The Genetic, Epigenetic, and Environmental Factors of Dental Abnormalities Development: Literature Review

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Abstract. Proper anamnesis of clinical practice in giving clear diagnosis is important for specific possible dental care. Disturbance in tooth development by any aetiologic factors result in dental anomalies. The variation aetiologies of the dental anomaly are diverse but mainly caused by three main factors which are genetic, epigenetic, and environmental. From genetic mechanisms, where parents or siblings have a specific pattern of tooth, a bigger probability for an individual to have the same tooth pattern with his relatives, included gender differences. Based on epigenetic mechanisms, environmental chemicals, pharmaceuticals, aging, and dietary intake are a few factors that made up a tooth pattern. Repeated signaling molecules which received by protein receptor and induced by transcription factors between epithelial and mesenchyme in tooth development stages are relayed to transcript continued process of tooth development and become tooth anomalies. Orthodontists can be the ones to first diagnose and aware of the etiology and related characteristics with dental anomalies and further can cause malocclusion. An optimal and efficient integrated treatment plan of these anomalies should include the genetic profile of an individual to understand the developmental process and the aetiological factors for specific possible dental care. This paper aims to inform about the genetic, epigenetic, and environmental factors that involve in dental abnormalities development.

1. Introduction
The main anatomy of a living cell is the nucleus. In every cell, there are genes which will be transcripted by numerous factors. These transcription factors are activated by the signaling molecule that is received by the protein receptor, then relayed to activate express genes in the nucleus.[1] There are correlations of genetic, epigenetic, and environmental factors in the progression of individual tooth development, a group of teeth, and overall dentition. An orthodontist should pay more attention to little details especially the causes of malocclusion like size and shape anomaly of the tooth. The etiology behind it is diverse.[2] It includes molecular and cellular interactions which gave macroscopic outcomes upon the tooth. There are four different forms of human teeth and their macroscopic forms come from morphogenetic, reflecting the Spatio-temporal (three dimensions and temporary) control of development. Phenotype produces rare characteristics on specific mutations in members of a family, teeth in the same member, and teeth in a similar morphogenetic region.[3] Diversification of tooth morphology is not controlled by genetics only, but also several external factors like environment. These controllers will give enough impact to tooth developmental structure in number, size, and shape. Tooth development is multilayered and will continue or stop at a certain point. Thesleff in 2006 states that more than 300 genes influence the tooth development process. Most of those 300 genes interact as signaling molecules on tooth development, but there are 4 signals which are most studied: TGFb (BMPs and Activins), FGF,
hedgehog (Shh), and Wnt. Those 300 genes exist and communicate in dental development. Few signaling factors influence chain connections at the epithelial and mesenchymal layer, they are FGF (Fibroblast Growth Factors), BMP (Bone Morphogenetic Proteins), Shh (Sonic Hedgehog), Wnt (Wingless-Related Integration Site), and TF (Tumor Necrosis Factor). sequential and reciprocal between the ectoderm and mesenchyme and also regulate key transcription factors [4].

Tooth anomalies can be caused by a few factors. Mutation can cause dental anomalies regulated by certain genes. These repeated signaling molecules between ectodermal and mesenchyme are relayed to transcript continued process of tooth development and become tooth anomalies. Epigenetic of tooth development's genes can be the result of additional or removal of methyl cluster or also called demethylation and histone modification. These changes in gene expression will influence the phenotype of tooth structure without changing its nucleotide sequencing. Repetitive interactions at ectodermal and mesenchymal layers control every phase of tooth development from a place, amount, and structure of teeth included mineralization. Dental anomalies are regulated by a gene that is usually mutated. Factors that may be an issue in dental development is presented by abnormalities in clinical syndromes like Ectodermal Dysplasia. Epigenetics and environments are important roles in tooth growth and development accompanied by histone demethylase. Further, they control the differentiation of cells.[5] Good knowledge in the process of tooth development and anomalies is very important for a multidisciplinary clinical team in making an integrated treatment plan.

2. Discussion

2.1. Tooth Development

2.1.1 Initiation

The initiation process occurs by sending signals to mesenchyme, inducing specialized dental cells, and thickened oral epithelial on a region to be dental placodes as a site of tooth buds. Further, the oral epithelium sends Fgf, Bmp4, and other transcription factors such as msx (msh homeobox), lhx (LIM homeobox), and dlx (distalless-related) families to influence the location of mesenchymal expression. In return, Pax9 is created as a limb, tooth, and craniofacial development. This Pax9 is very important in morphogenesis. It can be mutated and influences molar teeth.[4][6] At the same time, Wnt and Bmp regulate interactions of mesenchyme and epithelium as tooth number pathway. Fgfs will then be identified as activators of bud formation and Bmps will be the inhibitors.[7] Tooth reduced size usually occurs without systemic conditions, but part of a syndrome. At Syndrome related mutations such as ectodermal dysplasia, the transcription factor named p63 causes the syndrome with a severe characteristic (phenotype) in the form of multiple missing and peg-shaped. At here the dental lamina will be thickened but the development site will fail to go further formation. This transcription factor also induces Fgf, Bmp, and Notch1 signaling. Other than that, the X-Linked mutation of Ectodermal Dysplasia causes Eda is encoded by Eda and Edaradd. This signaling will cause the formation and growth of dental placodes. If they are expressed and over-activated, they will be bigger than normal causing microdontia [4], [8].

