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Dentistry

"TOOTH AGENESIS: A REVIEW OF MOLECULAR BASES"

Luciani F.	"Tor Vergata" University of Rome School of Medicine and Surgery "Oral Surgery" Specialization
Papa E.	"Tor Vergata" University of Rome School of Medicine and Surgery "Oral Surgery" Specialization
Costantini R.	"Tor Vergata" University of Rome School of Medicine and Surgery "Oral Surgery" Specialization
Condò R.	"Tor Vergata" University of Rome School of Medicine and Surgery "Oral Surgery" Specialization
Prof. L. Calabrese	Director and chief, "Tor Vergata" University of Rome School of Medicine and Surgery "Oral Surgery" Specialization

ABSTRACT Both recent progresses reached in molecular genetics and "Genoma Umano" project have collected positive results for the identification of those different genes involved in pathogenesis of human race pathologies. Just like any other medicine branch, dentistry could profit from molecular biology recent progresses, showing several answers to unknown questions. This knowledge also concerns genesis of pathologies interesting tissues (enamel, dentin, pulp, cementum), teeth formation and development.

Our work aims at verifying, by means of a literature review, the current knowledge and the state of art of dental agenesis molecular bases, in order to better understand the etiopathogenetic role of inheritance and transmission of hypodontia.

Our literature review elaborates on dental agenesis biomolecular bases, in order to group in one review all the new findings in genetic field about dental anomalies, attempting to give the clinician more information to make easier to manage one of the most discussed surgical dental pathology.

KEYWORDS : agenesis, tooth and genetics, dental anomalies

INTRODUCTION

Both recent progresses reached in molecular genetics and "Genoma Umano" project have collected positive results for the identification of those different genes involved in the pathogenesis of human race pathologies. Just like any other medicine branch, dentistry could profit from molecular biology recent progresses, showing several answers to unknown questions. This knowledge even concerns genesis of pathologies interesting tissues (enamel, dentin, pulp, cementum), teeth formation and development. **(1)**

Tooth genetic diseases have been classified depending on the hill tissue (enamel, dentin, pulp or cementum), on the site-specificity (syndromic or non-syndromic pathologies) or depending on their mendelian pattern of hereditary transmission: autosomal dominant (AD), autosomal recessive (AR), or X-linked (XLR). Most frequent hereditary oral pathologies are those affecting teeth; hypodontia, supernumerary teeth, diastema and enamel formation defects are statically frequent in the majority of world populations (Fig.1). Despite of this high incidence, knowledge about aetiology and physiopathology of these diseases is still lacking **(2)**.

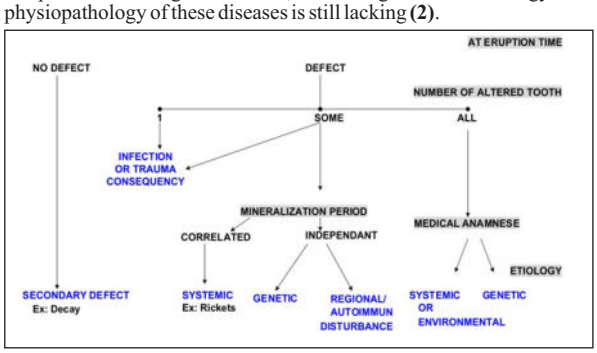

Fig. 1: Structural Defect of Teeth

Our work aims at verifying, by means of a literature review, the current knowledge and the state of art of dental agenesis molecular bases, in order to better understand the etiopathogenetic role of inheritance and transmission of hypodontia **(3)**. We employed "PUBMED" as Web search engine: this is a bibliographical database containing information about biomedical scientific literatures from 1949 till nowadays. It is produced by the National Center for Biotechnology information (NCBI) at the National Library of Medicine (NLM). The database is commonly searched to identify medical and chemical information. **(4)** With the Key-Word "agenesis", "tooth" and "genetics", we could observe 1798 articles concerning our research object, 28 of these only in the first semester of 2018. Systematic reviews are 246, only 3 of which from 2016 to 2019. In order to develop our research we have studied the 88 more recent and significant abstracts; among these we have selected 30 articles, which we were able to study thanks to the Digital-Library service of "Tor Vergata" 2nd University of Rome.

