Whole Exome Sequencing of *SMO, BRAF, PTCH1* and *GNAS* in Odontogenic Diseases

MICHIKO SHIMURA[1], KOH-ICHI NAKASHIRO[2], YUTA SAWATANI[1], TOMONORI HASEGAWA[1], RYOTA KAMIMURA[1], SAYAKA IZUMI[1], YUSKE KOMIYAMA[1], CHONJI FUKUMOTO[1], SHUMA YAGISAWA[1], ERIKA YAGUCHI[1], MASAYO HITOMI-KOIDE[1], TOSHIKI HYODO[1], DAISUKE UCHIDA[2] and HITOSHI KAWAMATA[1]

[1]Department of Oral and Maxillofacial Surgery, Dokkyo Medical University School of Medicine, Tochigi, Japan;

[2]Department of Oral and Maxillofacial Surgery, Ehime University Graduate School of Medicine, Ehime, Japan

Correspondence to: Hitoshi Kawamata, Department of Oral and Maxillofacial Surgery, Dokkyo Medical University School of Medicine, 880 Kitakobayashi, Mibu, Shimotsuga, Tochigi 321-0293 Japan. Tel: +81 282872169, Fax: +81 282867644, e-mail: h-kawama@dokkyomed.ac.jp

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Abstract

Background/Aim: Odontogenic diseases are diagnosed based on clinical course, imaging, and histopathology. However, a definitive diagnosis is not always possible. Materials and Methods: We analyzed whole exons of *SMO, BRAF, PTCH1* and *GNAS* using next-generation sequencing (NGS) in 18 patients. Results: Of the 6 patients with ameloblastoma, 2 patients had the same missense mutation in *BRAF*, and 1 patient with peripheral ameloblastoma had a missense mutation in *PTCH1*. Of the 7 patients with odontogenic keratocyst, 4 patients had a missense mutation in *PTCH1*, 2 patients had missense mutations in *BRAF*, and 1 patient had a missense mutation in *SMO*. The patient with odontoma had missense mutations in *SMO*, *BRAF* and *PTCH1*. One patient with cement-osseous dysplasia had missense mutations in *SMO* and *PTCH1*. The patient with adenomatoid odontogenic tumor had missense mutations in *SMO*. Conclusion: Whole exome sequencing of the above genes by NGS would be useful for the differential diagnosis of odontogenic diseases.

Odontogenic diseases (tumors, cysts and dysplasias) are diagnosed based on clinical course, several X-ray images, and histopathological findings, but a definitive diagnosis is not always possible (1). Odontogenic tumors derive from cells involved in tooth development, and in many cases, it is difficult to make a diagnosis due to varying histological findings. Alterations in some genes in odontogenic diseases have been identified (2, 3), but a few studies have described the analysis and application of this information for diagnosis (4).

Regarding the classification of odontogenic tumors, the “WHO histological typing of odontogenic tumors, jaw cysts, and allied lesions, Geneva: World Health Organization 1971” was published by the World Health Organization (WHO) in 1971 (5), and revised in 1992 (6), 2005 (7), and 2017 (2). In the 2005 version of WHO classification of tumors (7), pathology and genetics of tumors of the head and neck, odontogenic keratocyst (OKC) and calcifying odontogenic cyst (COC) were classified as a keratocystic odontogenic tumors (KCOT) and calcifying cystic odontogenic tumors (CCOT), respectively. In the 2017 version WHO classification of head and neck tumors (2), these diseases were re-classified from tumors to cysts (OKC and COC). However, some patients with OKC have clinically clear neoplastic characteristics and sometimes show recurrence (8). On the other hand, even when a neoplastic disease like ameloblastoma is strongly suspected based on X-ray images and clinical course, some cases might be

diagnosed as a cystic disease, because tumor cells cannot be identified in the histopathological analysis.

We believe that these problems in diagnosis may be solved by performing genetic analysis, in addition to X-ray images and histopathological findings. In most genetic analyses for odontogenic tumors, only a previously reported specific site (hot spot) in a gene is analyzed (9). There have been no reports of systematic examination of whole exons of multiple genes in odontogenic diseases. In this study, we analyzed whole exons which covered the open reading frame for smoothened (*SMO*), *BRAF*, patched 1 (*PTCH1*) and *GNAS* using an in-house next-generation sequencing (NGS) panel for odontogenic diseases. Then, we attempted to examine the usefulness of genetic analysis for the diagnosis for odontogenic diseases.

