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Phenotypic heterogeneity of non-syndromic supernumerary teeth: genetic study

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Abstract

Background: Numerical dental anomalies, through their phenotypic diversity and etiological complexity, represent a very topical chapter in dental practice. In Romania, there is no recent complex genetic study, regarding supernumerary teeth (ST), as a whole. *Patients, Materials and Methods*: In this research, through the specific genetic study of the phenotypic variability of ST, completed with clinical examinations and paraclinical investigations, to which statistical determinations were added, we performed a complex genetic-clinical and statistical analysis of ST, within a representative group, consisting of 574 patients, who came for specialized dental treatment, between 01/01/2018–05/30/2019, at the private dental offices (Lucky Dental), in Bucharest, Romania. *Results*: Following this study, it was possible to characterize the phenotypic variability of ST, to analyze the pattern of abnormality genetic transmission in the families of investigated patients, to identify people at risk, and specify the therapeutic conduct of choice, specific to each case. *Conclusions*: We consider this paper to be of interest for medical practice by bringing new, recent data on the current prevalence of non-syndromic ST, their clinical phenotypes, and the specifics of their genetic determinism in the studied population group.

Keywords: supernumerary teeth, genetic study, phenotypic heterogeneity, family tree, genetic transmission.

Introduction

Numerical dental anomalies, represented by all the changes that affect the normal number of teeth, either due to lack of dental agenesis or due to the additional presence of one or more teeth, supernumerary teeth (ST) [1, 2].

Numerical dental anomalies appear to be the result of local transformations that interfere with the induction and differentiation phenomena of the dental plate during the process of tooth development. The action of a causative agent on the dental plate or tooth buds can result in an alteration of the normal number of teeth [3].

The prevalence of ST in the general population is 0.3–3.8%, and in the Caucasian population it varies between 1% and 3%, the male being twice as frequently affected *versus* the female gender [4–9]. ST may be single or multiple, present unilaterally or bilaterally, with normal or altered morphology, erupted or included, and may affect both temporary and permanent dentition, located both in the maxilla, mainly in the anterior jaw in 62–90% of cases, as well as at the mandibular level, less often [10–14].

Despite the progress made in order to identify the teeth morphodifferentiation, relatively little is known about the etiology and especially the intimate, molecular, and cellular mechanisms that underlie the development of ST [15–17].

The complex, multifactorial etiology of ST development has been explained over time by multiple phylogenetic etiopathogenic concepts and ontogenetic etiopathogenic concepts [18]. Based on these concepts, numerous theories and assumptions have been issued, which partially explain the ST production mechanisms [19, 20].

The phenomenon of developing ST after the loss of permanent teeth, known as "post-permanent dentition" is very rare. It seems that most of the teeth that appear after the extraction of permanent teeth come because of the final eruption of a previously included tooth [21, 22].

The genetic transmission of ST can sometimes follow the autosomal model, but also the recessive model related to gender, a model that can explain the predilection of the male gender, to the detriment of the female gender [3, 19].

Although the etiology of ST is still uncertain, the results of epidemiological and clinico-immuno-genetic research have indicated with certainty that much of the dental pathology is genetically or epigenetically conditioned or modified and many of the dento-maxillary apparatus defects may be related only to some parts of it, or they may be a sign, sometimes pathognomonic, in a generalized syndrome [20].

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Aim

The general scientific objective of the research was represented by the genetic study of the phenotypic variability of ST, the possibility of integrating theoretical data in patient-oriented medical practice, from prevention to diagnosis and specific treatment, with implications in medical research.

The scientific objectives specific to the study were represented by determining the prevalence of ST in the study group, characterizing the distribution by age groups and gender of patients with ST, genetic study, characterization, and illustration of phenotypic heterogeneity of ST, in cases with the hereditary transmission, followed by the comparison of the results obtained in the present study with the data from the specialized literature.

Patients, Materials and Methods

The study was performed on a representative group of 574 Caucasian patients, of Romanian nationality, residing in Bucharest or in the surrounding areas, who came between 01/01/2018–05/30/2019 for a dental consultation and specialty treatment in the private dental offices (Lucky Dental) in Bucharest, Romania, to whom were presented and explained all the data contained in the informed consent of the patient and all the elements related to the confidentiality of the medical act and research, as well as personal data protection.

Study group

The study group was made according to the study inclusion/exclusion criteria. For this reason, there were included in the study group, patients with ST in temporary and/or permanent dentition, children, and adults, belonging to both genders, aged between seven and 50 years, who accepted the inclusion in the study and who did not give up the study during its progress.

Patients with uncooperative ST who refused to be included in the study, patients who did not have ST, and patients who dropped out of the study during its development were excluded from the study group.