FROM GENE TO FUNCTION:

Before focusing on the heart of the topic, it's necessary to revise some concepts, distant from dental surgery clinical practise, but related to the transcription and translation processes which bring to the formation of the nucleic acids into cells. **(5)** Underlining the concept of gene, like a DNA portion codifying for a protein, we have to quickly revise what's happen during Protein synthesis, a molecular biology key passage. **(6)**

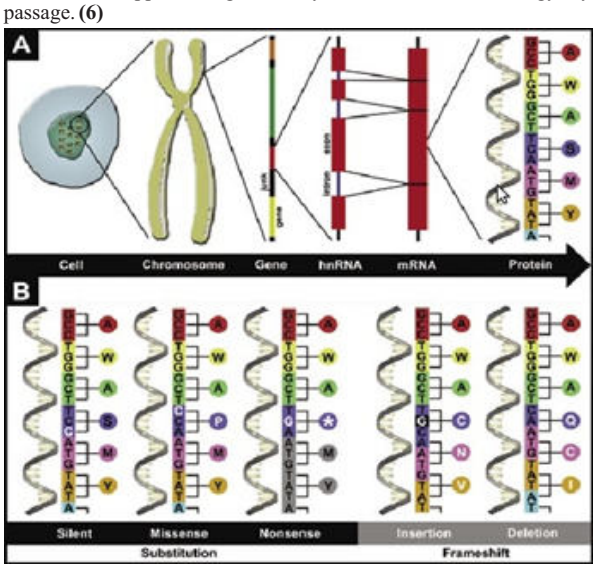

Fig. 2: Mutations Gene

The different phases of protein synthesis can be so outlined (Fig. 2):

I. The production of a specific protein is demanded to RNA

messenger;

II. DNA double helix opens itself in correspondence of the gene, which has to produce that specific protein. The DNA opening happens thanks to the presence of an enzyme, the RNA polymerase.
III. Nuclear free nucleotides bind the opened DNA complementary bases. In this way RNA messenger is transcribed. mRNA is transcribed starting from the DNA copy in the nucleus.
IV. mRNA (a single-stranded long molecule), which contains the code to synthesize the protein, subsequently migrates into the cytoplasm, on a ribosome, between the two subunits **(7)**.
V. RNA transfer is a single-stranded molecule, folded upon itself in order to form some handles, which are kept together thanks to hydrogen binds between complementary bases. The tRNA central part has a triplet, named anticodon. Anticodons pair with the mRNA complementary bases during protein synthesis. Each kind of tRNA catches a specific amino acid.
VI. Each tRNA is transferred by means of enzymes into the ribosome: here the mRNA codon pair with the tRNA anticodon. Inside the ribosome, two tRNA at time are processed because there are two sites for two amino acid triplets.
VII. In the cytoplasm there are several tRNA, which bind other amino acids. When codon and anticodon react a peptide bond is formed between the two tRNA amino acids that in that moment are been processed. When the bond between second and third amino acid is made, the first goes out from the ribosome and a peptide bond is obtained. In this way is formed an extending polypeptide chain, which will form a protein. **(8)**

ODONTOGENESIS OUTLINES

The layer that leads to the stomatognathic apparatus is the ectoderm. Ectoderm is the most outer layer because it undergoes to an invagination towards the mesenchyme generating a laminar structure called dental lamina, which is horseshoe shaped. Then ectodermal cells are into the mesenchyme. These changes happen around the sixth week of development. Each lamina, towards the internal or lingual side, will generate 10 proliferation centres, from where deciduous teeth are going to form.. (Fig. 3) Dental buds are then formed, being made from ectodermal cells, which get deeper inside the mesenchyme below. These structures are linked to the outermost ectodermal part by means of a tiny cellular chord, called "gubernaculum dentis". **(9)**

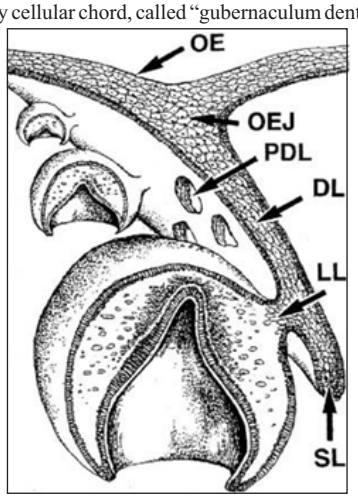

Fig. 3: Dental Proliferation Centre

Towards the eighth week, while epithelial cells keep on proliferating, the dental bud grows cap shaped. This structure is called enamel organ and it covers the mesenchymal cells below. The enamel organ is formed by an external and an internal epithelium. Between these two layers there is the enamel pulp, or stellate reticulum, formed by cells star-shaped. These cells are so shaped because cells are bound together by means of desmosomes, in a fluid environment, so that they stretch themselves getting that shape. In the same time, mesenchyme around the ectodermal formation starts an intensive proliferation producing the dental sac. **(10)** At this point, the evolution and the differentiation of the embryological components of the dental gem are complete. Subsequently cells differentiate from the internal epithelium into ameloblasts, which will form prisms and the whole dental crown enamel, originating the ectoderm.

From the dental papilla, cells differentiate into odontoblasts, which will form the dentin. Located below enamel, forming the tooth structural skeleton and the pulp, which is the soft tissue in charge of tooth vascularization and innervation. At last, periodontal tissues will origin from dental sac. These tissues will give the support and contact with alveolar bone. **(11)**

NUMBER ANOMALIES: ETIOPATHOGENESIS AND CLASSIFICATION

Dental anomaly is defined as an alteration of one or more teeth external appearance, inner structure or topography, due to a defect that could be genetically derived, congenic or acquired.

