Review Article

Enamel Renal Syndrome: A Systematic Review

Maria Luiza Morais Farias, Gabriela Oliveira Ornela, Rodrigo Soares de Andrade[1], Daniella Reis B. Martelli[2], Verônica Oliveira Dias[2], Hercílio Martelli Júnior[2]

Medicine School, Institute of Health Sciences, State University of Montes Claros, Unimontes, [2]Dentistry School, State University of Montes Claros, Unimontes, Minas Gerais State, [1]Department of Oral Diagnosis, School of Dentistry, State University of Campinas, FOP-UNICAMP, Piracicaba, São Paulo, Brazil

Abstract

The enamel renal syndrome (ERS) is a rare autosomal recessive disease that is associated with mutations in the *FAM20A* gene. The syndrome is characterized by impaired amelogenesis of the hypoplastic type and nephrocalcinosis, presenting with presence of thin or absence of enamel, late dental eruption, intrapulpal calcifications, bilateral nephrocalcinosis, and normal plasma calcium level. The objective is to characterize ERS by systematically literature reviewing, highlighting the main findings of the syndrome to increase knowledge about this condition in the health professionals. The study is a systematic review of the scientific literature, whose research was developed in the PubMed database in March 2018. A total of 69 articles were found. Two authors analyzed their abstracts and selected, according to the language and main subject, 30 articles to write this study. A total of 69 patients were cited in the studies and their data were analysed. There was gender equivalence and the ages ranged from 1 to 64 years old. There is a clear hereditary relation of the syndrome, since there was consanguinity in 18 cases, indicating a percentage of 26.08% and family history in 30 cases (43.47%). Laboratory changes vary greatly from patient to patient and may even remain unchanged. The relationship between the syndrome and the mutation in the *FAM20A* gene can be proven from the data, since all patients with ERS screened by the mutation were positive. With the advancement of the ERS studies, some associations with the syndrome are suspected, such as the presence of gingival fibromatosis, hearing loss, and hypertrichosis. Thus, it is noticed that the syndrome does not show a predilection for gender or age and there is a strong hereditary character, marked by the consanguinity and family history of the patients. The association with the *FAM20A* gene is reinforced, since the mutation was identified in all patients analyzed.

Keywords: *Amelogenesis imperfecta, enemal renal syndrome, nephrocalcinosis*

Introduction

The enamel renal syndrome (ERS) is considered a rare disease according to the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH), affecting less than 200,000 people in the United States population.[1] It is an autosomal recessive disorder characterized by amelogenesis imperfecta of the hypoplastic type and nephrocalcinosis (OMIM #204690), presenting with presence of thin or absence of enamel, delayed dental eruption, intrapulpal calcifications, bilateral nephrocalcinosis, and normal plasma calcium level.[1]

Amelogenesis imperfecta (AI) is a hereditary group of disorders that affects the quality and quantity of enamel on deciduous and/or permanent teeth, and may affect all or only a few teeth.[2,3] The clinical characteristics of AI vary depending on the type: in the hypoplastic, which is present in the syndrome, the teeth have a white to dark brown chalk color, occlusal surfaces, and incisal edges are generally worn, and occasionally complete loss of enamel is observed; In the hypocalcified, the enamel exhibits a consistency of cheese and can be easily removed with a sharp explorer and in the hypomaturated is characterized by the enamel with normal thickness and white opaque areas on the incisal surfaces.[4]

Nephrocalcinosis is a condition characterized by calcium deposition in renal tissue and may be predominantly cortical or, more commonly, medullary. It is found in conditions, such as primary hyperparathyroidism, distal renal tubular acidosis, spongy spinal cord kidney, hypervitaminosis D, oxalosis, and some forms of Bartter's syndrome.[3,5,6] Nephrocalcinosis may remain unnoticed until patients have recurrent urinary tract infections, pyelonephritis, or the passage of a stone, leading to renal failure.[7]

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Address for correspondence:
Ms. Gabriela Oliveira Ornela, Rua Porto Seguro, 1100, Montes Claros- Minas Gerais, Postal Code: 39.401-290, Brazil. E-mail: gabrielaornela@gmail.com

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The ERS diagnosis is clinical, based on orodental alterations and renal findings that represent the degree of impairment of the kidneys.[8] However, as renal changes occur late, the presence of the characteristic oral phenotype, even in the absence of other manifestations, is sufficient to clinically diagnose this syndrome.[9]

Thus, the objective of the systematic review is to present and discuss the characteristics of the ERS, which is relevant due to the scarcity of studies and knowledge about the syndrome.

