Article type: Clinical Research

Title: Enamel renal syndrome: a novel homozygous FAM20A founder mutation in 5 new Brazilian families

Running title: FAM20A founder mutation in enamel renal syndrome

Mauricio Rocha Dourado\textsuperscript{a,c}, Cássio Roberto Rocha dos Santos\textsuperscript{a}, Simona Dumitriu\textsuperscript{b}, Daniela Iancu\textsuperscript{b}; Saleh Albanyan\textsuperscript{b}, Robert Kleta\textsuperscript{b}, Ricardo D. Coletta\textsuperscript{c}, Ana Terezinha Marques Mesquita\textsuperscript{a}

\textsuperscript{a}Department of Dentistry, Federal University of Jequitinhonha and Mucuri Valleys, UFVJM, Brazil
\textsuperscript{b}Center for Nephrology, University College London, United Kingdom
\textsuperscript{c}Department of Oral Diagnosis, School of Dentistry, University of Campinas, UNICAMP, Brazil

Corresponding author: Mauricio Rocha Dourado, Department of Oral Diagnosis, School of Dentistry, University of Campinas, Piracicaba-SP, CEP 13414-018, Brazil. E-mail: mauricio_mrd@hotmail.com, phone: +55 19983279255.

Conflict of Interest: The authors of this study have no conflicts of interest to disclose.
Abstract

Enamel renal syndrome (ERS) is a rare autosomal recessive disorder that still not fully characterized. Here we investigated ERS characteristics in 11 patients from 5 Brazilian families through clinical examination, imaging, renal ultrasonography, laboratory tests and DNA sequencing. The patients’ age ranged from 6 to 25 years old, and the presence of hypoplastic amelogenesis imperfecta, microdontia, intra-pulpal calcification, impacted posterior teeth with hyperplastic pericoronal follicles, gingival fibromatosis, ectopic calcifications on gingival and pericoronal tissues, and nephrocalcinosis were common findings to all patients. Only 4 patients showed abnormal laboratory tests (vitamin D, parathyroid hormone, phosphate, calcium). Intellectual disability and renal cysts were present in 2 patients each. Biallelic loss of function mutations in FAM20A gene, characterized by one base pair deletion in exon 11, resulting in a frameshift replacing a glutamine at codon 483 for a lysine and terminating at position 24 [NG_029809.1: c.1447delG; p.(Glu483Lysfs*24)], were detected in all patients, strongly suggesting a founder effect. Our results reinforce the distinct orofacial features of ERS, which are the clue for kidney examination and genetic testing. Early diagnosis is essential to minimize the deleterious effects related to ERS. Here we report the largest series of patients with ERS in the same population, and describe, for the first time, a founder mutation for FAM20A.

Keywords: amelogenesis imperfecta; nephrocalcinosis; gingival fibromatosis; syndrome; FAM20A
Firstly described in 1972 by McGibbon as “generalized enamel hypoplasia and renal dysfunction”\textsuperscript{1}, enamel renal syndrome (ERS, OMIM #204690) is a rare autosomal recessive disorder that remains not fully characterized. Similar phenotypes have been described under different names, including amelogenesis imperfecta and nephrocalcinosis syndrome\textsuperscript{2,3}, amelogenesis imperfecta and gingival hyperplasia syndrome\textsuperscript{4} and enamel-renal-gingival syndrome\textsuperscript{5,6}. It is believed that these conditions represent in fact the same disease, caused by underlying $FAM20A$ gene mutations\textsuperscript{4,7,8,9}.

Clinically, the common oral characteristics include hypoplastic amelogenesis imperfecta (AI), delayed tooth eruption, pulp calcifications, hyperplastic dental follicles, and gingival hyperplasia with variable severity and presence of calcified nodules\textsuperscript{9}. In addition, nephrocalcinosis (NC) and other kidney disorders have been included as frequent findings, especially in the early adulthood\textsuperscript{10,11}. In that sense, it is speculated that even those individuals with the oral characteristics showing no renal defects, but with biallelic $FAM20A$ mutations, will eventually develop NC\textsuperscript{7}. The protein encoded by $FAM20A$ is expressed in the ameloblasts during secretory and maturation stages of enamel development, in suprabasal cells of the gingiva, odontoblasts, and dental pulp cells, indicating its fundamental role in enamel development and gingival homeostasis\textsuperscript{4}. Several $FAM20A$ mutations have been described in individuals with the ERS phenotype, including stopgain, frameshift, missense, and splice-site mutations\textsuperscript{7,8,12-16}.

