

# Enamel Renal Syndrome: A Scoping Review Protocol

Imaan Amina Roomaney (✉ [iroomaney@uwc.ac.za](mailto:iroomaney@uwc.ac.za))

University of Western Cape Faculty of Dentistry <https://orcid.org/0000-0001-6789-5484>

Salma Kabbashi

University of Western Cape Faculty of Dentistry

Manogari Chetty

University of the Western Cape

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## Protocol

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# Abstract

**Background:** Enamel Renal Syndrome (ERS) (OMIM # 204690) is a rare autosomal recessive disorder characterized by hypoplastic amelogenesis imperfecta (AI), failed tooth eruption, intra-pulpal calcifications, gingival enlargement and nephrocalcinosis. The rarity of the condition and the variability of the phenotype has led to ERS not being fully characterized. This scoping review aims to account for the range and current state of knowledge on ERS and synthesize these findings into a comprehensive summary, focusing on the pathophysiology, genotype-phenotype correlations and patient management from a dental perspective.

**Methods:** The authors will conduct a systematic search of PubMed (MEDLINE), BioMed Central, EbscoHost Web, Web of Science and WorldCat. We will include all studies with human participants with a confirmed diagnosis of ERS. Articles will be screened in two stages i.e. initially by title and abstract screening and then full-text screening by two independent reviewers. Data extraction will be conducted using a customised electronic data extraction form. We will provide a narrative synthesis of the findings from the included studies. We will structure the results according to themes.

**Discussion:** Dentists should be able to identify patients with clinical features of ERS so that they receive appropriate referrals for renal evaluation, genetic counselling and oral rehabilitation to increase the patient's quality of life. A scoping review is the most appropriate method to conduct this comprehensive exploration of the current evidence which may be sparse due to the rarity of the condition. It will also enable us to identify gaps in the research.

**Registration:** This study is registered with the Open Science Framework (OSF) (<https://osf.io/cghsa>).

## Background

Enamel Renal Syndrome (ERS) (OMIM # 204690) is a rare autosomal recessive disorder characterized by hypoplastic amelogenesis imperfecta (AI), failed tooth eruption, intra-pulpal calcifications, gingival enlargement and nephrocalcinosis (1). In 1972, MacGibbon described a condition presenting with renal dysfunction and enamel hypoplasia in several members of the same family (2). Although there has been an increasing number of publications about ERS in recent years, the rarity of the condition and the variability of the phenotype has led to ERS not being fully characterized.

Several phenotypes have been identified under various terms, including amelogenesis imperfecta syndrome, AI with inter-radicular dentine dysplasia, AI with odontogenic fibroma-like hamartomas around non-erupted teeth, AI with gingival fibromatosis (AIGFS) (3), MacGibbon syndrome, and Lubinsky-MacGibbon syndrome (4). The lack of strict diagnostic criteria has led to patient's renal status being overlooked within those phenotypes, along with underestimation of the actual disease prevalence (3). This rare genetic entity accounts for less than 1 in 100,000 individuals of the global population, with only 70 cases in 50 different families being documented at present (5).

Recently, high throughput genetic technologies such as whole-exome sequencing (WES), next-generation sequencing (NGS), and bioinformatics analysis implicated mutations in FAM20A (FAMily with sequence similarity 20A) as the defective gene in “Amelogenesis Imperfecta and Gingival Fibromatosis Syndrome” (AIGFS) (OMIM #614253). A comprehensive review of AIGFS clinical aspect delineated a similar distinctive oral phenotype to ERS (6). It is believed that both syndromes reflect different phenotypes of the same disease with frequent renal dysfunction association in the ERS (3). More than forty homozygous or combined heterozygous FAM20A mutations have been identified in families (Human Gene Mutation Database, HGMD®). The protein encoded by FAM20A gene is secreted by ameloblasts, odontoblasts, gingival and dental pulp cells, reflecting a crucial role during enamel development and gingival homeostasis (1, 7).

Generally, ERS patients seek dental management as the initial chief complaint relates to the lack of enamel and failure of permanent tooth eruption at a young age (6). A review by de la Dure-Molla and colleagues (3) suggested a distinctive pathognomonic oral profile for ERS patients (Table 1).