Following the research of the 574 patients included in the initial group, we found that seven patients met the inclusion criteria in the study group.

Protocol of clinical evaluation

The protocol of clinical evaluation of patients with ST in order to correctly diagnose their phenotype included the following stages of clinical and paraclinical examination: exobuccal and endobuccal clinical examination of the patient, with analysis of each dental unit and notation of dental abnormalities, radiological examination with intraoral film (retroalveolar film radiography), radiological examination with extraoral film (orthopantomogram), cone-beam computed tomography (CBCT) and photographic examination. Diagnostic extraoral and intraoral medical photographs were taken with a high-performance camera and performed with the consent of patients or close relatives, in the case of children, after being informed about the protocol and procedures to be followed. Most of the time, we used special soft parts spacers to take intraoral photos, to make it easier to see all the teeth, but in some cases, to minimize the anxiety induced by the patients, we took these photos without using the spacer.

Evaluation protocol specific to the family genetic study

The evaluation protocol specific to the family genetic study of patients with ST was represented by the family survey, the elaboration, and the analysis of the genealogical tree. In the family survey, for each patient with ST (proband), we completed a standard form called “sheet for congenital malformations and hereditary diseases”, in which we recorded the patient’s identity, anamnestic data, results of the general clinical examination on devices, and systems, local oro-maxillo-facial examination results, the laboratory results, paraclinical and specific genetic examinations, as appropriate. Based on these data, we established a positive diagnosis of certainty for the patient. Next, we extended the family survey to other family members, looking for whether any of them have or have had the same dental abnormality as the proband or similar dental abnormalities.

Based on the data contained in the file for congenital malformations and hereditary diseases, we proceeded to the next stage, represented by the construction of the family tree with the help of conventional international signs. The graphic representation of the genealogical tree began with the positioning of the proband, followed by the graphic representation of the members of the direct ascending, descending, and collateral affiliation.

The analysis of the genealogical tree materialized in the diagnosis of non-hereditary forms of ST and the diagnosis of hereditary forms of ST with the establishment of their mode of genetic transmission, in the studied family.

Statistical evaluation protocol

The statistical evaluation protocol of patients with ST, completes the study, through statistical analysis of results and computerized data processing. The data we collected from the patients’ files were systematically ordered, statistically computerized, tabulated, and graphically illustrated, allowing a more accurate interpretation of the obtained results.

Results

Following the research performed for the group of 574 patients, we calculated the ST frequency, which registered a value of 1.21%. Regarding the age distribution of patients with ST-type dental anomalies, almost half were children (43.75% of cases), aged between seven and 17 years (three cases, all male). The study of the gender distribution of patients with ST-type dental anomalies revealed: 57.14% male gender (four men) and 42.85% of patients belonged to female gender (three women). So, the prevalence of ST-type dental anomalies was 1.33 times higher in males compared to females. This result is also explained by the fact that almost half of the

patients diagnosed with ST were children, aged between seven and 17 years, and this age group is particularly represented in the study group, only by patients belonging to the male gender.

In patients with ST-type dental anomalies, we recorded a significant difference in the location of the condition, in the upper arch, or the lower arch. Thus, in most cases (85.71%), ST were located only at the maxilla, the mandible being affected in a small percentage, of only 14.28% of cases (Figure 1).

ST present unilaterally recorded a significantly increased incidence, being diagnosed in 85.71% of cases (six patients), compared to ST located bilaterally, which we found only in one case (14.28%) (Figure 2).

We also analyzed the type of dentition in which ST were identified, and we found that, in most cases, ST were detected in permanent dentition (six cases, representing 85.71% of patients) (Figure 3).

Regarding the number of ST present per studied case, in 85.71% of cases, one patient presented a single ST, this being the most common form (Figure 4).

In total, in the study group of patients with ST-type number dental abnormalities, we highlighted eight additional teeth. Most ST (75%, representing six teeth) belonged to the permanent dentition, and only 25% (two teeth) belonged to the temporary dentition. Single ST were the majority, being found in 75% of cases (six teeth), while multiple ST were found in only one case (25%) (Figure 5).

We also found that most ST (75%, representing six cases) were included ST (Figure 6). Erupted ST were met in just one case (25%), being teeth resulting from bigemination (Figure 7).

The groups of teeth at which we encountered the highest number of ST were the maxillary teeth (87.5%), respectively the upper frontal group (four cases, totaling a number of five frontal ST), followed in their frequency descending order by teeth from the upper lateral group (two cases, 25%) and teeth from the lower lateral group (one case, 12.5%).