Here we describe 11 unreported patients with ERS from 5 different Brazilian families harboring a homozygous founder loss of function mutation in $FAM20A$. The early diagnosis can have an impact on the overall morbidity caused by ERS, hence it is important that child caregivers are aware of the main features beginning during the childhood.
Patients and Methods

The patients included in this study were evaluated at the Stomatology Clinic of the Dental School at the Federal University of the Jequitinhonha and Mucuri Valleys (UFVJM, Brazil). This study was approved by the Research Ethical Committee of UFVJM (number 074/12), and a written informed consent was obtained from patients, parents or guardians, as appropriate. In general, the oral aesthetics and functional impairment caused by the ERS were the main complaints of the patients seeking professional care. The probands and the relatives up to three generations were evaluated and the families’ pedigrees were built to verify the inheritance pattern of the syndrome.

The clinical examination was focused on oral aspects of the syndrome (teeth and gingiva conditions, alveolar ridge shape, and tooth absence). The patients were evaluated by periapical and panoramic x-ray, in addition to renal ultrasonography (USS), which was analyzed by an experienced nephrologist. Furthermore, the patients were tested for alterations in their blood (calcium, ionized calcium, phosphate, parathyroid hormone, vitamin D (25OH and 1,25(OH)2), alkaline phosphatase and creatinine) and urine collected during 24 hours (calcium, phosphate, creatinine, osmolarity, specific gravity and glomerular filtration rate). Gingival tissues, teeth and pericoronary tissues removed for the purpose of oral rehabilitation were evaluated by classic H&E staining, and by screening electron microscopy (SEM) as published previously.

For sequencing analysis, genomic DNA was extracted from oral mucosa cells through saliva collection as previously described. Exons and flanking splice junctions of FAM20A were amplified with specific primers by polymerase chain reaction, followed by bidirectional sequencing in an ABI Prism 3500 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). Sequencing data were analyzed and compared with the published reference sequence for FAM20A (NG_029809, February 2018).
Results

The age of patients (7 males and 4 females) ranged from 6 to 25 years-old. Pedigrees from the 5 families revealed an autosomal recessive transmission pattern. In 7 patients from 3 different families, consanguineous marriage of parents and/or grandparents were observed (Fig. 1). The patients' previous medical history did not reveal any significant information, especially regarding renal or urinary disorders. Two patients from Family 1 (1.III-5 and 1.III-11) presented intellectual disability (ID) concomitant to other ERS features (Table 1).

Table 1 summarizes the most common clinical and imaging findings in the diagnosed patients. Clinical examination revealed that all individuals presented microdontia, spaced teeth with yellow-brownish discoloration, occlusal and incisal wear with molars showing flat cusps characterizing hypoplastic AI, and gingival overgrowth in different levels of severity (Fig. 2). Besides, other findings were also observed although not always present, such as tooth translucency caused by reduced enamel thickness, rough tooth surface, prolonged retention of deciduous teeth, malocclusion (loss of the vertical occlusion dimension, anterior open bite, crossbite) semi-lunar shape of central incisors edges, in addition to loss of periodontal support (Fig. 2). Those later findings were related to the time of tooth eruption. According to patients’ reports and direct observation of remaining deciduous teeth, the dental defects are present since the first dentition and, usually, the patients did not report any tooth pain or sensitivity.

The radiographic analysis confirms the delayed eruption of permanent dentition, revealing impacted teeth with crown resorption and incomplete rhizogenesis in some cases (Fig. 3 A-D). Those impacted teeth were localized in aberrant areas, crossing the cortical bone and inducing an irregular shape of alveolar ridge, with agenesis of permanent teeth being sporadically observed (Table 1; Fig. 3 A-D). A common finding on the unerupted teeth was the presence of pericoronal
radiolucencies with sclerotic margins (hyperplasia of dental follicle), sometimes even covering the root (Fig. 3A-D). Intra-pulpal calcifications were frequently found, assuming a needle shape in the incisors and a round shape in the molars (Fig. 3A-D). There was a lack of regular contrast between enamel and dentin, representing tissue hypomineralization (Fig. 3A-D).

In the USS analysis, the renal parenchyma was hyperechoic in 5 cases, and corticomedullar dedifferentiation was a common finding. Eight patients showed bilateral NC with mineralization foci of different sizes and 1 patient (1.III.5) developed NC only in the right kidney (Fig 3E-F). Two patients showed cystic areas adjacent to the lower pole of left kidney (2.III.1) and in the cortical portion (1.III.11) (Fig. 3G). Two patients could not be investigated for renal calcifications (4.III.1 and 4.III.2).

