventually recommended her to receive genetic counseling for an appropriate diagnosis. When the patient came to our tertiary center, a simple X-ray confirmed that she had multiple tiny calcified opacities in the anterior subcutaneous layer of her proximal lower legs and an incompletely fused lateral malleolar growth plate, as well as juxtacortical nodular calcified opacities at their lateral aspect (Fig. 1A, B). Moreover, computed tomography (CT) analysis revealed a nodular calcification in the nasal cartilage on the axial plane at the maxillary sinus level (Fig. 1C). We decided to send her peripheral blood sample to the Baylor College of Medicine (Houston, TX, USA) for whole exome sequencing. The patient did not present the pathogenic variants of the *PTCH1* or *SUFU* genes. However, a heterozygous 2-base-pair deletion, c.1172_1173delCT, was detected in exon 9 of the *PTCH2* gene; NM_003738.4:c.1172_1173del, p.(Ser391*). This variant was confirmed by Sanger sequencing. This pathogenic variant caused a frame-shift and premature termination at the deletion site, resulting in a truncated form of the protein, PTCH2 p.Ser391*. The patient was eventually diagnosed with the Gorlin–Goltz syndrome, but did not undergo any familial genetic test.

After diagnosis, she asked us whether this condition would hamper her fertility or pregnancy. We informed her about the disease and suggested appropriate management. We eventually recommended her to visit a doctor specializing in obstetrics and gynecology for further examination and consultation regarding her birth related queries. Fortunately, she neither had ovarian fibromas nor did she need ovary preservation.

DISCUSSION

Gorlin–Goltz syndrome is a rare disease that is known to be caused by the pathogenic variants of the *PTCH1* and *SUFU* genes. A missense pathogenic variant of *PTCH2* in a Chinese family, and a frame-shift pathogenic variant of *PTCH2* in a Japanese girl have been previously reported [4, 5]. In this report, we observed a case with the exact same pathogenic variant as that reported for the Japanese girl [4], which could be a third germ-line pathogenic variant of *PTCH2*, c.1172_1173del. This pathogenic variant created a premature termination codon at the deletion site in the mutant allele, resulting in the truncation of the PTCH2 protein. The report on the Japanese girl mentioned that she had keratocystic odontogenic tumors and a bifid rib anomaly, which were not present in our patient, who only had multiple calcifications; however, both phenotypes were milder than the typical Gorlin–Goltz syndrome caused by *PTCH1* gene variants.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) guideline suggests that variants with an odds ratio more than 4.0 are counted as mutations. We searched the odds ratio for the rs56126236 variant as it was present in the database containing information on healthy population variants. Only two reports for *PTCH2* gene variants were found in PUBMED search. One case in Japan was reported to possess this variant in *PTCH2* gene [4], and one Chinese family was reported to have different variants in the gene [5]. According to the Genome Aggregation database (gnomAD), the allele frequency of the rs56126236 is single nucleotide polymorphism (SNP) 0.316% (63/19,948) in the East-Asian population. However, the allele frequency is reported as 0.48% (6/1,238) in the Korean reference genome database (KRGD) of Center for Disease Control and Prevention (http://coda.nih.go.kr/coda/KRGDB/index.jsp), which contains genetic information on 622 healthy individuals. The odds ratio is calculated as $(a \times d)/(b \times c)$, and was

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found to be 316.6 (confidence interval 19.59–511,852) in case of the East Asian data and 206.3 (confidence interval 11.52–3,696.24) in KRGDB, respectively. The prevalence of this disease is known to be 1 in 57,000 [6]. Considering this rare prevalence and limited cases by pathogenic variants of *PTCH2* gene, the calculated odds ratios indicate that this variant could be a causative variant which affects the disease, based on the ACMG/AMP guidelines [7]. Penetrance of the Gorlin–Goltz syndrome and the related mild phenotypes as observed in this report and in the Japanese report could be considered for this relatively high allele frequency (0.48%).

A genotype–phenotype correlation in the Gorlin–Goltz syndrome remains unclear [8]; however, the pathogenic variant of the *SUFU* gene is frequently reported in patients with medulloblastoma [9]. Moreover, numerous deletions in *PTCH1* manifest atypically, presumably due to the effect on the adjacent genes [10]. A Japanese research group has suggested that the Gorlin–Goltz syndrome in patients with *PTCH2* pathogenic variants could be milder phenotype than that in patients with *PTCH1* pathogenic variants based on the number of major/minor criteria analyzed by a nationwide survey in Japan [4]. Our patient met only one major criterion, that is, multiple calcifications, and did not present jaw keratocysts or macrocephaly. Therefore, we could presume that the phenotype of the *PTCH2* gene pathogenic variant is different from that of the classical phenotype presented by the *PTCH1* gene pathogenic variant.

In the present case, the main reason why the patient considered genetic counselling was to determine whether she would face any complications during pregnancy and delivery. In a previous case report, a patient suffering from the Gorlin–Goltz syndrome had a normal pregnancy and labor [11]; however, it is advisable to receive appropriate genetic counseling in order to stay informed on the inheritance of genetic disorders.

요 약

기저세포모반 증후군(basal cell nevus syndrome)으로도 알려져 있는 Gorlin-Goltz 증후군은 신체의 많은 부위에 영향을 주며, 종양 및 비종양의 발생 위험을 높인다. *PTCH1* 유전자의 pathogenic 변이는 Gorlin-Goltz 증후군의 대부분의 원인으로 알려져 있지만, 질환 자체의 유병률은 매우 낮다. Gorlin-Goltz 증후군의 원인 유전자로 *PTCH1*, *SUFU*가 알려져 있으나, *PTCH2* 유전자 역시 중국과 일본에서 원인으로 밝혀진 적이 있다. 여기서 우리는 임상적으로 다발성 석회화가 있는 증상과, *PTCH2* 유전자의 frame shift pathogenic 변이를 바탕으로 Gorlin-Goltz 증후군으로 진단한 30세 여성의 증례를 보고한다. 환자는 증후군의 전형적인 대두증, 치원성 각질화낭종 등의 증상은 없었다. 이런 소견을 바탕으로 *PTCH2* pathogenic 변이의 경우 전형적인 Gorlin-Goltz 증후군보다 경한 증상을 보일 수 있다고 제안한다.

Conflicts of Interest

None declared.

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