Table 1  
Common oro-dental features of ERS according to de la Dure Molla et al (3)

<b>Generalized thin hypoplastic or absent enamel</b>
Primary and permanent teeth affected
Flat cusps on posterior teeth
Relative microdontia and spaced teeth
Intra-pulpal calcifications
Delayed tooth eruption
Impacted posterior teeth with hyperplastic follicle (hamartoma-like) and altered eruption pathway
Root dilacerations of impacted teeth
Gingival fibromatosis (variable severity)
Gingival and dental follicle ectopic calcification on biopsies
Semi-lunar shape of central incisor edge
Crown resorption of non-erupted teeth
Anterior open-bite
Root hypercementosis and inter-radicular dentine dysplasia
Supernumerary teeth

In addition to the “common profile” of ERS, several atypical features have been reported in the literature. Pêgo *et al* (8) reported an association of hypertrichosis and hearing loss in two ERS patients. Hearing

loss is a common feature of Rain syndrome, a syndrome caused by FAM20C mutation. This may explain the presence of such a feature in ERS (8). A few characteristics which are considered atypical manifestations in individuals with ERS have been documented in a study conducted by Dourado *et al* (1). These were malocclusion, periodontal disease, supra-incisive diastema, and intellectual disability. One study documented a case in which all the permanent teeth had erupted which is considered highly atypical of ERS (5).

It is clear from the growing list of atypical features of ERS that there is still much that is not known and poorly understood about ERS. The present scoping review aims to account for the range and current state of knowledge on ERS. These findings will be synthesized into a comprehensive summary, focusing on the pathophysiology, genotype-phenotype correlations and patient management from a dental perspective. The authors also aim to elucidate research gaps to inform future research and provide a useful summary for clinicians treating patients with ERS.

## Methods

We will undertake this scoping review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension for scoping review guidelines (9). This study is registered with the Open Science Framework (OSF) (<https://osf.io/cghsa>).

## Research questions

The primary research question is, “what is known from the existing literature about the oro-dental features of ERS”. The research sub-questions are as follows:

1. Which methods are employed to diagnose ERS?
2. What is the clinical and radiographic finding in patients with ERS?
3. What are the oral histological findings in patients with ERS?
4. What phenotype-genotype correlations have been established?
5. What guidelines exist for dentists and dental specialists managing patients with ERS?
6. What gaps in the literature exist regarding ERS from the dentist's perspective?

## Information sources and search strategy

The authors will perform a search of the following online databases: PubMed (MEDLINE), BioMed Central, EbscoHost Web, Web of Science and WorldCat. Additional studies will be sought using the reference lists of included studies and searching Google Scholar. An example of the search strategy is presented in Table 2. The search will be tailored to each database. The search will be limited to title and

abstracts to find studies focused on ERS. No other limiters will be used in the search. References will be managed in Zotero reference manager software.

**Table 2**  
**Example of Search Strategy to be used in this study**

Database	PubMed (Medline)	
Date	23/07/2020	
Limits	None	
No	Search	Result
1	enamel renal syndrome[Title/Abstract] OR FAM20A[Title/Abstract]	52
2	((ENAMEL-RENAL-GINGIVAL SYNDROME[Title/Abstract]) OR (AMELOGENESIS IMPERFECTA, HYPOPLASTIC, WITH NEPHROCALCINOSIS[Title/Abstract])) OR (AMELOGENESIS IMPERFECTA[Title/Abstract] AND GINGIVAL FIBROMATOSIS SYNDROME[Title/Abstract])	19
3	amelogenesis imperfecta type IG[Title/Abstract]	1
4	#1 OR #2 OR #3	60

## Inclusion criteria

This scoping review will include all research related to our objectives. All primary studies will be included, and review articles will be used for hand-searching of reference lists. No restrictions will be placed on the timeframe, language or grey-literature. The population of interest will be limited to human participants (of any age) with a confirmed molecular or clinical diagnosis of ERS. ERS (OMIM #204690) is also known as Amelogenesis Imperfecta type IG or AI1G, Enamel-Renal Gingival Syndrome, Amelogenesis Imperfecta and Gingival Fibromatosis Syndrome (AIGFS), and Amelogenesis Imperfecta with nephrocalcinosis. ERS is caused by homozygous or compound heterozygous mutation in the FAM20A gene (gene number 611062) on chromosome 17q24. The oral clinical features of ERS are considered to be pathognomonic (3) thus, a clinical diagnosis is considered acceptable for inclusion.