The most common dental number anomalies of the ST-type that we identified were the following: bilateral supernumerary upper central incisor included in the temporary dentition (one case, 14.28%), single supernumerary superior lateral incisor erupted in the permanent dentition (one case, 14.28%), single superior supernumerary upper third molar included in the permanent dentition (one case, 14.28%), single supernumerary superior central incisor included in the permanent dentition (one case, 14.28%), single superior supernumerary canine included in the permanent dentition (one case, 14.28%), single supernumerary lower third molar included in the permanent dentition (one case, 14.28%) and upper supernumerary second premolar included in the permanent dentition (one case, 14.28%).

The study of heredity, family survey, elaboration, and analysis of the genealogical tree of patients with ST-type dental number anomalies, included in the study group, identified the isolated, sporadic character of this dental number anomaly, suggesting in most cases, a *de novo* spontaneous mutation.

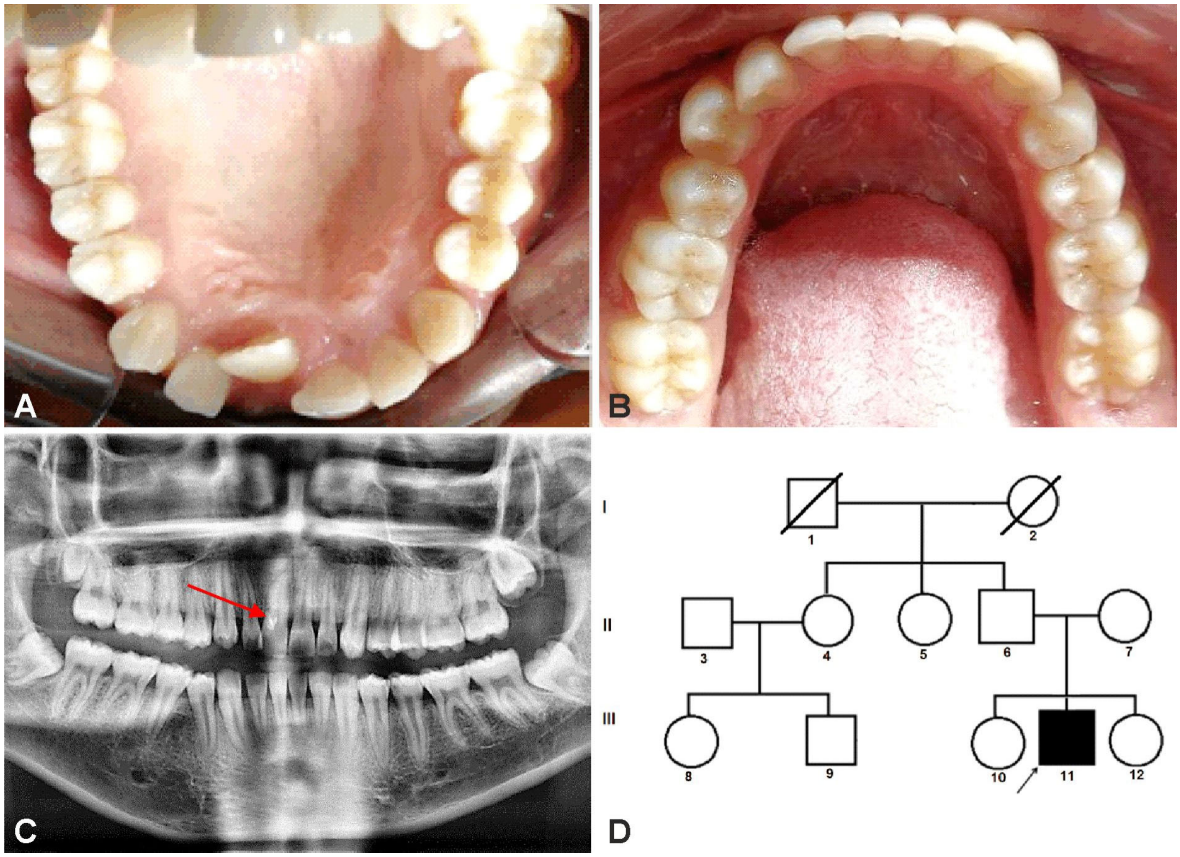

Figure 1 – ***Supernumerary upper central incisor (1.1 bis) – isolated, sporadic, non-hereditary, nonsyndromic case (16-year-old boy). Intraorally occlusal views: upper arch (A) and lower arch (B) denoting the clinical dental phenotype; panoramic radiograph showing the supernumerary tooth (C); the family tree: isolated, sporadic case (D).***