The blood and urine tests revealed values within the normality parameters for most of the patients (Table 1). In 4 patients the values were altered for D vitamin, calcium, parathyroid hormone, urine phosphate and alkaline phosphatase. Patient 1.III.11 showed low levels of 25OH vitamin D (27.9 ng/mL) and urine phosphate (395 mg/24 h), patient 2.III.3 presented low levels of 25OH D vitamin (23.3 ng/mL) and ionized calcium (1.15 mmol/L), patient 3.III.4 showed slightly higher levels of parathyroid hormone (62 pg/mL), and patient 5.III.4 had higher levels of parathyroid hormone (70 pg/mL), alkaline phosphatase (493 U/L) and 1,25(OH)2 D vitamin (80 pg/mL).

Decalcified teeth showed intra-pulpal calcifications in both crown and root, sometimes even obliterating the area (Fig. 4A-B). Microscopic analysis of the gingival tissue revealed epithelial hyperplasia and a dense and fibrous connective tissue (Fig. 4). Deep in the connective tissue, large areas of dystrophic calcifications arranged in lobes and surrounded by fibrous tissues with mild chronic inflammatory infiltrate were commonly found (Fig. 4C-D). The hyperplastic
dental follicles also presented lobular dystrophic calcifications, apparently originated from small islands of odontogenic epithelium scattered in a collagenous stroma (Fig. 4E). These odontogenic epithelium islands showed vacuolated cells, probably representing a degenerative process (Fig. 4F). SEM analysis of extracted teeth revealed surface wear and oblique enamel cracks, areas of uneven mineral deposition, rough, porous, and void spaces (Fig. 4G-I).

For the genetic analysis, saliva from affected patients and their relatives was collected. Sanger sequencing revealed that all evaluated patients presenting ERS phenotypes showed a novel FAM20A homozygous one base pair deletion in exon 11, causing a frameshift and a premature stop codon [NG_029809.1: c.1447delG; p.(Glu483Lysfs*24)] (Fig. 5). Fitting the expected recessive segregation, the relatives investigated showed a heterozygous state for the deletion (Fig. 5B).

After considering the findings above mentioned, the 11 individuals were diagnosed with autosomal recessive ERS caused by a founder FAM20A mutation. The patients are under oral rehabilitation and are monitored by a nephrologist. They also received genetic counseling.

Discussion

This study detailed the clinical and imaging characteristics of multiple patients with ERS from 5 different Brazilian families, all originated from the same geographic region, and possibly with the same ethical background. In Brazil, three main population groups, Europeans, Africans and native American Indians (Amerindians), substantially contribute to the variable ancestry within Brazilian population, and each Brazilian contains different proportions of genomic DNA from these 3 main groups. The families in this study are from a geographic area of Brazil with great African immigration.
Indeed, clinical, imaging, laboratory and genetical analysis were combined for diagnosis process to cover the syndrome spectrum. De la Dure-Molla et al. suggested the following pathognomonic features in ERS: hypoplastic or absent enamel, primary and permanent teeth affected, flat cusps on posterior teeth, microdontia and spaced teeth, intra-pulpal calcifications, delayed tooth eruption, impacted posterior teeth with hyperplastic follicle, root dilacerations of impacted teeth, gingival fibromatosis, and gingival and dental follicle ectopic calcifications on biopsies. All these characteristics were presented in the patients evaluated in this study. Besides, other less common characteristics presented in this current series, such as malocclusion, periodontal disease, supra-incisive diastema, the semilunar shape of central incisors and dental and bone resorption, have been reported before.

ERS was associated with ID in 2 patients from Family 1, and was also reported in 2 previous studies. Martelli-Junior et al. considered ID as a characteristic superimposed on ERS phenotype in their case since other 6 relatives presented this feature as an isolated entity. Interestingly, in our study ID was presented only in association to ERS and its interpretation as an uncommon ERS finding cannot be excluded. On the other hand, the Family 1 is highly consanguineous, and ID could represent an unrelated condition to ERS. The genetic profile associated to ID was not addressed in this study and should be further confirmed in ERS patients.