Etiological factors can be general (such as endocrine factors, metabolic disorders, chemical agents, infective diseases, genetic mutations, etc.), or local (such as traumas, surgery, dento-basal disharmonies and muscle derangements, etc.). **(12)-(13)**

Number anomalies can be classified in hyperdontia (supernumerary or supplementary teeth) and hypodontia. Our topic will be hypodontia, so that we will not discuss about hyperdontia.

Tooth agenesis is the congenital lack of one or more teeth. By definition, it is a dental follicle disease, which could suffer from several pathologic processes not allowing its normal formation: for example, follicle cannot develop due to a genetic defect, can stop its development due to external factors such as traumas, infections, nutritional deficiency, neuroendocrine diseases, toxic molecule exposure.

Deciduous tooth total absence is called agenodontia and it is a very rare event in humans. Agenodontia obviously involves the lack of both deciduous and permanent teeth, which develops from a gubernaculum dentis cellular proliferation; the lack of permanent teeth is called ablastodontia. Agenodontia and ablastodontia are two exceptional clinical conditions; they are always linked to other pathologies, inside serious genetic syndromes, and frequently not coexistent with life because the lack of dental development does not allow an upper aerodigestive tract regular growth.

Partial agenesis can be symmetric or random, classified depending on the missing teeth number: if missing teeth are more or less than hemi-arch the partial agenesis is called oligodontia and hypodontia.

Oligodontia is the lack of more than half of the normal dentition; it is possible to identify both oligodontia with the lack of more than 10 teeth in deciduous dentition and oligoblastodontia with the lack of more than 16 teeth in permanent dentition, commonly composed by 32 teeth. Hypodontia is the lack of fewer teeth than the half of the normal dentition; it is possible to identify hypogenodontia with the lack of less than 10 deciduous teeth and hypoblastodontia with the lack of less than 16 permanent teeth. Partial agenesis is a rare clinical condition too, often linked to genetic syndromes such as Crouzon syndrome, Down syndrome (21 trisomy) and Ellis Van Crevelt Syndrome, **(14).**

Single agenesis, the absence of a single tooth, is more frequent; the mostly involved teeth are the last of the series: upper lateral incisors, third molars and second premolars. In the last 50 years, the single agenesis incidence has widely increased, probably due to adaptive phenomena in the population, in which intercanine and intermolar diameters are continuously decreasing: this is a sign of a dental substance decrease instead of a neurocranium greater development. Several genetic studies link dental agenesis in females to an increased ovary cancer incidence, while in males to an increased large intestine cancer incidence. In broad terms, the moment a pathogenic agent hits the odontogenesis determines the pathology: if the event happens while the initial proliferation is taking place, the number of ectodermal thickenings (which dental gems will made from) will be different: hyperdontia or hypodontia; if the pathologic agent hits while the hystodifferentiation is taking place, different pathologies, linked with tooth shape, dimension and appearance will appear. **(15)-(16)**

TOOTH DEVELOPMENT MOLECOLAR BASES

While the sixth-seventh week is taking place, from the initial dental bud, due to a proliferation of those cells forming the cord which binds the bud to the oral epithelium, a son-bud is formed, which diphyodont teeth will originated from. Simultaneously, a prolongation with other 3 buds per hemiarch is originated from dental lamina; these buds will form monophyodont teeth. If a diphyodont deciduous bud does not

form, the corresponding permanent tooth cannot be formed; so if there is a deciduous tooth agenesis, there will be the corresponding permanent tooth agenesis too (Fig. 4).

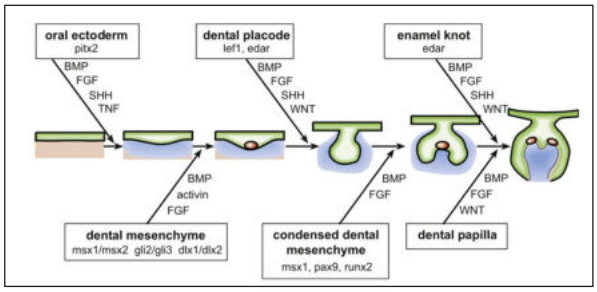

Fig. 4: Molecular's Odontogenesis

The complete lack of deciduous teeth can stand for a critical problem occurred during the dental lamina formation. Hence, neither monophyodont teeth will be formed. **(17)** Tooth agenesis is the most common human craniofacial malformation. More than the 25% of world population is affected by the lack of at least a third molar.