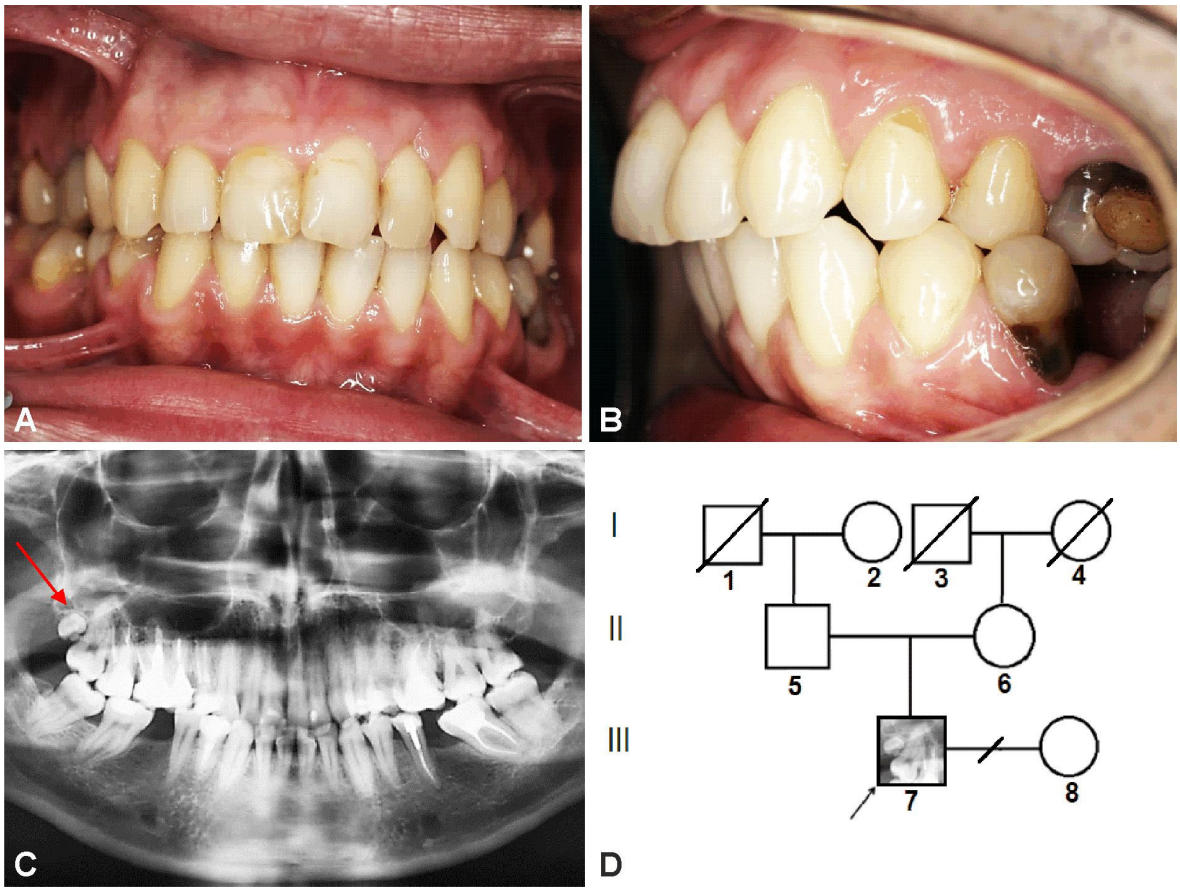

Figure 2 – ***Impacted upper permanent distomolar (1.8 bis) – isolated, sporadic, non-hereditary, nonsyndromic case (33-year-old male). Intraorally in occlusion: frontal (A) and lateral (B) views revealing the clinical dental phenotype; panoramic radiograph showing the supernumerary tooth (C); the family tree: isolated, sporadic case (D).***