Methodology

The present review was carried out in accordance with the Cochrane Collaboration Group protocol for systematic reviews. Our review was performed in March 2018, when we searched on PubMed database the following terms: '*Enamel Renal Syndrome*' [title/abstract] OR '*Enamel Renal Gengival Syndrome*' [title/abstract] OR '*Amelogenesis imperfecta and nephrocalcinosis syndrome*' [title/abstract] OR '*Enamel hypoplasia and renal dysfunction*' [title/abstract], including a literature search strategy, selection of papers through the inclusion and exclusion of criteria, data extraction, and quality assessment. Meta-analysis was not possible since selected studies did not observe the same variables, methods, participants, and outcomes, which prevented comparisons.

As seen in figure 1, in the search, 108 studies were identified and after removing the repeated results, 69 articles remained. Of these, 39 were excluded, after 2 authors analyzed their abstracts, as criteria not to approach the ERS and non-English language; thus remaining 30 studies. From each of these articles, the following data were extracted for analysis: type of study, first author, publication year, country of publication, age, sex, family history, consanguinity, presence of amelogenesis imperfect, nephrocalcinosis and gingival fibromatosis, laboratory tests results, and mutation in the *FAM20A* gene.

Results

The results found with the research are summarized in Table 1. Of a total of 69 articles found after research, only 30 (43.47%) were in agreement with the methodology,[1,7-34] of these 27 (39,13%) were case reports,[1,7,8,10-18,20,21,23-34] 1 (1.44%) was case series[22] and 2 were review of scientific literature.[9,19] The most recent publication date was in May 2018[34] and the older was in February 1972.[11]

Among the case reports, we can observe that the average age was 38.3 years old. The youngest age reported was in the first year of life[25] and the highest age was at 64 years old.[21] In ten (14.4%) patients,[7,8,11,14,17,27,33] there was a difference between the ages of diagnosis of AI and nephrocalcinosis. In 6 (8.64%) patients,[7,8,14,33] AI was first identified at 1,[8] 6,[33] 8[7,14] and 12 years[7,33] and in 4 patients[11,17,27] nephrocalcinosis was first diagnosed at 8,[27] 11,[11] and 15 years.[11,17] When it comes to gender,

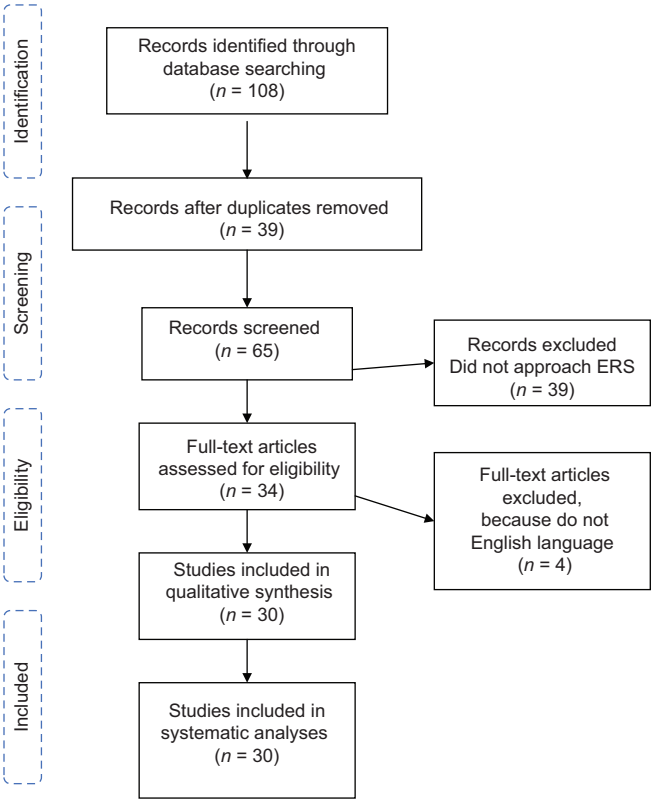

Figure 1: Flowchart of process of systematic literature search, using Cochrane and flowchart of process of systematic literature search