The beginning of epithelium buds formation is the thickening of mesenchymal cells and the inducting signal center at the enamel knot. It expresses enough molecules of TGFb (BMPs dan Activins), Fgf, hedgehog (Shh), dan Wnt which required for shifting to cap stage as the formation of the tooth crown. It is again controlled by interactive signaling at the epithelial and mesenchymal layers.[9] Bmp4 on mesenchyme controls the enamel knot by regulating p21 expression. Wnt controls Fgf4 expression in the enamel knot. Fgf is then expressed to regulate cell differentiation around the tissue at the epithelial and mesenchymal layers.[10] The proliferation of the epithelium is signaled by Shh interacting with mesenchyme.[8] Msx 1 (Msh homeobox 1) and Osr 2 (Odd-skipped related transcription factor 2) act differently in molding tooth structure by controlling the gene's expression and deployment of mesenchymal odontogenic signals along dental placodes.[11] Msx1, Pax9, and Runx2 are transcription factors on mesenchyme controlled by signaling molecules at epithelium. Pax9 (paired box 9) and Runx2
(runt-related protein 2) are triggered by Fgf (fibroblast growth factor), and Msx1 (Msh homeobox 1) is triggered Fgf and in additional Bmp familial.[6], [11], [12].

2.1.2 Differentiation.
Differentiation occurs on the bell phase when the cusp structure has been finished, continued by odontoblast secretion. The odontoblasts produce dentinal components and epithelial differentiation becomes ameloblasts that produce enamel contents. Most enamel contents are gathered with proteins that produce the DSPP gene. Dpp, Dsp, and Dgp are produced by DSPP which in reverses expression from Tgf-β. Dpp will form hydroxyapatite and be molded by Dlx3. Osteoblasts in the form of tooth cells then become cells that control the stages of mineralization of tooth structure. Other than that, there is PTN (pleiotrophin) which is found in ameloblast and played as an important part of dentinogenesis [15].

2.2. Epigenetic Mechanism
The Histone modification with demethylase of Jmjd3 controls dental stem cells by differentiation. Jmjd3 will decrease signaling of dentinal contents at extracellular by bothering RNA. Jmjd3 also regulates the homeobox and BMP (bone morphogenetic proteins) signaling by DNA methylation. Certain gene's upregulation and downregulation effects will result in histologically and clinically on tooth structure development. For example in Peterkoya, 2006, hypodontia with or without the combination of microdontia (peg-shaped teeth) occurs in mammalian with a lack of Eda-signaling molecules.[16][17] Amelogenin at tooth development will be regulated by Dlx genes that will influence enamel forms. Enamel thickness is gained by Runx2 which inhibits the protein expression in its final phase.[18] After the normal forming of enamel thickness, histodifferentiation begins its root forming. The epithelium spreads to apical, then both of surfaces (in and out) are developed by odontoblast and cementoblast. Further, fibroblast and osteoblast are formed as a periodontal system located at the dental follicle [19].

2.3. Clinical Structure
The outcome of tooth development will be based on every interaction at epithelium and mesenchyme of signaling molecules, protein receptors, and transcription factors within specific initiation and maturation times. In this way, each tooth in the oral region of an individual will be on different phases. They may have the same developmental phase, but also can be a very different phase in a time. These all are seen in the complexity of the tooth structure, even from the anomaly. Not only by genetics, but these reflections are also in correlation with environmental and epigenetic factors that change the surrounding tissue. It can be from intake foods, drugs, or environmental chemicals that make up a tooth germ to be matured. The clinical structure of the tooth should be correlated to tissue alterations and molecular genetics, epigenetics, and environmental interactions. It also reflects its own in the morphogenetic area that affects the clinical phenotype [20].
2.4. Size and Shape of Developmental Anomalies
Continuous signaling on initiation and morphogenesis make up tooth anomalies in the form of structure. Its correlation has been compared to laboratory experiments in humans and models. Individuals with hypodontia often accompanied by microdontia. Lateral incisor and molar misshaping are often found as a companion of hypodontia with distinct tapered crown characteristics on lateral incisive and less cusp shape with more spherical on molar's occlusal.[22] Pax9 that is found in dental mesenchyme together with Msx1 is often mutated by missense. This kind of mutation is not always affected the same and has its protein interactions. Pax9 has a critical role in regulating homeobox proteins and major impacts on early tooth development.[23] Based on its cluster, Asian has the largest teeth especially in the anterior regions and Caucasians has large molar.[24] Individuals with Ectodermal Dysplasia frequently loose permanent dentition such as M3, P2, I2 upper, or I1 lower. This individual also reflects some kind of microdontia. Different teeth will express different degrees of tooth size reduction. Canine permanent is the most affected in tooth size if compared to others. In contrast with hypodontia, individual with extra teeth (supernumerary) has a bigger tooth than controls. It is seen if upper central incisors are affected compared to lower incisors. The shape will be more cylindrical seen from the labial [22].