## Study selection

Articles will be screened in two stages i.e. initially by title and abstract screening and then full-text screening by two independent reviewers (SK and IR). Any failure of consensus will be resolved by a senior third party (MC). The degree of agreement between reviewers for each of these steps will be quantified with a kappa statistic with a 95% confidence interval.

# Data items and extraction

Data extraction will be conducted by each reviewer independently (IR and SK). An electronic data extraction form will be custom-made for this review, piloted and amended as required. The data collection form will include the fields in Table 3.

Table 3  
Data extraction fields

<b>Study information</b>	<b>Author(s), title, year of publication, journal</b>  <b>Study setting</b>  <b>Study design</b>
Study population	Sample size  Baseline characteristics, demographics  Any additional abnormalities or medical conditions  Any therapies that the patients might have received
Enamel Renal syndrome	Method of diagnosis  Family history of the condition  Genetic variation
Outcome	Prevalence of ERS  Molecular findings  Clinical findings- intraoral, extraoral, haematological and other biomarkers, Nephrological, other findings  Radiographic findings  Transcriptomic findings of oral tissues  Dental ultrastructural findings  Any additional findings

# Synthesis of results

We will provide a narrative synthesis of the findings from the included studies. We will structure the results according to themes in the following manner to provide a coherent summary of findings: characteristics of included studies (location, study design); baseline characteristics of the participants/population e.g. age and sex; the prevalence of ERS; methods of diagnosis; clinical findings- oral and

extraoral; radiographic findings; histological findings; nephrological findings; atypical findings; biomarkers; genotype-phenotype correlation; atypical/ novel findings, additional findings.

## Discussion

The present scoping review aims to determine the current state of knowledge on ERS and synthesize these findings into a comprehensive summary, focusing on the pathophysiology, genotype-phenotype correlations and patient management from a dental perspective. We also aim to identify research gaps to inform future research and provide a useful summary for clinicians treating patients with ERS.

ERS is a rare disorder and not much awareness exists around the condition, even within the dental fraternity (10). Conversely, AI is a relatively common disorder of enamel formation encountered by dentists and often occurs as an isolated trait, or part of a syndrome (1). Because dentists are often the first point of call for these patients, it is important that the dentist is able to identify patients with ERS and differentiate it from AI so that they receive appropriate referrals for renal evaluations and genetic counselling (5). It is also important to provide the patient with oral rehabilitation to increase the patient's quality of life, which can be severely impaired by this condition (5). Primary failure of eruption is difficult to manage, and there is no current literature about assisted eruption with orthodontic traction in patients with ERS (10). It does appear that the normal eruptive process of teeth is altered leading to impaction and ankylosis (10). Progressive embedding of the teeth has also been reported (5). Therefore, orthodontic treatment may be unpredictable. Current management involves surgical interventions and the placement of a fixed or removable dental prosthesis (11, 12). There is a need for guidelines on the dental management of patients with ERS and the development of referral protocols.

Identifying patients with ERS may not be as straightforward as it was previously believed to be. According to de la Dure-Molla *et al* (5), the oral features of ERS described in Table 1 are considered pathognomonic. However, more recent studies have found significant variability in phenotypes including identifying a patient with a pathogenic variant of the FAM20A gene and a full complement of erupted permanent teeth (5). Therefore, a review is needed to consolidate this growing body of evidence and present it in a manner that is practical for the dental clinician. We believe that a scoping review is the most appropriate method to conduct a comprehensive exploration of the current evidence, which may be sparse due to the rarity of the condition. It will also enable us to identify gaps in the research.

## List Of Abbreviations

AI- Amelogenesis imperfecta

AIGFS- Amelogenesis imperfecta with gingival fibromatosis

ERS- Enamel Renal Syndrome

OSF- Open Science Framework

PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analysis

NGS- Next-generation sequencing

WES- Whole-exome sequencing

## Declarations

### Ethics approval and consent to participate

Ethics approval was not required for this study

### Consent for publication

Not applicable

### Availability of data and materials

Not applicable

### Competing interests

None to declare

### Funding

None

### Authors' contributions

SK and IR were jointly responsible for the development and write-up of this protocol. MC was responsible for the conception of the study and acted in a supervisory capacity. All authors read, edited and approved the final manuscript and are jointly responsible for the work.

### Acknowledgements

none

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## Supplementary Files

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- [ERSPRISMAPchecklist.docx](#)