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A case of amelogenesis imperfecta, cleft lip and palate and polycystic kidney disease

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Structured Abstract

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Objective – Amelogenesis imperfecta (AI) is a heterogeneous group of genetic disorders characterized by developmental abnormalities of tooth enamel. The AI is also seen as part of multi-organ abnormalities, e.g. with cone-rod dystrophy, hypothalamo-hypophyseal insufficiency and renal failure. The present patient with AI and nephrocalcinosis exhibited a phenotype different from previous cases with renal failure. To highlight the characteristics of this rare case, extensive analysis that included histological, biochemical and genetic examinations was performed.

Patient – The present Japanese male patient exhibited dentition with AI and bilateral cleft lip and palate. Ground sections of his extracted tooth showed that it was hypomaturation-type AI, unlike previous cases with nephrocalcinosis were hypoplastic-type. He showed nephrocalcinosis and hematuria at 15 years of age but these symptoms appeared to be secondary to polycystic kidney disease. He showed skeletal Class II pattern with a retrognathic profile and retroclined incisors of both arches. A dolicofacial appearance was seen with an enlarged gonial angle. Biochemical makers including serum alkaline phosphatase, parathyroid hormone, calcitonin, calcium, and phosphate, were all in the normal range. Sequence analysis of the genes encoding amelogenin and enamelin, which are known to be responsible for hypoplastic-type AI, did not reveal any mutations. Since mouse null mutant of homeobox transcription factor, Msx2, exhibits a phenotype resembling AI, the human homolog of this gene, MSX2, was sequenced. There was a missense mutation of T447C that resulted in the conversion of methionine to threonine at 129.

Key words: amelogenesis imperfecta; cleft lip and palate; MSX2; polycystic kidney disease

Introduction

Amelogenesis imperfecta (AI) is a heterogeneous group of genetic disorders characterized by developmental abnormalities in the quantity and/or quality of tooth enamel in the absence of generalized or systemic disease (1). It has been reported that the prevalence of AI is 1/14 000 and 1/700 in America (1) and northern Sweden (2), respectively. AI is divided into three types; hypoplastic-type (secretory defect), hypocalcified-type (crystallite nucleation defect) and hypomaturation-type (maturational stage defect). It is currently classified into 14 distinct subtypes, based on the clinical manifestation and the mode of inheritance (3). Both X-linked and autosomal forms of AI have been reported (4–6). Mutation in the gene encoding amelogenin, localized at Xp22.1–p22.3, was discovered in X-linked AI (4). The locus of the autosomal forms of AI is mapped to 4q11–q21 (5,6) and mutations have been identified in the gene encoding enamelin (6).

AI is also seen as part of multi-organ abnormalities, e.g. 1) cone-rod dystrophy (1), 2) hypothalamo-hypophyseal insufficiency (1) and 3) renal failure (7–11). Nephrocalcinosis and hypoplastic-type AI were commonly seen in the last type of cases and they were frequently accompanied with delayed tooth eruption, an elevated level of plasmatic creatine and low calcium excretion.

We report here a Japanese male patient with AI and renal failure who had clinical manifestations completely different from those in previous studies (7–11). Extensive examinations, including histological, biochemical and genetic analysis, were performed. This report describes a rare case of multi-organ abnormalities including AI, cleft lip and palate, and polycystic kidney disease (PKD).

Case report

The present male patient was born to a healthy mother as a fourth child. His father had PKD but did not have any other disease including AI. His paternal and maternal grandmothers were sisters, which implied that his father and mother were cousins. He was born by a normal delivery in full term but was only 46 cm long and weighed 2550 g at birth, which is much lower than the Japanese norms (3200 g). He showed microcephaly and blepharoptosis, and had bilateral cleft lip and palate. Bilateral lip repair and palatal closure were performed at 8 months and at 2 years of age, respectively. His height and weight were much smaller than the Japanese norm throughout the growth period. He had slight mental retardation and underdescended testis. Surgical repositioning of the testis was carried out at 8 years of age. At 15 years of age, he had hematuria and nephrocalcinosis. The result of an ultrasonographic examination led to a diagnosis of PKD. Discharge of the calculus and medication were carried out for his treatment. Considering that his father also was with PKD, it was possibly inherited in an autosomal dominant manner (autosomal dominant PKD, ADPKD; OMIM 173900).