Incidence of Permanent tooth agenesis, with the exception of third molars, ranges from 1.6% to 9.6%, depending on studied population. This anomaly can involve deciduous dentition too, but with lower incidence (from 0.5 to 0.9%). Most people affected by hypodontia (80%) lack one or two permanent tooth; generally, the last in the series, (second premolar and lateral incisors). Nevertheless, about the 1% (0.08-1.1%) of population is affected by hypodontia. **(18)**

Tooth development is an elaborate process that involves molecular interaction between primitive dental lamina epithelium, arisen by neural crest cells, and the mesenchyme below. At first, primitive tooth epithelium expresses signal molecules that induce below mesenchyme proliferation (Dental Placode Stage). Then odontogenic potential moves towards dental mesenchyme, which has been activated by primitive dental lamina epithelium. The produced mesenchymal factors direct all the dental bud morphogenetic modifications, comprising those molecular factors that induce future tooth crown shape. **(19)**

Epithelial-mesenchymal odontogenic interactions produce a cascade of molecules which involve receptor signals FgF, Bmp, Shh, Wnt, etc. Possible disorders of the right evolution of these molecular signals can cause odontomorphogenic defects, producing dental anomalies of number (hyperdontia or hypodontia), of dimension, of morphology and of cytodifferentiation of the several cellular clones that are into dental bud. Animal studies, especially those carried out on mice, have been crucial for the comprehension of the genetic principles at the bottom of hypodontia. It seems difficult to recreate, in an animal affected by oligodontia, a phenotype that presents hypodontia in few generations; however, despite of these substantial differences between mice and humans, the odontogenesis first phases are mostly similar. **(20)**

Employing techniques of molecular genetics in mice, researchers highlighted in several knockout species a phenotype that had a tooth agenesis. Dental development stops at bud stage for Pax9, Msx, Pitx2, Gli2/3, p63 and Lefl gene, while for Dlxl/2 the development will stop at upper molar formation. On the contrary, the lack of Activin β a expression originates an opposite phenotype, with the loss of lower molars and incisors, while the upper molar right development. Denaturation and consequent non-working of these molecules causes dental development interruption, even in humans with clinical appearance of agenesis. **(21)**

ANOMALIES OF NUMBER MOLECULAR BASES

While the sixth week of development is taking place, an oral epithelium cellular clone migrates towards the primitive dental lamina in order to form the dental bud, which develops going deeper in the mesenchyme below. Mutual interactions between epithelial and mesenchymal tissues manage dental development process.

While this process leads to differentiation of deciduous teeth, the peduncle binding enamel organ to dental lamina produces an expansion, which follows the same differentiation process and leads to the formation of permanent teeth.

A dental lamina distal extension provides for monophyodont teeth. Mineralization of tooth calcific structures lasts for 14-18 weeks and crowns of the 20 deciduous teeth are mineralized at birth. Studies on dental development, mostly employing mouse teeth, revealed that tooth position, number, dimension and shape are genetically controlled.

Tooth development starts from molecular signals of dental lamina epithelium. Once these signals are received, mesenchyme is appointed to manage epithelium morphogenesis. Enamel organ works like a great regulation centre of the signals involved in the dental shape regulation. **(22)** While odontogenesis is taking place, epithelium and mesenchyme interact by means of several signal molecule families. These include T.G.F.-β, B.M.P., fibroblast growth factors (F.G.F), epidermal growth factors (E.G.F.) and SHH and WNT molecular families. In addition to these signals, Thesleff proposed model includes different genes too, governed by tissue answer signals. It has been observed that mutations in much of these genes can cause dental development defects both in mice and in humans. A tooth is defined genetically missing if it does not erupt in the oral cavity and it does not appear in radiographies. **(22)** At birth, the test of Van der Linden apical region reveals each deciduous tooth and lacunae holding permanent first molar gems are radiographically visible. Oligodontia is often linked to real genetic syndromes, such as different kinds of ectodermal dysplasia, where developed teeth are often small and shapeless. A meta-analytic statistic study shows that permanent tooth agenesis incidence differs depending on sex and on sample origin; prevalence for both sexes is higher in Europe (male 4.6%; female 6.3%) and in Australia (male 5.5% and female 7.6%) than North American people (male 3.2%; female (4.6%). Dental agenesis prevalence in females is 1.37 times higher than in males. Lower second premolar is the most involved tooth, followed by upper lateral incisors and upper second premolar. **(22)**

Unilateral agenesis is more frequent than bilateral agenesis; however, upper lateral incisors bilateral agenesis is more common than lower lateral incisors bilateral agenesis. Upper dental arch agenesis prevalence is comparable with the lower one, but there is a statistically significant difference depending on the involved tooth.

Several studies on dental agenesis in upper dental arch revealed that anodontia of permanent teeth is determined by an homozygote status of the gene in charge of the presence or absence of maxillary incisors. **(23)**

Although the great part of dental anomalies are caused by genetic factors, lot of environmental factors, such as chemotherapeutics and radiations, can disturb the right dental development. Some studies on families of affected patients by dental anomalies show that both hypodontia and oligontia can be transmitted with dominant autosomal trait with incomplete penetrance and variable expressivity. **(23)**

The reduction of lateral incisor mesio-distal diameters are often linked to second premolars agenesis. Frequency and heredity pattern of lateral incisors agenesis, or their mesio-distal diameter reduction, suggest that there are different expressions of autosomal-dominant trait gene.