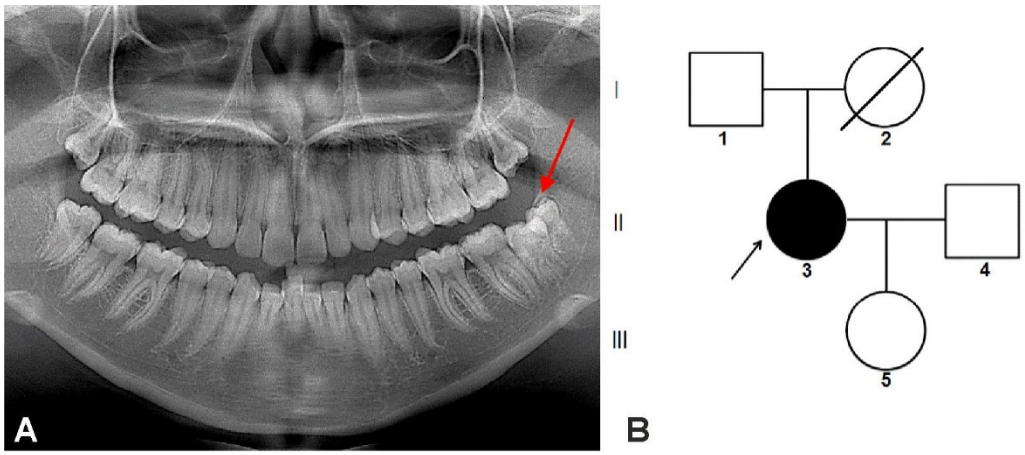

Figure 3 – ***Lower permanent distomolar (3.8 bis) – isolated, sporadic, non-hereditary, nonsyndromic case (32-year-old woman). Panoramic radiograph showing the supernumerary tooth (A); the family tree: isolated, sporadic, non-hereditary case (B).***

Discussions

ST is a complex pathology, which raises, through the many negative occlusal, esthetic, and functional consequences, a series of problems for both the patient and the physician. Thus, patients with ST have a variety of clinical and psycho-emotional problems, which are mainly determined by the physiognomic appearance.

ST have been defined as teeth that numerically exceed normal dental formulas, regardless of their position and shape [23]. In terms of terminology, most authors use the name ST or hyperdontia [24]. Other names encountered in the literature are additional teeth, polyodontia, additional teeth, post-permanent teeth, extranumerical teeth, additional dentition, or polydontism [25–27].

The prevalence of ST varies between 0.003 and 0.008 in temporary dentition and between 0.15–0.35 in permanent dentition [28].

The complex etiopathogenesis of ST development, still uncertain, is materialized by the existence of an

important genetic component, which suggests that it would not be a simple, Mendelian heredity but a polygenic, multifactorial heredity [29]. Multiple theories issued over time, such as atavistic theory, third dentition theory, multiple adamantine bud theory, dental blade hyperactivity theory, dental bud division theory, adamantine epithelial evagination theory, and delayed abnormal proliferation of paradental epithelial remnants, only partially explain the complex phenomenon of ST [30–32].

Recent research on the intimate, molecular mechanisms involved in dental embryogenesis has identified the role of the genetic component in odontogenesis. Thus, it appears that heredity plays an important role in the etiopathogenesis of ST, and especially of multiple ST and bilateral ST, whose development is induced by the existence of abnormal mutant alleles. However, non-syndromic multiple STs, as a family character, are very rare, which means that, at this time, despite the progress made, knowledge related to initiation, molecular mechanisms, and genetic control of ST development is still limited [33].

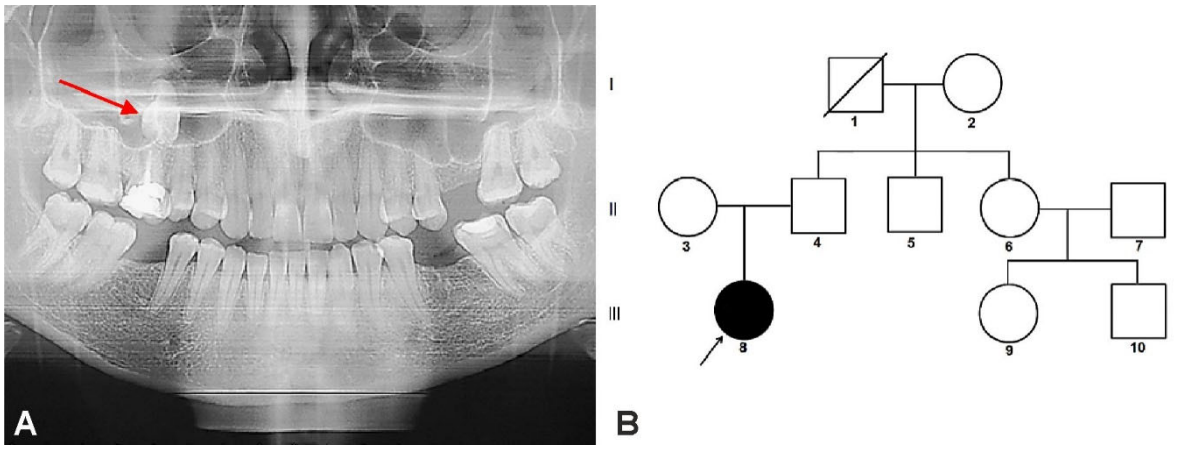

Figure 4 – ***Impacted upper parapremolar (1.5 bis) – non-hereditary, nonsyndromic case (58-year-old woman). Panoramic radiograph showing the supernumerary tooth (A); the family tree: isolated, sporadic case (B).***