AI represents a complex group of inherited conditions causing dental enamel malformations in quantity or quality, either as an isolated finding or as a characteristic of a syndrome, such as ERS. In this study, AI was subclassified as hypoplastic type, represented by defects in the primary organic matrix of the enamel that may be thin and smooth, rough and with craters, or even presented as enamel agenesis. The presence of abnormalities in tooth shape and intra-pulpal calcifications suggests that morphogenesis and dentinogenesis are also affected by
ERS\textsuperscript{20}. Previous reports have identified reparative and amorphous dentin inside the pulpal chambers of erupted and non-erupted teeth in ERS\textsuperscript{21}. Similarly, irregular dentine with dilated tubules and pulpal calcifications showing osteodentine tissue were also found in the present study. In addition, the histopathological analysis of the hyperplastic gingiva and dental follicle revealed dystrophic calcification bodies related to islands of odontogenic epithelial cells, similar to previous reports\textsuperscript{5,13}. The hypothesis is that the odontogenic epithelial cells might have roles in the formation of these calcified bodies, but subsequently degenerate and remain as epithelial rests\textsuperscript{11}. Future studies should be performed to define the nature of these calcifications.

Another classic finding of ERS is NC, though kidney phenotypes are not always present\textsuperscript{1,10,25}. All patients in this study investigated by renal USS showed renal calcifications, but none developed renal complications. Renal complications in ERS range from renal failure\textsuperscript{1,10,26} to recurrent infections\textsuperscript{1,10}, pyelonephritis\textsuperscript{3}, polycystic kidney and distal renal tubular acidosis\textsuperscript{22,25,27}, occurring between the second and third decades of life. Some studies have explained NC as an epithelial and paracellular disorder in calcium transport, predominantly caused by mutations in calcium channel proteins\textsuperscript{28, 29}. These systems either reabsorb calcium filtered from the urine through the tubular renal cell or release calcium from the tubular cell into the interstitial compartments. When dysfunction is present, increased urinary calcium precipitates in the interstitium, resulting in NC, which is invariably accompanied by hypercalciuria\textsuperscript{7}. However, this does not appear to be the mechanism by which patients develop NC in this syndrome since 5 reports have shown hypocalciuria in their patients\textsuperscript{2,10,30-32}. Another hypothesis is that NC is associated with an increase of urate or oxalate, or even a decrease in inhibitors of crystallization, such as citrate\textsuperscript{33}. NC was not associated with changes in calcium levels in our patients, which suggests its genetic etiology. The formation of renal calcifications is probably the result of
synergistic effects of altered function in many predisposing genes (including FAM20A) to increase individual susceptibility above the threshold of stone formation\(^6\). Despite the typical absence of alterations in the laboratory tests, previous cases reported hypocalciuria and hypophosphaturia\(^30\), elevated alkaline phosphatase\(^{20,32}\), low levels of vitamin D 25-OH\(^{32}\), and high parathyroid hormone\(^{5,10,27}\). Changes in levels of alkaline phosphatase, vitamin D, parathormone and phosphate in urine were also found in 4 patients of this study.

FAM20A is considered a pseudokinase due to a mutation within its catalytic site, but it can form a functional complex with FAM20C and can enhance the capacity of the latter to phosphorylate extracellular proteins in their secretory pathways\(^{17,34}\). The role of FAM20A in amelogenesis may be indirect, and it can be hypothesized that FAM20A loss of function would result in reduced phosphorylation of enamel matrix proteins, thus disrupting amelogenesis beyond the first stages of inner enamel deposition, and leading to a poorly mineralized matrix\(^{17}\). Several FAM20A mutations including missense, nonsense, splice site, and insertion/deletion, have been previously reported in ERS patients\(^8\). Combining homozygosity mapping and whole exome sequencing, O’Sullivan et al.\(^4\) identified the first homozygous mutation in FAM20A in a consanguineous family with ERS. Using genome-wide linkage analysis, exome capture, next-generation sequencing and Sanger sequencing, Jaureguiberry et al.\(^7\) described 20 different biallelic FAM20A mutations segregating with the disease in 25 ERS patients from 16 families.

Previous reports have shown homozygous mutations in all 11 exons, and some introns, of FAM20A in ERS, whereas heterozygous carriers appear to be phenotypically healthy\(^9\). Most of the previous studies reported ERS-associated mutations inducing protein truncation (premature stop codons) and only 4 missense mutations have been reported\(^7,13,14,23\). In the current report, all ERS patients were identified with a novel homozygous nonsense mutation in exon 11 [NG_029809.1:
This led us to speculate that this mutation is probably have arisen from a common ancestor with a founder effect.