Several researches let the identification of gene expression domains that can determine dental development. Msx1, Msx2, PAX9 are expressed in the supposed region for incisor development; AXIN2, Barx1, Dlx1 and Dlx2 are likely to be expressed in the region for molar development. **(22)**.

GENES INVOLVED IN HYPODONTIA

MSX1

MSX1 human gene is formed by two exons; the second exon has a homeodomain which binds DNA and makes the interactions between MSX1, PAX9 and other odontogenic molecules, such as AXIN2, Eda, Edar, Nemo, BMP, SHH, etc. easier.

The first scientific demonstration of the correlation between MSX1 and hypodontia has been shown thanks to genetic analysis carried out on families of subjects affected by upper second premolar and lower third molar agenesis. The gene has been localized on the chromosome-4 short arm (locus 4p16.1). (Fig. 5)

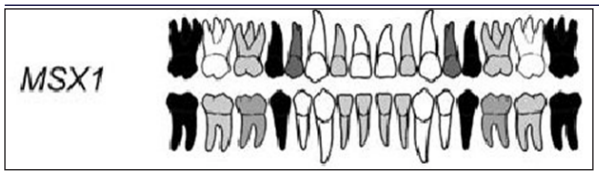

Fig. 5: MSX1 Anomalies

Then, sequences analysis confirmed the presence of an Arginine 31, responsible of a missense mutation in the MSX1 homeodomain. Three mutations on exon 1 and four mutation in exon 2 are linked with second premolar and third molar agenesis; moreover, genetic syndromes with agenesis (Witkop Syndrome) have been described being linked with maxillofacial clefts.

Mutations linked with MSX1 gene are transmissible with autosomal-dominant with incomplete penetrance inheritance pattern; however autosomal recessive patterns have been described. (Fig. 6) **(24)**

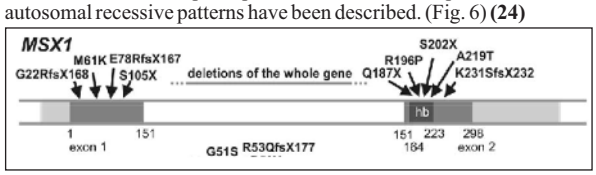

Fig. 6: MSX1

PAX9

PAX9 is a polymorphic gene localized on chromosome 14 short arm, probably responsible of hypodontia; it is involved in those molecular signs responsible of primitive dental lamina distal proliferation which induces monodiphyodont tooth bud formation. PAX9 gene is formed by codifying regions (exons) and by non-codifying regions (introns) highly preserved. Recently, 14 PAX9 different mutations affecting odontogenic processes have been described. (Fig. 7)

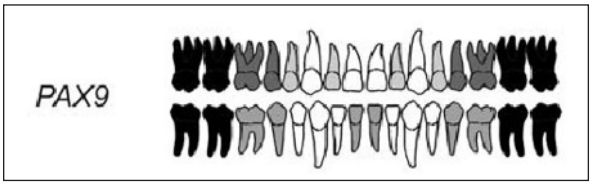

Fig. 7: PAX9 Anomalies

The structure of the gene consists of 5 exons. The first exon represents only 5'-untranslated region (UTR) while the following exons 2 to 5 contain 1026 bases (including the stop codon) encoding 341 amino acids constituting the human PAX9 protein. The initiation codon and the first base of the second triplet are the only coding elements of the second exon. The rest of the second exon is also a UTR. The most interesting protein element—the paired domain—is encoded in the third exon. The rest of the coding sequence and 3'-UTR are located in fourth and fifth exon. **(27)** (Fig.8)

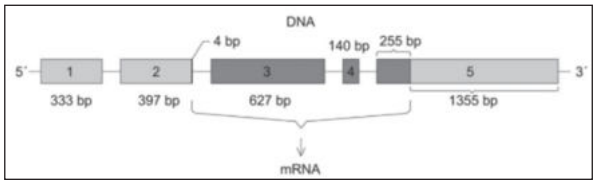

Fig. 8: mRNA and protein structure of the PAX9 gene.

The most relevant and studied exons are:

- Exon 2: Some authors suggested haploinsufficiency of PAX9 gene because of impossibility of the ribosome to initiate translation of the affected mRNA. In both cases, this resulted in non-syndromic oligodontia with similar patterns of missing teeth in the affected families. Most of the individuals lacked the first or second premolars and all permanent molars. In some individuals, at least one of the canines was missing and some teeth were "peg shaped". One of the families had only their permanent teeth affected with no apparent defects in the primary dentition.

- Exon 3: The first mutation in PAX9 gene associated with oligodontia was found in exon 3; this sequence represents by far the largest coding region of the gene. The exon 3 region has recently been the subject of in-depth studies. Several authors have carried out findings that appear to be in accordance with the proposed loss of function of PAX9 protein resulting in haploinsufficiency, thus plausibly explaining the altered odontogenesis.

- Exon 4: There is no unanimous agreement on the possibility that the mutations associated with exon 4 would lead to significant correlations with missing / malformed teeth.