Materials and Methods

Patients and samples

The subjects were 18 patients with odontogenic diseases who underwent diagnosis and treatment in the Department of Oral and Maxillofacial Surgery, Dokkyo Medical University Hospital from January 2014 to December 2018. The patients included 6 cases with ameloblastoma, 7 with OKC, 2 with cemento-osseous dysplasia (COD), 1 with adenomatoid odontogenic tumor (AOT), 1 with odontoma, and 1 with dentigerous cyst

(Table I). This study was approved by the Ethics Committee of Dokkyo Medical University Hospital (No. R35-23J).

DNA extraction

DNA was obtained from 14 frozen specimens collected from the central area of a tumor and 4 formalin-fixed paraffin-embedded (FFPE) sliced specimens. For the frozen specimens, hematoxylin and eosin staining was performed to confirm that the specimen included the tumor. DNA was extracted with Isogen (Qiagen, Hilden, Germany) from approximately 50 mg of frozen specimens (cases 1 and 6-18) or 10 slices of FFPE specimens cut at 10 μm thickness (cases 2-5) in 250 μl of lysis buffer. Phenol extraction and ethanol precipitation were performed. DNA samples were dissolved in Tris-EDTA buffer (pH 7.4) for quantitative determination. For our NGS analysis, at least 646 ng of DNA was required. Sufficient DNA was obtained from all 18 of the above samples.

Next Generation Sequencing

NGS analysis was performed using an in-house panel. Sequences of whole exons which covered the open reading frame of *SMO*, *BRAF*, *PTCH1* and *GNAS* were analyzed. First, 646 ng of genomic DNA were fractionated into pieces of several hundred base pairs, and the library was constructed using TruSeq Custom Amplicon Low Input

(Illumina, San Diego, CA, USA) and individual custom oligonucleotides for *BRAF*, *SMO*, *PTCH1*, and *GNAS*. Using TruSeq Custom Amplicon Index Kit (Illumina), an identification sequence and two types of adapters were added. The concentration of the library was adjusted for each specimen, and sequencing was performed with a next-generation sequencer (MiSeq, Illumina) using a MiSeq Reagent Kit v2 (300 Cycles) (Illumina) after mixing of the library. Data were uploaded to Illumina Variant Studio 3.0 to extract mutations.

Results

Clinicopathological characteristics of the patients

The 18 patients with odontogenic disease who underwent NGS were diagnosed according to the 2017 WHO classification of head and neck tumors (2). Histopathological diagnosis was finally determined in consultation with an oral pathologist (Prof. Naozumi Ishimaru, Department of Oral Molecular Pathology, Tokushima University Graduate School of Biomedical Sciences) after provisional diagnosis by general pathologists at our hospital. Gender, age, histopathological diagnosis, site of onset, and X-ray findings are shown in Table I.

Patients 1 and 5 had peripheral ameloblastoma, and patient 1 showed follicular type-dominated histopathological findings (Figure 1A). Patients 2-6 had plexus type

ameloblastoma. All ameloblastoma in the study developed in the mandible. Two patients (cases 2, 3) had multilocular cyst, 4 patients (cases 1, 4, 5, 6) had monolocular cyst, and 1 patient (case 4) showed a knife cutting image of the dental root.

Patients with OKC analyzed in this study were diagnosed as KCOT based on the 2005 WHO classification (cases 7-13, case 9: Figure 1B, case 12: Figure 1C). OKC developed in the maxilla of 3 patients (cases 11, 12, 13: Figure 2E, F, and G) and in the mandible of 4 patients (cases 7, 8, 9, 10: Figure 2A, B, C, and D). Three patients with OKC had multilocular cyst (cases 7, 9, 10: Figure 2A, C, and D), 4 patients had monolocular cyst (cases 8, 11, 12, 13: Figure 2B, E, F, and G), and 1 patient showed a knife cutting image of the dental root (case 7: Figure 2A).

The patient with odontoma (case 14) was an extraordinal case in which hard tissues occupying the maxilla and soft tissues around the hard tissues were mixed. The soft tissues were mainly inflammatory maxillary sinus mucosa with no clear odontogenic epithelium (Figure 1D). A patient with COD (case 15) had a typical X-ray image of a lesion in the bilateral posterior mandible, and a family history was also confirmed. The other patient with COD (case 16) also had lesions in the bilateral posterior mandible. The left lesion gave a typical X-ray image, but the right lesion had a cementum/bone-like radiopaque image surrounded by a soft tissue-like radiolucent image. Thus, for the right

lesion, genetic analysis of the squamous epithelium-like soft tissues connecting to hard tissues was performed (Fig.ure1E).

In the patient with AOT (case 17), the maxillary canine was pushed to the upper part of the maxillary sinus, and the cyst occupied the entire maxillary sinus (Figure 1F). A patient with dentigerous cyst (case 18) was also analyzed as a negative control. During postoperative follow up of 11 months to 4 years, there was no recurrence in any patients.