He was seen at our dental hospital at 24 years of age. All teeth were mottled brown and black, and showed the typical appearance of AI (Fig. 1A–C). The lingual displacement of the mandibular lateral incisors was noted. On a panoramic radiograph, enamel had

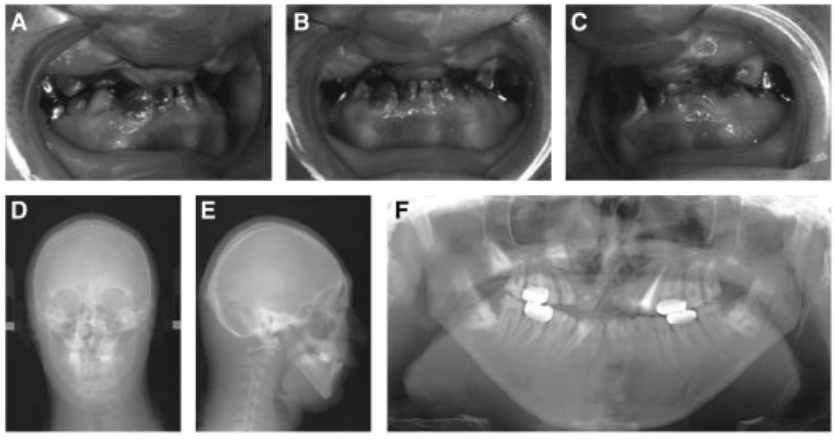

Fig. 1. Oral photographs (A–C) and radiographs (D–F). Frontal (D) and lateral (E) cephalograms and panoramic radiographs (F).

approximately the same radiodensity as dentin (Fig. 1F). A dolicofacial skeletal pattern was seen with an enlarged gonial angle (Fig. 1E). The maxillary right and left lateral incisors and the right canine were impacted (Fig. 1D, F). During orthodontic treatment, the mandibular lateral incisors were extracted and ground sections were prepared (Fig. 2). The section showed that the enamel thickness was almost normal but the structure was immature (Fig. 1A, B) and torn off (Fig. 1A, C). Based on these observations, his AI was classified as hypomaturation type (3).

Analytic measurements from the lateral cephalogram are shown in Table 1. The SNA and SNB angles were smaller than Japanese norms (12). The ANB angle was 9.2°, which showed skeletal Class II characteristics. Maxillary and mandibular incisors were both significantly retroclined. Gonial and mandibular plane angles were much larger than the Japanese norms (12).

Serum albumin, LDH, γ-GTP, ALP, creatinin, urea, sodium, potassium, calcium, chloride and phosphate, were all in the normal range. Parathyroid hormone (PTH), calcitonin, osteocalcin and 1.25(OH)2VitaminD were also measured. All of these markers were also in the normal range, which would exclude the involvement of metabolic hard tissue disease.

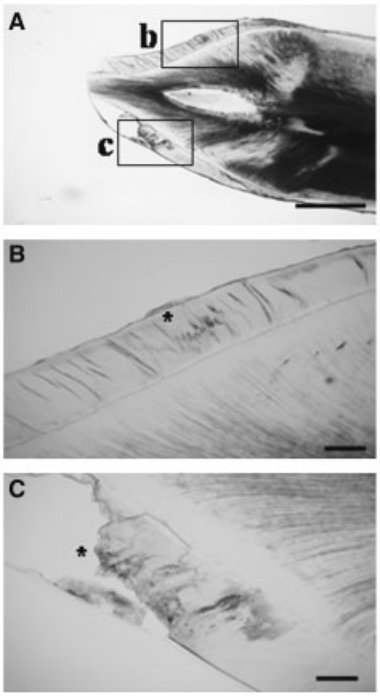

Fig. 2. Ground sections of the present patient. Boxed areas (b and c) in A are shown in higher magnification in B and C, respectively. The integration of the enamel structure was disturbed (asterisk in B) and detached (asterisk in C). Bars = 100 μm.

Table 1. **Analytical measurement (degree)**

	values	Japanese norm[12]
SNA	75.1	81.8
SNB	65.9	78.6
ANB	9.2	3.3
U-I to FH plane	51.9	108.9
L-I to mandibular plane	71.2	94.7
Mandibular plane angle	52.1	26.3
Gonial angle	144.9	119.4

S, sella turcica; N, nasion; A, point A; SNA, angle between SN and NA; B, point B; SNB, angle between SN and NB; U-I, long axis of maxillary central incisor; U-I to FH plane, angle between U-I and FH (frankfort horizontal) plane; L-I, long axis of mandibular central incisor; L-I to mandibular plane, angle between L-I and mandibular plane; Mandibular plane angle, angle between mandibular plane and FH plane; Gonial angle, angle between mandibular plane and ramus plane.