- Exon 5: So far, only 1 mutation in exon 5 has been identified. This was present in all affected family members suffering from oligodontia. The mutation would have resulted in adding 51 nonsense amino acids followed by premature termination of translation. **(27)**

OLIGODONTIA WITH MSX1 MUTATION (4p16.1)

Mutations in MSX1 gene homeobox lead to a specific hypo or oligodontia. Second premolars and third molars are the most affected teeth. However, upper first premolar, lower first molar, upper lateral incisors and lower central incisors could also be affected. Primary dentition is usually regular. A MSX1 gene nonsense mutation is linked with tooth agenesis and, with several combinations, with maxillofacial development changes which lead to several maxillary-mandibular clefts. **(24)**

OLIGODONTIA WITH PAX9 MUTATION (14q12-q13)

Mutations in PAX9 gene transcription factor lead to permanent molar non-development, with the occurrence or not of hypodontia in deciduous dentition. Some subjects affected by this gene mutation have been observed; they were lacking of upper and lower premolars or lower central incisors.

The littlest teeth observed in affected subjects suggest that PAX9 is not only involved in tooth locating and development, but also in their right morphogenesis.

Several researches observed a certain correlation between genotype and phenotype in PAX9 mutations; missense mutations lead to milder phenotype in comparison with frameshift mutations. **(25)**

OLIGODONTIA WITH AXIN2 MUTATION (17q23-q24)

AXIN2 gene mutations have been often linked to colorectal cancer and to hypodontia in permanent dentition. (Fig. 9) Patients carrying this mutation express high risk of colorectal cancer onset and of molar agenesis. Deciduous dentition defects are very rare and they have been observed and described only in a young patient. **(24-25)**

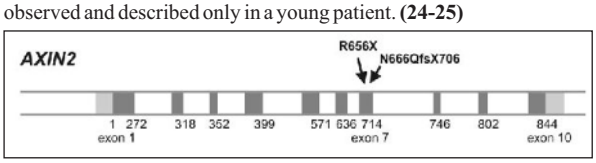

Fig. 9: AXIN2

OLIGODONTIA WITH KROX26 MUTATION (20q11.2)

He-Zhao deficiency is a Chinese children disease that manifests itself with a distinct kind of permanent tooth agenesis. Oligodontia is a pathology transmitted by means of autosomal-dominant with incomplete penetrance inheritance pattern. Affected subjects have a right deciduous dentition, followed by the lack of permanent teeth, first and second molars and upper central incisors excepted. Genic locus has been mapped on 10q11.2 chromosome. KROX-26, expressed during human dentition development, is a gene being potentially able to cause He-Zhao deficiency. **(26)**

OLIGODONTIA WITH EDA (ectodysplasin A) MUTATION

More recently, *EDA* was found to be involved in isolated hypodontia. Mutations in this gene cause X-linked hypohidrotic ectodermal dysplasia (*HED*), which is characterised by sparse hair, fewer and smaller teeth, and a lack of sweat glands. Several studies have reported sporadic hypodontia in families affected by mutations in *EDA* and *EDA* receptor gene. *EDA* has also been shown to be involved in missing maxillary lateral incisor cases. **(28)**

SYNDROMES LINKED TO HYPODONTIA

Teeth are highly specialized structures, being part of maxillofacial skeleton. They represent a very complex component both from

embryological and topographical-functional point of view; they actually are the only structures which have an inner-body part (root-alveolar bone) and an external part (crown-oral cavity), hermetically bound by means of one of the most fascinating structure in nature: periodontium. Tooth development involves a complex and delicate number of molecular cascade interactions between ectoderm, which forms primitive dental lamina, and below mesenchyme. **(24-26)** These biomolecular interactions generate a number of proliferation and cytodifferentiation reactions during embryonic development early phases, which are commonly known as the most delicate ones; obviously a pathogenic noxa, which carries out its damaging action during these phases, can generate a number of damages to the right embryo development, besides dental structure and subject's all genotypic and phenotypic inheritance. These damages can cause a number of real genetic diseases with many symptoms, among which dental anomalies are only a little peculiarity in comparison to the other more serious problems. **(26)** Patients with syndromic tooth agenesis can easily have other dental abnormalities that occur alongside the agenesis itself. These anomalies are in most cases: microdontia, short roots, dental impacts, delayed tooth formation, delayed eruption, transposition of canines and premolars, taurodontism and enamel hypoplasia. **(29)** (Fig. 10)

Common Syndromes and Conditions Manifesting With Tooth Agenesis

Syndrome or Condition	Dental Manifestation
Ectodermal dysplasia	Hypodontia, oligodontia, anodontia, conical teeth
Orofacial digital syndrome	Hypodontia, oligodontia, supernumerary teeth, dental malocclusion
Orofacial clefting (cleft lip and/or cleft palate)	Hypodontia, oligodontia
Pierre Robin sequence	Hypodontia, microdontia, supernumerary teeth
Van der Woude syndrome	Hypodontia, cleft lip, cleft palate
Apert syndrome	Hypodontia, enamel hypoplasia
Moebius syndrome	Hypodontia
Down syndrome	Hypodontia
Ellis-van Creveld syndrome	Hypodontia (incisors), conical teeth, taurodontism
Witkop tooth and nail syndrome	Hypodontia
Soto syndrome	Hypodontia (premolar), enamel hypoplasia
Wolf-Hirschhorn syndrome	Hypodontia, taurodontism, microdontia

Fig. 10

Our literature review revealed 159 genetic syndromes having hypodontia among the other symptoms. We are going to briefly present the 9 most statistically recurrent and significant syndromes.