Eda-signaling is one of the most important tooth size signaling to get it normal. The absence of Eda will cause the primary knot to be reduced and loose molecules' expression. In the return, the structure will be smaller in size and the cusp will be decreased in number.[26] The ectodin is expressed by BMP2 and BMP7 as a reaction upon controlling BMP's (bone morphogenetic protein) work in the ectodermal organ. The excitation of ectodin's spark by BMP is inhibited by Shh (Sonic hedgehog) and Fgf4
(fibroblast growth factor 4). Thus, ectodin plays an important role in determining tooth formation at its exact spatiotemporal domain around ectodermal signaling centers. Decreased ectodin will cause more Shh expression area with primary enamel knots with macrodontia (molars) and supernumerary teeth. These also happen the same with the spark of Edar receiver urged by K14. [14], [27] The study is confirmed by studies of Roman-British where women had more microdontia and hypodontia prevalence, and men had more macrodontia prevalence and supernumerary teeth. Other than that, this cluster had a smaller tooth than modern Britons because of genetics and environmental correlations.

2.5. Etiology of Tooth Anomalies

Until now, researchers still look for the exact pattern of tooth development based on its genetics, epigenetics, and environmental factors. These communications during tooth development are found, complicated clinicians. The etiology is multi in factors, levels, dimensions, and progress in a specific period. These factors play an important role in an individual. From genetic mechanisms, where parents or siblings have a specific pattern of tooth, a bigger probability for an individual to have the same tooth pattern with his relatives, included gender differences. Based on epigenetic mechanisms, environmental chemicals, pharmaceuticals, aging, and dietary intake are a few factors that made up a tooth pattern. Even when an individual is diagnosed to have a distinct mutation on his gene or there is an impact from the environment, the structure still has obvious differences between relatives and even dentitions in the same dentition. Mutations in some of the main genes are also occurred especially found in MSX1, PAX9, AXIN2, and EDA.[6], [14], [27] There are four main etiology of dental phenotype [13]:

- Multi-factors à Various factors to be considered are abnormalities in a chromosome, epigenetic effects, and broad changes in gene excitation, and environmental effects. They are the main causes of tooth development.
- Multi-level à Tooth development inductions and outcomes happen at a different level of studies: molecular, intracellular, and extracellular.
- Multi-dimensions à Interactions between molecules and cells included their results are multidimensions. The three-dimensional form of a tooth or also called Spatio-temporal structure in the developmental phases are impacted at various extents by specific genes, resulting in the individual tooth structure. They are controlled by signaling and also apoptosis in enamel knots. A substantial disruption over a while will cause an obvious anomaly in various teeth, depending on the development phase of each tooth bud.
- Progressive in a specific period à Period of a specific time is another important part of normal and anomaly of tooth development. Various genes give various phases of the differentiation process with switched on and off genes. The germ which is not going to develop further may undergo apoptosis.

These reiterative and continuous signaling paths in a specific period during the process of tooth development phases are seen in the macro-clinical structure of abnormalities.
Tooth growth and development are controlled by reiterative interactions in epithelium and mesenchyme. WNTs (Wingless-Related Integration Site), Fgfs (Fibroblast Growth Factors), TGFb, and Shh (Sonic Hedgehog) are factors in tooth development that control function exerting organogenesis signals. This signaling pathway is most likely seen by multilayers systems both in genetics and epigenetics. Ameloblasts from the epithelium and pulp dentinal complex from mesenchyme forms tooth structure.[4], [9] All of this tissue will proliferate with repeated signaling communications to form a mature tooth. Tooth anomalies can be subdivided based on tooth developmental stages: (1) Initiation and Proliferation: Number of teeth (supernumerary teeth or hypodontia), ectodermal dysplasia, germination, fusion, cleidocranial Dysplasia; (2) Histo-differentiation: Odontodysplasia; (3) Morpho-differentiation: Macrodontia, microdontia, dens invaginatus, dens evaginatus, Hutchinson's teeth, talon cusp, taurodontism, and dilaceration [13].

3. Conclusion
Orthodontists can be the ones to first diagnose dental anomalies which impact the anomaly of occlusion. The variations of dental anomalies' etiology in this paper are diverse but mainly caused by three main factors which are genetic, epigenetic, and environmental. An optimal and efficient integrated treatment plan will be obtained by early diagnosis. However, it makes it difficult to clearly define one or multiple factors which impact the anomaly of occlusion.

Acknowledgments
The authors wish to gratefully acknowledge financial support from the University of Indonesia to EIA.

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