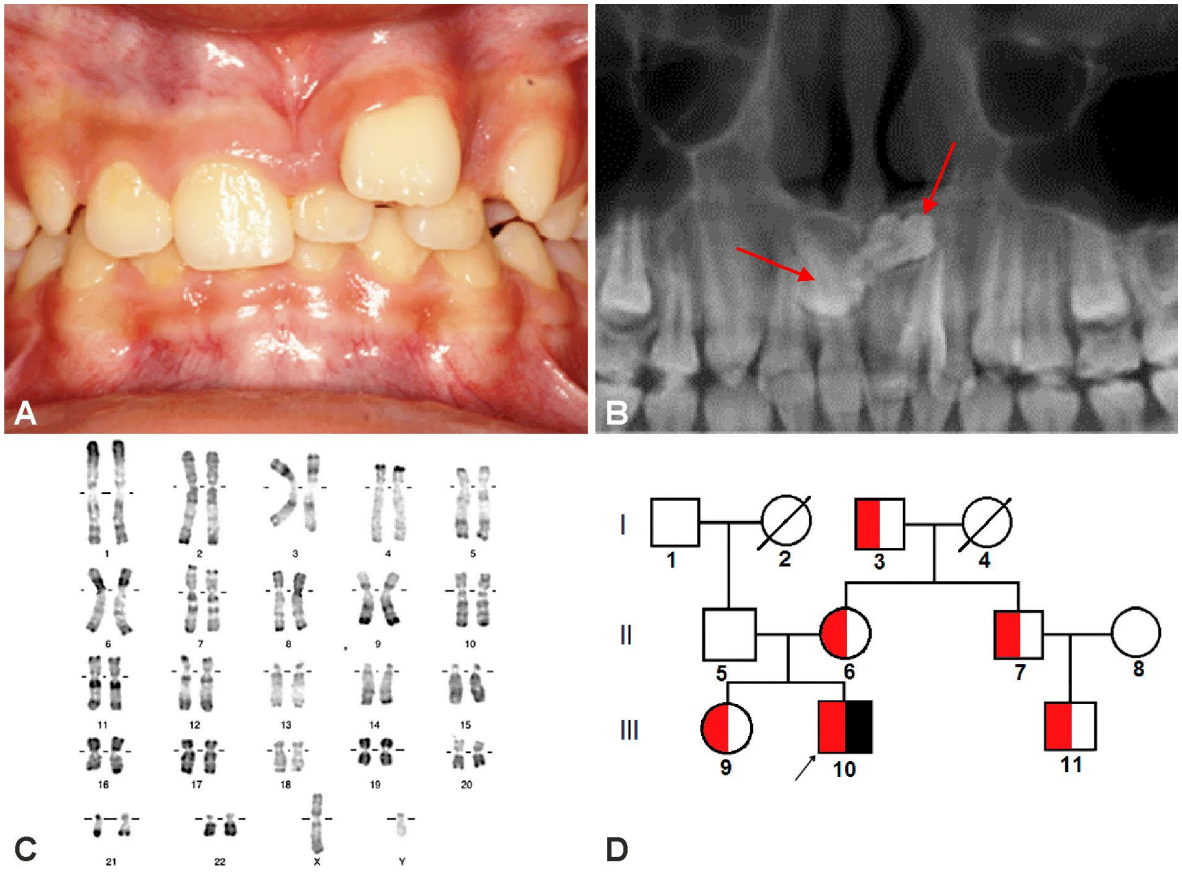

Figure 5 – ***Supernumerary teeth: upper anteriors deciduous teeth (mesiodens) – isolated, sporadic, non-hereditary, nonsyndromic case associated with dental crowding, familial character, expression variability (12-year-old boy). Intraorally frontal view in occlusion reveals the clinical dental phenotype (A); panoramic radiograph: location of the two supernumerary upper anteriors (B); karyotype 46,XY: normal male (C); the family tree: isolated, sporadic case (D).***