1. **Down syndrome** (trisomy-21): Down syndrome is one of the most known diseases caused by an autosomes anomaly. Its name derives from John Langdon Down who described the syndrome in 1862, employing the term mongolism due to patient's face features, which remind those of oriental Asiatic peoples. In 1959 Jerome Lejeune discovered that Down syndrome is caused by the presence of an extra chromosome 21 (or part of it), then the trisomy 21 definition; in the 95% of cases the cause of this genetic anomaly is the chromosome non-separation, which happens during one of the meiotic divisions leading to the mother gamete formation; then the zygote will have a 47 chromosome arrangement, with a supernumerary chromosome 21 in each affected subject cell. Syndrome can also be caused by the robertsonian translocation, which happens in one of the parents: a fusion between a chromosome 21 arm and another acrocentric chromosome (usually the 14th). Subjects carrying this translocation are phenotypically normal, but they are likely to generate down sons. Down syndrome can affect each ethnic group, both male and female and manifest itself every 700-1000 born alive. Actual conceptions involving trisomy-21 are many more, but three out of four cases end up aborting or with death babies. If this would not happen the ratio would be roughly 1:200.

2. **Wolf-Hirschern Syndrome**: this syndrome mostly affect males (2.5:1), with an incidence of 1/35000 born alive; it is caused by the chromosome 4 subterminal region delection, where the MSX1 gene is located. Among general symptoms, there is a number of disorders affecting odontogenesis, causing tooth eruption delay, fusion between upper central incisors, oligoblastodontia and oligogenodontia.

3. **Holoprosencephaly**: is a congenital defect affecting slighlty more males than females (1.5:1), concerning an incidence of 1/20000 born alive. Genetic analysis led on these subjects reveal 19 different mutations, 7 genes being responsible; the most affected one seem to be SHH gene, localized on chromosome-7, locus q36. Classic phenotype identifying affected subjects is characterized by craniofacial development anomalies, rectum and sigmacolon stenosis and achalasia, with an upper central incisor agenesis and the unusual presence, perfectly median, of the contralateral homologous.

4. **Ectodermal Dysplasia**: development anomalies of ectodermal organs and tissues, characterized by anomalies of hair, nails and sudoriferous and sebum glands and by tooth anomalies, alone or linked to each other. It affects mostly females (3:1), with an incidence of 1/18000 born alive. Roughly 170 clinical kinds and over 30 genes involved have been described in literature; among involved genes: MSX1, PAX9, AXIN2, SHH and KROX26, each one combined with hypodontia.
   Researchers subdivided all the ectodermal dysplasia clinical kinds into 4 groups:
   a. Anomalies of the molecular sign exchanges among cells;
   b. Anomalies of cell-to-cell adhesion;
   c. Anomalies of genic transcription regulation;
   d. Anomalies of cellular and subcellular development.

5. **Hypohidrotic Dysplasia** (Incontientia Pigmenti): it is a genetic disease inherited with X-linked dominant transmission Mendelian model, fatal for males. It affects 1/46000 females born alive, which have tooth, eye and nervous system development serious anomalies. Responsible mutation is a deletion affecting the NEMO gene, which is an essential modulator of NFkB factor. Both deciduous and permanent dentition are affected, with the incisors and premolars agenesis and/or morphological development alteration, but it does not seem to affect monophyodont teeth, suggesting that chromosome-X and NEMO gene do not influence primitive dental lamina distal proliferation that forms molar teeth.

6. **Reiger Syndrome**: it is a genetic disease that could be transmitted in an autosomal dominant with incomplete penetrance pattern. It affects PITX2 transcriptional factor. Both females and males can be affected with an incidence of 1/56000 born alive. Different mutations have been identified, mostly affecting FOXC1 and GJAI genes. Even if rarely, missense mutations of PAX9 gene, on locus q12-13, on chromosome-14 short arm, have been described. The main clinical features involve eye anterior chamber, hypodontia both in deciduous and permanent dentition with canine and incisor agenesis; developed teeth have enamel hypoplasia, short roots and rarely taurodontism.