In closing, we reported a large cohort of patients with ERS, illustrating the clinical and imaging features and revealing one novel and founder mutation in FAM20A. It is suggested that patients presenting hypoplastic AI in association with delayed teeth eruption, intra-pulpal calcifications, gingival hyperplasia, and hyperplastic pericoronal radiolucences should be referred for renal investigation of NC. Genetic counseling is important given the inheritance pattern of the disease. Finally, early diagnosis and treatment of this condition will decrease the renal effects of ERS, and oral rehabilitation is a must to provide better function, aesthetics and improve the patients’ quality of life.

Acknowledgments

We are thankful to the Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG, Brazil) for providing financial support in this study.
Figure Legends

Figure 1. Pedigrees representing the five studied families.

Figure 2. Different clinical aspects of the orodental ERS findings in three different patients (4.III.2, 1.III.11, and 2.III.1, according to the pedigrees codes). In A, B, and C, it is possible to visualize the presence of a thin and smooth enamel layer, widely spaced and small teeth, flat molar cusp, the absence of molars, and gingival enlargement. In D, E and F, the enamel translucence, yellowish teeth color, teeth absence (upper and lower incisors), gingival enlargement, loss of the typical teeth shape and of the vertical occlusion dimension, are evident. Figures G, H, and I, show the absence of frontal and posterior teeth, gingival enlargement, loss of the periodontal support in an inferior molar, and anterior open bite.

Figure 3. Imaging findings on panoramic radiography of four different ERS patients: 1.II.4 (A), 1.III.11 (B), 2.III.1 (C), and 5.III.4 (D), according to the pedigrees codes. In general, the pattern is unique and the images reveal delayed eruption and several impacted permanent teeth, intra-pulpal calcifications (arrow), pericoronal radiolucences (asterisks), crown reabsorption of impacted molars ($) as in A and B, and teeth in aberrant location like the impacted molars invading the cortical mandibular bone in Figure C. Figures E and F represent the findings on renal ultrasonography of both right and left kidneys, respectively. Hyperechoic areas of different sizes represent the calcified bodies and were interpreted as a sign of nephrocalcinosis. Figure G shows the renal cyst in the patient 1.III.6, which is an uncommon finding in ERS patients.
**Figure 4.** Microscopic findings common in ERS. Figure A shows incisive in a longitudinal section, and the squared area is presented in a higher magnification of the pulp region in B, revealing the presence of multiple calcified bodies. Figure C represents the histologic findings of the gingival tissue, where the specimen shows epithelial hyperplasia and the presence of dystrophic calcified lobular tissue deep in the connective tissue in the absence of inflammatory infiltrate. The squared area in C is in higher magnification on D, showing basophilic, strongly stained lobular osteodentine tissue. E shows the histologic findings in the pericoronal tissue of impacted teeth, also presenting dystrophic calcification bodies in a fibrous stoma, and the higher magnification in F highlights the presence of odontogenic epithelial cells surrounding calcified tissue. G, H, and I are SEM images showing the rough, irregular enamel surface (G), the presence of cracks and intra-pulpal calcified tissue (H), and irregular dentin deposition around the pulp chamber (I). Figures A, B, C, D, E, and F are regular H&E stained sections (A and B were previously decalcified). (Original magnification: A, C:50x; B, E:100x; D: 200x; F:400x. e= enamel, d= dentin, ct= calcified tissue.

**Figure 5.** Representative images from the sequencing chromatograms of FAM20A exon 11 analyzed in the patients of this study. This homozygous loss of function mutation, characterized by one base pair deletion, as shown in the proband 2.III.1 (A), resulted in a premature stop codon [NG_029809.1: c.1447delG; p.(Glu483Lysfs*24)]. Fitting the expected recessive segregation, his mother (2.II.10) revealed heterozygosity for this deletion (B). The analysis of a healthy non-affected control showed a normal FAM20A sequence (C).
Table 1. General clinical, imaging and laboratory findings of the patients diagnosed with Enamel Renal Syndrome.

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<th>Clinical Features</th>
<th>1.III.1 (M/18)</th>
<th>1.III.4 (F/11)</th>
<th>1.III.5 (M/25)</th>
<th>1.III.6 (M/14)</th>
<th>1.III.11 (M/14)</th>
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<th>2.III.3 (F/13)</th>
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<td>Blood and urine tests alterations</td>
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<tr>
<td>Other alterations</td>
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<td>No</td>
<td>ID/RC10</td>
<td>MR</td>
<td>RC</td>
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<td>-</td>
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1Case report presenting the oral rehabilitation of this patient previously published36.

1ID=intellectual disability; RC=renal cyst. The subjects are identified by their code on the pedigrees, with information regarding sex (M=male, F=female) and age at the diagnosis (in years) inside the parenthesis.
References