To identify the gene responsible for AI, three genes, amelogenin, enamelin and MSX2, were sequenced. After the extraction of genomic DNA, the polymerase chain reaction using specific primers for amelogenin (13), enamelin (6) and MSX2 (14) was performed. Mutations in amelogenin (4) and enamelin (6) have been reported to cause hypoplastic-type AI. As expected, no mutations in these genes were identified in this patient with hypomaturation-type AI. Since the mouse homeobox transcription factor, Msx2, is related to AI (15) in rodents, the human homolog of this gene, MSX2 (gene accession number NM_002449), was sequenced. The results showed there was a mutation in T447C that resulted in the conversion of methionine (M) to threonine (T) at position 129 in exon 2 (Fig. 3).

Discussion

This report describes a rare case of AI, cleft lip and palate, and PKD. The ground section, panoramic radiograph and clinical symptoms indicated this AI was hypomaturation-type rather than hypoplastic- or hypocalcified-type (3). In previous reports of AI with renal failure, all cases were hypoplastic-type, suggesting that the present patient had a distinct origin and phenotype compared to previously reported cases.

The present patient showed nephrocalcinosis, as in previous patients (7–11). However, he was diagnosed as PKD, probably ADPKD based on the condition of his father. ADPKD is one of the most common inherited

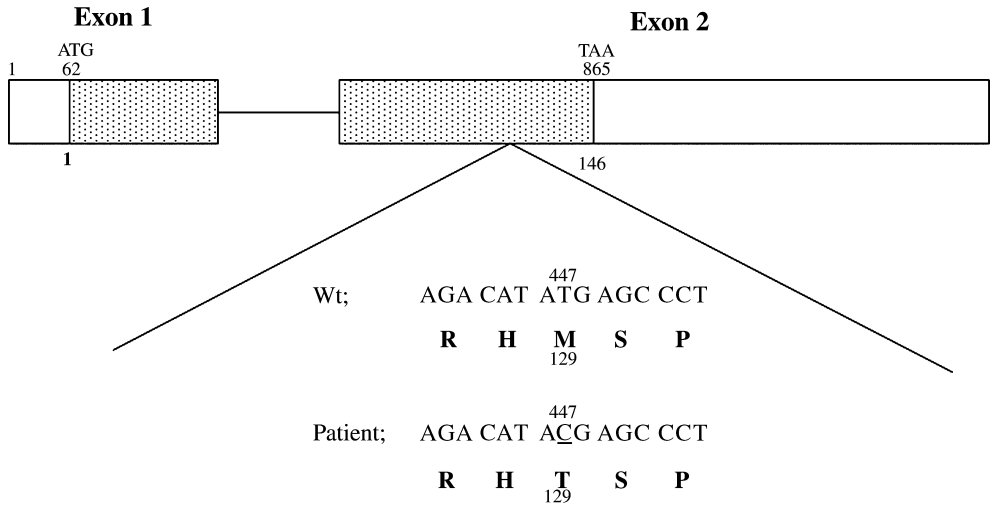

Fig. 3. The structure of the gene encoding MSX2. Dotted area denotes the coding region. Regular and bold letters represent DNA and amino acid sequences, respectively. T447C resulted in the conversion of methione (M) to threonine (T) at position 129.

disorders, with the incidence of 1/1000 (16). This disease is characterized by the progressive replacement of renal parenchyma by gradually enlarging cysts. Approximately 50% of affected individuals develop renal failure and these patients compromise 4–5% of the dialysis population. Nephrocalcinosis and hematuria are known to be major symptoms of ADPKD (16). Thus, nephrocalcinosis in the present patient was likely to be secondary to ADPKD and the origin appeared to be different from those of previously reported cases. All of the serum markers (albumin, LDH, γ-GTP, ALP, creatinine, urea, sodium, potassium, calcium, chloride, phosphate, PTH, calcitonin, osteocalcin and 1.25(OH)2VitaminD) were in the normal range, which excludes the involvement of metabolic disorder in the present condition.

Several genes have been suggested to be related to AI, e.g. the genes encoding amelogenin, ameloblastin, enamelin, tuftelin, enamelysin, kallikrein 4 and MMP-20 (17–19). However, mutations have only been identified in cases exhibiting hypoplastic-type AI (4,6). As expected, there were no mutations in genes encoding amelogenin or enamelin in the present case of hypomaturation-type AI.

Homozygous Msx2 null mutant mice exhibit a tooth abnormality resembling AI (15). Thus, genetic analysis of MSX2 was carried out and the result showed a missense mutation of T447C that resulted in the conversion of methionine to threonine at position 129. Interestingly, this point mutation is identified in 10% of non-syndromic sagittal craniosynostosis (submitted SNP as ss6313877). Further studies are required to clarify the precise involvement of MSX2 gene and the function of methionine at position 129 in the process of enamel formation.

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