there were 33 (47.82%) women[1,6,7,9-13,16,17,19,21-23,25,27,29,31] and 36 (52.17%) men.[6,7,9-12,14,15,17,21,22,24-26,28-34]

The presence of consanguinity was reported in 18 (26.08%) cases[1,6,14-17,19,22-24,26,29,31,32] and in 30 (43.47%), there were positive family history for ERS.[6,9-12,15,17,20-24,29,32] Among the 69 evaluated patients, all had AI.[1,6,7,9-17,19-34] 62 (89.85%) presented with nephrocalcinosis,[1,6,7,9-16,19-22,24-34] 46 (66.66%) had gingival fibromatosis[1,7,12-14,17,19,31-33] and in 4 (5.79%) patients there was no appearance of this affection.[23,26-28]

In the laboratory evaluation of patients, several types of alterations were reported, as seen in Table 1. In 35 cases (50.72%), there was no description of laboratory tests.[7,17,21,23,31,34] Thus, the laboratory parameters were evaluated in 34 cases (49.27%):[1,6,7,10,12-14,16,20,26-28,32] in 18 (26.08%) no abnormalities were found[9,11,12,15,19,22,24,25,29,30,32,33] and the main alterations identified were: hypocalciuria (11.59%),[1,6,10,13,27] elevated serum creatinine levels (7.24%),[6,12,20,27] reduced phosphate excretion (5.79%)[1,10,13] and hypocitraturia (5.79%).[13,26,28,32]

Since the discovery of the relationship between the syndrome and the gene *FAM20A*,[21] 51 patients were analyzed in 17 of the 28 case report studies.[7,8,17,21-34] Among these 51 patients, 41 (80.39%) were screened by mutation in the gene and all 41 (100%) were positive.[7,17,21,23,25,29,31,32] A total of 10 (19.60%) of the 51 patients analyzed after the discovery were not investigated about mutation on

Table 1: Articles from the literature that evaluated with Renal Enamel Syndrome that fulfilled the inclusion criteria of this study

Reference	Patient					Clinical and laboratory findings				
Author/date	Location	Age of diagnosis	Sex	Family history	Consanguinity	Imperfect amelogenesis	Nefrocalcinosis	Gingival fibromatosis	Laboratory tests	Mutation FAM20A
MacGibbon, 1972	Australia	15 (N) 25 (AI)	F	No	No	Yes	Yes	-	No alterations	Not described
	-	11 (N) 26 (AI)	M	No	No	Yes	Yes	-	No alterations	Not described
Lubinsky *et al*., 1985	USA	11	M	Yes	No	Yes	Yes	Not described	Reduction of creatinine clearance, low calcium and phosphate excretion	Not described
	-	9		F	Yes	Yes	Yes	Not described	Not described	Not described
Phakey *et al*., 1995	Holland	10	F	-	-	Yes	Yes	-	Normal levels of vitamin D, PTH, and calcium	Not described
	-	14	M	-	-	Yes	Yes	-	Normal levels of vitamin D, PTH, and calcium	Not described
Hall *et al*., 1995	Greece	8 (AI) 10 (N)	F	Yes	No	Yes	Yes	Yes	No alterations	Not described
	-	14		M	Yes	Yes	Yes	Yes	Yes	Not described
Dellow *et al*., 1998	England	12 (AI) 40 (N)	F	Yes	Yes	Yes	Yes	Not described	Increased creatinine, proteinuria, hypercholesterolemia, hypocalciuria	Not described
	-	8 (AI) 32 (N)	M	Yes	Yes	Yes	Yes	Not described	Increased creatinine, proteinuria, hypercholesterolemia, hypocalciuria	Not described
Tranchade *et al*., 2003	France	15	F	-	-	Yes	Yes	Yes	Increased creatinemia, impaired glomerular filtration, low calcium, citrate and phosphate excretion	Not described
Paula *et al*., 2005	Brazil	13	M	No	Yes	Yes	Yes	Yes	Slight increase in alkaline phosphatase	Not described
Suda *et al*., 2006	Japan	15 (N) 24(AI)	M	Yes	Yes	Yes	Yes	-	Normal values, cleft lip and palate, microcephaly and blepharoptosis	Not described
Fu *et al*., 2006	Japan	14	F		Yes	Yes	Yes	Not described	Hypokalemia, hypercalciuria, increase in glomerular filtration rate, increase in aldosterone levels	Not described
Elizabeth *et al*., 2007	India	23	F	Yes	No	Yes	Yes	Not described	Increased blood pressure, urea levels, creatinine, PTH, phosphate, serum calcium and potassium (renal failure)	Not described
	-	20	F	-	-	Yes	Yes	Not described	Presence of acidosis in renal tubules, low serum levels of potassium, calcium, phosphate and bicarbonate	Not described
Kirzioglu *et al*., 2009	Turkey	Article without case report	-	-	-	Yes	Yes	-	-	-