7. **Crouzon Syndrome**: it is an autosomal dominant diseases, belonging from craniosynostosis family, with an incidence of 1/45000 born alive and a slight prevalence for females (1.5:1). It consists in an early fusion of cranial sutures, middle third face hypoplasia and not very deep orbits with exophthalmos. Radiographically, cranium typically appears with a “hammered copper” appearance. Expanding encephalon is trapped inside the skull, which cannot expand itself due to the lack of fontanelles and the increase of endocranial pressure can lead to a cerebral damage and serious mental deficit. This is even a risk for blindness, which allows the early correction surgery of malformation (Le Fort 4 osteotomy moving the face forward). Symptoms are hypertelorism, exophthalmos, facial hypoplasia and syndactyly. This syndrome is caused by the mutation of FGFR2 gene. Treatment is only surgery; after surgery even an easy sinusitis is a risk factor for serious disease like meningitis.

8. **Ellis-Von Creveld syndrome:** this is a kind of ectodermal chondrodysplasia transmitted by an autosomal recessive pattern. Clinically presents the tetrad 1) chondrodystrophy, 2) polydactyly, 3) ectodermal dysplasia, 4) cardiac (and dental) anomalies. Syndrome incidence in general population is low (<1/350000 born alive), without any sex distinction.

   From the etiological point of view, responsible gene has been identified in p16 region of chromosome-4, next to gene codifying FGFR3 receptor, causing the classic achondroplasic phenotype in EVC patients. Prenatal diagnosis is based on the identification by means of ultrasound scans of skeletal anomalies, such as short limbs, polydactyly and cardiac anomalies; however, phenotype is

clear only after birth and its radiologically confirmed.
From the prognostic point of view, approximately 50% of affected patients die because of cardiac complications linked to those heart diseases appeared during first years of life.

9. **Wilkie syndrome**: it is transmitted by means of a dominant X-linked pattern, lethal for males, it affects females with an incidence of 1/80000 born alive. Mutation of BLC6 corepressor protein and missense mutation of BCOR gene (locus p11) are responsible for this syndrome. Microphtalmia, congenital cateratta, vitreous body primary hyperplasia, often linked with facial clefts, asplenia and/or deciduous and permanent dentition eruption delay.

NON SYNDROMIC HYPODONTIA

Tooth agenesis may show up in a syndromic form with the involvement of other organs or tissues, or in a non-syndromic form that only affects the dentition. Epidemiological studies indicate that the prevalence of non-syndromic tooth agenesis ranges from 1.6% to 9.6% in different geographical areas and races.

In non-syndromic agenesis the most important genes are: *AXIN2, EDA, LRP6, MSX1, PAX9, WNT10A* and *WNT10B.* PAX9 and MSX1, as said before, are the key to understand the molecular bases of tooth agenesis. They are both involved in the TGF-β/BMP pathway while AXIN2 is linked to the Wnt/β-catenin signaling. These two pathways, as well as Eda/Edar/NF-κB, are the three most common pathways involved in non syndromic Hypodontia. **(25)** (Fig. 11)

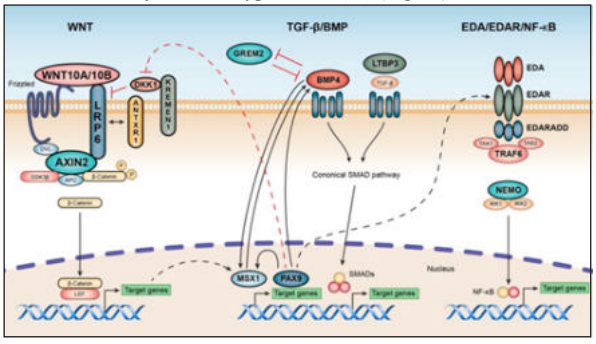

Fig. 11

It is clear how the key to understand the molecular bases of tooth agenesis is related to some specific agents, which are common for both forms (syndromic and non-syndromic). However, all these findings will need to be supported by studies involving larger populations in order to improve knowledge of these mechanisms.

FUTURE PROSPECTS

Recently, some researchers have brought new lymph to the study of the molecular basis of dental agenesis. They evaluated the possibility of using tooth agenesis as a predictive risk marker of malignant diseases in non-syndromic individuals. The reason behind this, as seen above, is that different genes and loci that are associated with non-syndromic developmental tooth agenesis have the same causation pathway in the development of tumors including breast cancer (BC), epithelial ovarian cancer (EOC), colorectal cancer (CRC) and lung cancer (LC). and the risk of cancer. However, the authors conclude that although the available evidence suggests a link, it has not yet been possible to demonstrate with certainty that tooth agenesis can hold a predictive value as a marker for cancers. **(30)**

CONCLUSIONS

Molecular biology recent progresses reached new horizons and a new knowledge about genetic code. The extension of known information within our DNA can largely improve knowledge on etiopathogenesis and therapy of several diseases affecting humans. Our literature review focuses on tooth agenesis biomolecular bases, trying to group in a single review all the new findings about genetics, helping clinicians with an easy guide to explain etiopathogenesis of tooth agenesis, which is one of the most discussed diseases in dentistry.

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