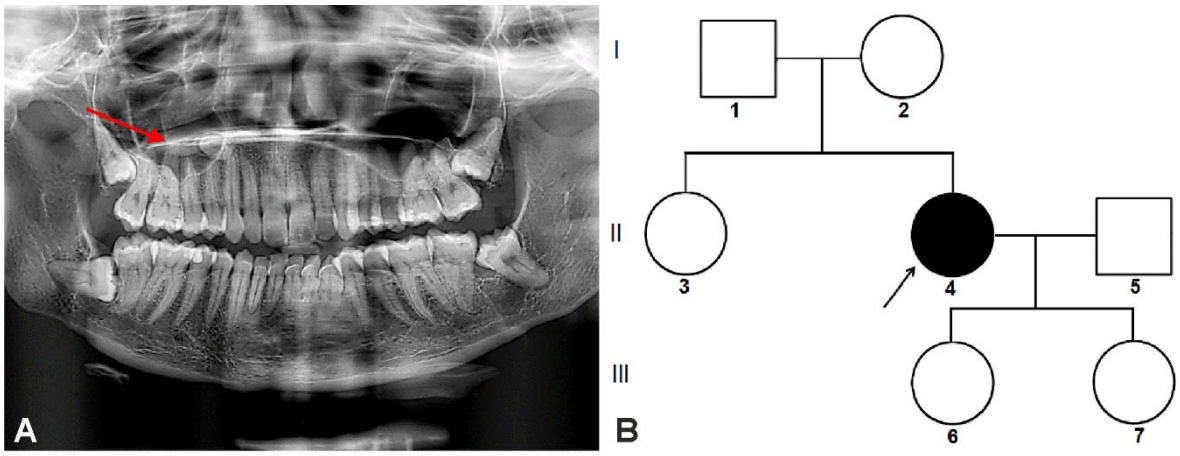

Figure 6 – ***Supernumerary upper permanent canine (1.3 bis) – isolated, sporadic, non-hereditary, nonsyndromic case (41-year-old woman). Panoramic radiograph showing the supernumerary tooth (A); the family tree: isolated, sporadic case (B).***