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Table 1: Contd...

Reference	Patient					Clinical and laboratory findings				
Author/date	**Location**	**Age of diagnosis**	**Sex**	**Family history**	**Consanguinity**	**Imperfect amelogenesis**	**Nefrocalcinosis**	**Gingival fibromatosis**	**Laboratory tests**	**Mutation FAM20A**
Martelli Júnior *et al.*, 2011	Brazil	9	F	No	Yes	Yes	Yes	Yes	No alterations	Not described
Kala Vani *et al.*, 2012	India	11	F	No	Yes	Yes	Yes	Yes	Hypocalciuria and reduction in phosphate excretion	Not described
Jaureguiberry *et al.*, 2012	London	23	M	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	25	F	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	21	M	No	Not described	Yes	Yes	Yes	Not described	Yes
	-	27	F	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	31	M	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	59	M	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	64	F	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	12	F	No	Not described	Yes	Yes	Yes	Not described	Yes
	-	20	M	No	Not described	Yes	Yes	Yes	Not described	Yes
	-	16	F	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	22	M	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	20	M	No	Not described	Yes	Yes	Yes	Not described	Yes
	-	13	M	No	Not described	Yes	Yes	Yes	Not described	Yes
	-	29	F	No	Not described	Yes	Yes	Yes	Not described	Yes
	-	19	F	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	20	M	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	18	F	No	Not described	Yes	Yes	Yes	Not described	Yes
	-	14	F	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	16	M	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	21	F	No	Not described	Yes	Yes	Yes	Not described	Yes
	-	24	M	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	31	M	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	37	F	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	17	F	Yes	Not described	Yes	Yes	Yes	Not described	Yes
	-	18	F	Yes	Not described	Yes	Yes	Yes	Not described	Yes
Wang *et al.*, 2013	EUA	Not described	M	Yes	No	Yes	Not realized	Yes	Not described	Yes
	Jordan	Not described	M	No	Yes	Yes	Yes	Yes	Not described	Yes
	Irã	Not described	F	Yes	No	Yes	Not described	Not described	Not described	Yes
Kantaputra *et al.*, 2013	Thailand	1 (AI) 14 (G e N)	M	No	No	Yes	Yes	Yes	Not described	Yes

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Table 1: Contd...