Mutations of SMO, BRAF, PTCH1, and GNAS in odontogenic diseases

Of the 6 patients histopathologically diagnosed with ameloblastoma in the mandible, 2 patients (case 1: Figure 1A, case 2) had a missense mutation (T440P) in *BRAF* (Table I). T440P is an activating mutation that has been reported in patients with lung cancer (10). The patient (case 5) with peripheral ameloblastoma in the mandible which showed the invasion in the masticatory space had a missense mutation (V582G) in *PTCH1*. The remaining 3 patients (cases 3, 4, 6) had no mutation in the four analyzed genes (Table I).

Of the 7 patients histopathologically diagnosed with OKC (Figure 2A-G), 4 patients (case 8: Figure 2B, case 9: Figure 1B, 2C, case 10: Figure 2D, case 11: Figure 2E) had a missense mutation in *PTCH1* (Table I). Among the 7 patients, two patients each with a large lesion in the right posterior mandible (case 7: Figure 2A, case 9: Figure 2C) had missense mutations in *BRAF* (T263P in case 7, and K51N and Y647D in case 9). The

patient with a large lesion in the left posterior maxillary, which pushed the wisdom tooth to the upper area and occupied the maxillary sinus (case 12: Figures 1C and 2F) had a missense mutation in *SMO* (N396T). Only 1 patient histopathologically diagnosed with OKC (case 13: Figure 2G) showed no mutation in the examined genes.

The patient histopathologically diagnosed with odontoma (case 14: Figure 1D) had missense mutations in *SMO* (Y394S), *BRAF* (T263P), and *PTCH1* (T456P and D461N) (Table I). No mutations of the examined genes were found in a patient with COD (case 15), which was thought to be a familial case. However, missense mutations in *SMO* (Y394S) and *PTCH1* (F725V) were found in patient 16 (Figure 1E) with COD, in which soft tissue with squamous cell like cells was found around a hard tissue lesion. The patient with AOT in the maxilla (case 17: Figure 1F) had missense mutations of *SMO* (Y394S and Y399S). The patient with a dentigerous cyst (case 18) had no mutations as we expected. Among all 18 subjects in the study, 7 had a V860G mutation in GNAS, which is considered to be a missense variant of single nucleotide polymorphism.

Discussion

For NGS analysis of *SMO, BRAF, PTCH1* and *GNAS* in odontogenic disease, DNA was initially extracted from 33 samples (16 frozen specimens, 17 FFPE specimens). However, we were able to extract the required amount of >646 ng of DNA for NGS from

only 18 samples (14 frozen specimens, 4 FFPE specimens). Thus, we successfully extracted the sufficient amounts of DNA for NGS analysis from 14 of 16 frozen specimens (87.5%), but from only 4 of the 17 FFPE specimens (23.5%). However, we were not able to extract the sufficient amounts of DNA for NGS analysis from any of decalcification FFPE specimens.

Regarding the functions of the protein products of the genes analyzed in the study, SMO encodes for a 7-transmembrane domain protein which can activate transcription factor Gli family. The function of SMO is suppressed by PTCH1, a membrane receptor of sonic hedgehog (SHH), and the suppression of SMO is released when SHH binds to PTCH1, which results in SMO activation and increased cell proliferation (11). An activating mutation in SMO has been reported to occur at a high rate in ameloblastoma developed in the maxilla (8). PTCH1 encodes for a 12-transmembrane domain protein (11) and is the gene responsible for the development of basal cell nevus syndrome (12). *A PTCH1* mutation has been found in sporadic OKC (KCOT in the 2005 WHO classification) (13). However, *PTCH1* is a large gene (24 exons with an open reading frame of 4,341 bp) with no hot spots of mutations, and studies on the sequences of whole exons have rarely been performed (14). BRAF directly binds to RAS protein, activates the MEK-ERK pathway, and is involved in cell proliferation and survival (15). Activating mutations in *BRAF*, such as V600E, are observed in various cancers (15, 16) and at a

high rate in ameloblastoma in the mandible (9). GNAS encodes for a Gs protein, and GNAS mutation is frequently found in fibrous dysplasia. This gene is also known as a gene responsible for McCune-Albright syndrome (17).

In this study, mutations in *SMO, BRAF*, and *PTCH1* were detected in several patients with odontogenic disease. The read depth was set at 200 (*SMO* and *PTCH1*) or 500 (*BRAF*) to extract mutations, which gives results with high specificity. Some patients showed suspected frameshift mutations, but mainly missense mutations were found in the study. The V600E mutation in *BRAF*, which has been reported to be a strong activating mutation (15, 16), was not found in our patients, but mutation sites located close to the activation domain were found, and it is likely that these caused functional changes. The T440P mutation in *BRAF* has been found in patients with lung cancer (10) and is considered to be an activating mutation. Among the *SMO* mutations, V394S was found in 3 patients and has not been recorded in SNP databases. Thus, if it is an activating mutation, it may be a new hot spot. Similarly, Y399S in *SMO* has not been reported as a SNP, but N396T may be a SNP. There was no mutation hot spot in *PTCH1* and mutations were observed over a wide sequence. The Y1316S mutation in *PTCH1* in case 9 has been found in basal cell nevus syndrome (18).