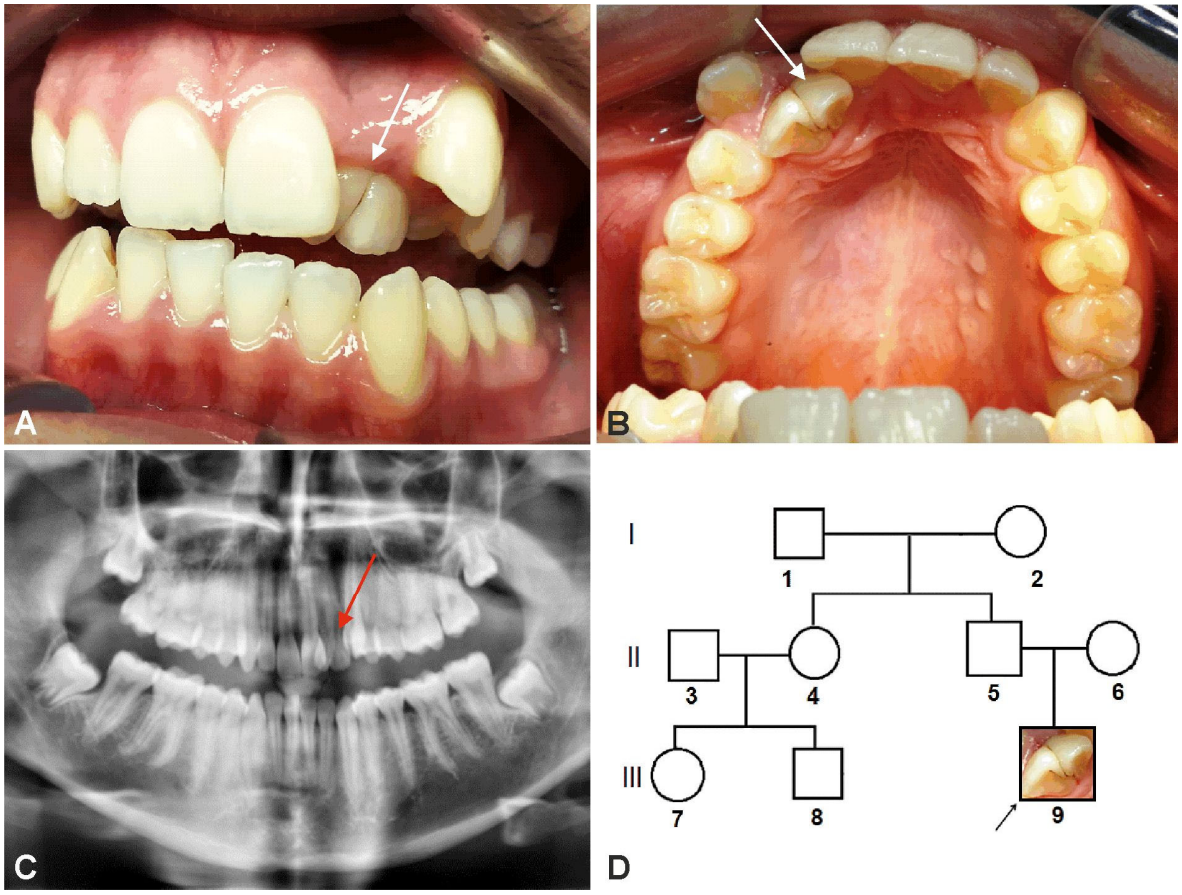

Figure 7 – ***Supernumerary upper permanent lateral incisor because of gemination (2.2 bis) – isolated, sporadic, non-hereditary, nonsyndromic case (15-year-old boy). Half-lateral intraorally view with teeth separated (A) and occlusal intraoral view of upper arch (B): clinical dental phenotype and particular appearance of the upper arch; panoramic radiograph showing the supernumerary tooth (C); the family tree: isolated, sporadic case (D).***

From a morphological point of view, ST are represented by ST that have morphological characteristics similar to those in the normal series, and dysmorphic ST, with atypical morphology: tuberculate, conical, or molariform [30, 34, 35]. After their localization on the arch, ST are represented by mesiodens – the most common form, paramolar – a rare form of ST, distomolar – small, rudimentary ST with different shapes, and parapremolar – ST duplicated premolars [36–38]. In relation to the number of ST present in addition to the arch, single ST is described, the most common form, in 76–86% of cases, and multiple ST, less common, which can be located unilaterally or bilaterally [14, 39–41]. Most often, single ST are non-syndromic, as opposed to multiple ST which are most commonly encountered in genetic syndromes, constituting the so-called syndromic ST [42]. Multiple ST exceptionally appear to be non-syndromic ST, the case presented by us in Figure 5, being one of the extremely

rare cases of isolated, sporadic, non-hereditary, and non-syndromic ST [43].

ST can be found both in temporary dentition, less often, in which case it affects both genders equally, and in permanent dentition, in which case the male gender is mainly affected [5, 44, 45]. ST can be included or erupted, syndromic or non-syndromic [41, 42].

In Europe, studies have shown that most ST were located in the anterior region of the maxillary, being represented in descending order of their frequency by mesiodens, maxillary incisors, and mandibular incisors, the results obtained by us being consistent with the data presented in the literature [8, 46, 47].

The clinical phenotype of ST is extremely varied. As a result, unique ST may have a normal or abnormal, dysmorphic configuration, a situation in which they may have the appearance of mesiodens or may be inverted teeth, with an intraosseous, inverted position [48, 49]. Multiple ST, phenotypically, can be fused or geminated, disorganoplastic ST of the "dens in dente" type or supernumerary dental inclusions represented by odontomas, the case presented by us in Figure 7, being one of the very special cases of non-syndromic ST as a result of gemination [18, 50].

In Romania, there is no recent complex global research on the ST study as a whole. An important statistic, referring to the study of dental number anomalies, which also included cases of ST, was performed many years ago, between 1990–1996 at the Orthodontic Clinic in Bucharest. Some of the results obtained in this study were consistent with the data mentioned in the literature; others were specific to the investigated group. Another research, somewhat more recent, dating from 2007–2010, refers to the study of a group of patients with ST in western Romania [46]. Those studies followed the clinical-statistical aspects of ST, without making considerations and conducting specific and detailed genetic studies to illustrate the involvement of genetic or epigenetic factors in ST determinism.

The research of the genetic component in ST determinism, research that we deepened in this study, is a difficult, complex, and exciting topic of great relevance, which allows new studies in the field and up-to-date scientific research, in order to prevent complications.

Conclusions

The prevalence of ST in the study group was 1.21%, 1.33 times more common in males, and half of the diagnosed patients were children, aged between seven and 17 years. Regarding the clinical phenotype, ST were detected, in most cases, in the permanent dentition (85.71% of patients), were included ST (75% of cases), located unilaterally (85.71% of cases), with predilection at the level of the upper arch (85.71% of cases), and more precisely at the level of the upper frontal group (87.5% of cases). In most cases, patients had only one ST (75% of cases). The importance of the involvement of genetic factors in the etiology of ST has been demonstrated by the genetic study of heredity, it has identified the isolated, sporadic, non-syndromic nature of ST, suggesting as a cause a spontaneous *de novo* mutation or a disorder of non-genetic odontogenesis. The complex clinical-genetic and statistical study illustrated the phenotypic heterogeneity of non-syndromic ST, allowing the assessment of ST recurrence risk in offspring, by identifying the mode of disease genetic transmission in affected families, allowing early diagnosis and favorable resolution of clinical cases.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Romina-Christiana Pavlovici has equal contributions to this paper as the first author.

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