Reference	Patient					Clinical and laboratory findings				
Author/date	**Location**	**Age of diagnosis**	**Sex**	**Family history**	**Consanguinity**	**Imperfect amelogenesis**	**Nefrocalcinosis**	**Gingival fibromatosis**	**Laboratory tests**	**Mutation FAM20A**
	-	10	F	No	No	Yes	Yes	Yes	Hyperparathyroidism, vitamin D deficiency and high level of alkaline phosphatase	Yes
Rajathi *et al.*, 2013	India	9	F	Yes	Yes	Yes	Yes	Not described	No alterations	Not described
	-	11	M	Yes	Yes	Yes	Yes	Not described	Not described	Not described
	-	13	M	Yes	Yes	Yes	Yes	Not described	Not described	Not described
Kantaputra *et al.*, 2014	Turkey	17	M	No	No	Yes	No	Yes	Not described	Yes
	-	14	F	No	No	Yes	Yes	Yes	Not described	Yes
Wang *et al.*, 2014	Ireland	2.5 (AI)	F	No	No	Yes	No	No	Not described	Yes
	Mexico	10	F	Yes	Yes	Yes	Not described	Yes	Not described	Yes
Chaitanya *et al.*, 2014	India	18	M	Yes	Yes	Yes	Yes	Not described	Not described	Not described
de la Dure-Molla *et al.*, 2014	France	Review Article	-	-	-	-	-	-	-	-
Ashkenazi *et al.*, 2014	Israel	8 (N) 13 (AI)	M	No	Yes	Yes	Yes	No	Hypocitraturia	Not described
Patel *et al.*, 2015	India	16	F	No	No	Yes	Yes	No	Vitamin D deficiency, reduced serum creatinine, reduced calcium and phosphorus excretion, vitamin D deficiency, hypocalciuria, and hypophosphatemia with metabolic alkalosis	Not described
Bhesania *et al.*, 2015	India	21	M	No	No	Yes	Yes	No	Hypocitratúria	Not described
Pêgo *et al.*, 2017	Brazil	10	F	-	Yes	Yes	Yes	Yes	Hypertrichosis and hearing problems	Yes
Pena *et al.*, 2016	Brazil	31	M	-	No	Yes	Yes	Yes	Hypertrichosis and hearing problems	Yes
Costa 2017	-	25	H	-	-	Yes	Yes	-	Calcium, phosphate, PTH, creatinine, alkaline phosphatase and vitamin D	Not described
Kantaputra *et al.*, 2017	Thailand	12	M	No	Yes	Yes	Yes	Yes	-	Yes
Kantaputra *et al.*, 2017	Turkey	11	F	No	No	Yes	Refused to do ultrasound	Yes	-	Yes
	-	11	M	No	No	Yes	No	Yes	-	Yes
Koruyucu *et al.*, 2018	-	12 (AI) 18(N)	M	Yes	Yes	Yes	Yes	Yes	Creatinine and electrolytes without changes, hypocitraturia	Yes

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Table 1: Contd...

Reference	Patient				Clinical and laboratory findings				
Author/date	Location	Age of diagnosis	Sex	Family history	Consanguinity	Imperfect amelogenesis	Nefrocalcinosis	Gingival fibromatosis	Laboratory tests	Mutation FAM20A
Koruyucu *et al.*, 2018	Turkey	6 (AI) 12(N)	M	Yes	Yes	Yes	Yes	Yes	Creatinine and electrolytes without changes, hypocitraturia	Yes
Torres *et al.*, 2018	Brazil	11	M	-	-	Yes	Yes	Yes	Calcium, phosphate and creatine unchanged	Not described
Mauprivez *et al.*, 2018	France	18	M	Not Described	Not Described	Yes	Yes	Not Described	Not Described	Not Described

(N) - Age of diagnosis of nephrocalcinosis. (AI) - Age of the diagnosis of imperfect amelogenesis

these gene,[22,24,26-28,30,33,34] that is, a total of 28 (40.57%) patients were not screened by mutation in the *FAM20A* gene.[1,9-16,18-20,22,24,26-28,30,33,34]

Discussion

MacGibbon was the first to conduct a study, in 1972, that associates age of the diagnosis of imperfect amelogenesis and nephrocalcinosis. The case of a young woman diagnosed with both pathologies was described when her 26-year-old brother died of nephrocalcinosis and teeth similar to her own. In the reported cases, renal function remained stable until the patient was 16 years old, but progressive renal insufficiency led to the death of the patient.[10]