Based on the genetic mutations found by NGS, the pathological diagnosis requires a re-evaluation. Of the diseases which could not be histopathologically diagnosed as

ameloblastoma (such as those diagnosed as OKC), those with a mutation in *SMO* in the maxilla (cases 12, 14, 17) and those with a mutation in *BRAF* in the mandible (cases 7, 9) may have characteristics of ameloblastoma or a related tumor. It was surprising that a mutation in *PTCH1* was found in 4 of the 7 patients diagnosed with OKC (KCOT in the 2005 WHO classification). Furthermore, a patient with a lesion in the mandible (case 7: Figure 2A) had a *BRAF* mutation, and another patient with a lesion in the maxilla (case 12: Figures 1C and 2F) had a *SMO* mutation. In these cases, differential diagnosis from ameloblastoma might be required, but no parts showed neoplastic ameloblastic cells, then it could not be histopathologically diagnosed as ameloblastoma. In addition, although a patient (case 10) was strongly suspected to have ameloblastoma based on X-ray images (Figure 2D) and clinical findings, there were no histopathological findings for ameloblastoma. Then, we diagnosed the disease in this patient as OKC. Since a *PTCH1* mutation was found in this patient, the diagnosis of OKC might be appropriate.

It was also difficult to make a histopathological diagnosis in patient 14 (Figure 1D), and the disease was clinically diagnosed as odontoma because of the dentine-like hard tissues, which were similar to odontoma. Since mutations in *BRAF, SMO*, and *PTCH1* were all found in soft tissues around the hard tissues in this case, a tumor related to ameloblastoma may be considered. However, since odontogenic epithelium could not be found in the tissue, a mutation in the odontogenic mesenchymal tissue might be present.

Patient 16 was diagnosed with cemento-osseous dysplasia, and mutations in *SMO* and *PTCH1* were found in soft tissues (Figure 1E), including squamous epithelium-like cells around hard tissues, suggesting the possibility of odontogenic tumor. Patient 17 (Figure 1F) showed typical images of AOT in the maxillary sinus, but a *SMO* mutation was also found. AOT has been shown to have mutations in RAS and beta-catenin (19), but there have been no reports of a mutation in *SMO* in this tumor.

In this study, NGS analysis of whole exons was shown to be useful for differential diagnosis of odontogenic diseases, although the specificity of mutations extracted from NGS should be confirmed. A re-consideration of KCOT as a potential neoplastic disease is required in diseases that are currently diagnosed as OKC. Integration of histopathological and genetic data is needed for more definitive diagnosis of odontogenic diseases.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Collection of the clinical information: Michiko Shimura, Yuta Sawatani, Tomonori Hasegawa, Ryota Kamimura, Sayaka Izumi, Chonji Fukumoto, Shuma Yagisawa, Erika Yaguchi; Next generation sequencing: Michiko Shimura, Koh-ichi Nakashiro, Daisuke Uchida; Collection of X-ray and histopathological information: Masayo Hitomi-Koide, Toshiki Hyodo; Data analysis: Michiko Shimura, Koh-ichi Nakashiro, Daisuke Uchida, Hitoshi Kawamata; A draft of the manuscript: Michiko Shimura, Yuske Komiyama, Hitoshi Kawamata.

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Figure 1. Histopathological findings of representative patients with odontogenic diseases.

A) (case 1): Ameloblastoma follicular type, B) (case 9): Odontogenic keratocyst, C) (case 12): Odontogenic keratocyst, D) (case 14): Odontoma, E) (case 16) Cement-osseous dysplasia, F) (case 17): Adenomatoid odontogenic tumor.

Figure 2. Panoramic X-ray images of patients with odontogenic keratocyst.

A: case 7, B: case 8, C: case 9, D: case 10, E: case 11, F: case 12, G: case 13.

Arrow heads show the area of the disease.

Odontogenic keratocyst developed in the mandible of 4 patients (cases 7, 8, 9, 10), and in the maxilla of 3 patients (cases 11, 12, 13). Three patients (cases 7, 9, 10) had multilocular cyst, 4 patients (cases 8, 11, 12, 13) had monolocular cyst. One patient (case 7) showed a knife cutting image of the dental root.