Nearly 40 years after the publication of the MacGibbon case report,[11] Jaureguiberry *et al*.[22] identified autosomal recessive *FAM20A* mutations as the cause of ERS. The study consisted in the genetic analysis of 25 patients from 16 families affected by the syndrome. As a result, all patients had biallelic mutations in *FAM20A*, with 20 different mutations. This gene, under normal conditions, has an inhibitory effect on mineralization, allowing it to occur only in bones and teeth. But in patients with homozygous mutation in *FAM20A*, an increase in the promoter activity and decrease of the inhibitory activity on the growth of oxalate crystals has been reported, so as to allow mineralization of the gingiva, kidneys, lungs, and dental follicles.[8,9,19,22,25,27]

Laboratory alterations are not always present and, when exist, are varied. Hypocalciuria was identified in 11.59% of the cases,[1,7,12,15,29] being common in patients with ERS, although hypercalciuria is an important cause of stones formation.[35] Hypocitraturia was found in 5.79% of the cases.[15,28,30,34] This alteration predisposes the formation of renal stones or nephrocalcinosis, because the citrate acts in the formation of soluble complexes with calcium, inhibiting the formation of renal stones.[30] The reduction of phosphate excretion was also identified in 5.79% of the cases,[1,12,15] as a consequence of the mutation on *FAM20A* that changes calcium and phosphate homeostasis in the kidneys.[25]

The hereditary relationship of the syndrome can be observed because there was consanguinity in 18 cases,[1,6,14-17,19,22-24,26,29,31,32] indicating a percentage of 26. 08% and family history in 30,[6,11-15,17,19,22-26,31,34] that is, 43.47%. Another relevant fact is the lack of relationship with gender, since it affects almost equally men and women. The relationship between the syndrome and the mutation in the *FAM20A* gene can be proven from the data, since all the patients with ERS analysed by the mutation were positive.

Some studies[3,7-9,14,16,17,20,21,27,30-32,34] cited the nationality of the patients and, according to these data, there was no association of a certain geographic area with the occurrence of the syndrome. The countries of origin were: Iran,[3] Caribbean,[3] Jordania,[3] England,[7] Turkey,[8] France,[9]

Macedonia,[14] Brazil,[16,20,30,31,34] Japan,[17] India,[21] Israel,[27] and Thailand.[32]

With the advancement of studies on ERS, it has been suspected to have some associations with the syndrome. Kantaputra *et al.* reported in 2014[26] two patients who presented, simultaneously, ERS and AI and gingival fibromatosis syndrome (AIGFS). Knowing that *FAM20A* gene is involved in both, the genetic study of the patients was carried out, confirming the presence of the mutation in the cases. Besides that, as several studies have cited the triad of AI, nephrocalcinosis, and gingival fibromatosis, the authors suggested that ERS and AIGFS would be the same entity with different manifestations, giving rise to the new term "Enamel-Renal-Gingival Syndrome".[9,27,31]

In 2016, Pêgo *et al.*, related two cases that presented typical features of ERS, such as hypoplastic AI, nephrocalcinosis, gingival overgrowth, and other dental abnormalities, besides the presence of *FAM20A* mutation. Both patients also presented hearing loss and hypertrichosis, without the presence of exposition to environmental factors and mutations frequently associated with nonsyndromic deafness in Brazil. Thus, the study suggested the association with ERS, *FAM20A* gene, hearing loss, and hypertrichosis as expansion of the phenotypic spectrum of the disease.[29]

With the data obtained from the discovery of the disease with Mac Gibbon until the last studies, it was possible to trace the profile of the patients with ERS and the main alterations found. There is equivalence between the genders and absence of predilection by any age group. The main laboratory findings were hypocalciuria, hypocitraturia, reduction of phosphate excretion, and elevation of serum creatinine levels. The presence of the hereditary character of the syndrome and the relationship with the *FAM20A* gene were also confirmed. But there is still a need for further studies to increase knowledge about the syndrome and its newly discovered phenotype expansions.

Conclusion

Among the data analyzed, it is possible to emphasize an equivalence of cases in men and women, excluding a possibility of any association with gender and the presence of ERS. The *FAM20A* gene was a finding of great relevance for the syndrome, since all patients with clinical characteristics have homozygous or heterozygous mutations in this gene.

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Conflicts of interest

There are no conflicts of interest.

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