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Precision dentistry in early childhood: the central role of genomics

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SYNOPSIS

Pediatric oral health, similar to other health conditions and traits, is determined by the interaction of environmental factors and genetic influences. This is the case for early childhood caries (ECC), the most common disease of childhood. The complexity of exogenous-environmental factors (e.g., knowledge, behaviors, cultural and social influences) interacting with innate-biological predispositions (e.g., large number of polymorphisms conferring small protective or deleterious effects) results in a remarkable continuum of normal variation, as well as oral health and disease outcomes. Optimal oral health and care or precision dentistry warrants comprehensive understanding of these influences as well as tools enabling intervention on modifiable factors. The article reviews the current knowledge of the genomic basis of pediatric oral health and highlights known and postulated mechanistic pathways of action relevant to ECC. Although validated and replicated loci and pathways remain elusive, the knowledge base of oral health genomics in early childhood is rapidly expanding.

Keywords

Children; oral health; dentistry; precision medicine; genomics

Early childhood caries and precision health care

During the last decades there have been remarkable improvements in our understanding of the underpinnings of children's oral health, including the fundamental proximal and distal determinants of oral diseases. Translating this body of evidence to actionable knowledge has not been realized to its full potential, and coordinated interdisciplinary efforts are warranted.[1] The elimination of oral health disparities should arguably be the first priority in any research and policy agenda.[2] A parallel and synergistic goal remains the development of

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optimal, personalized oral health care, tailored to individual profiles, risk factors and innate susceptibilities—a notion that has been termed “precision dentistry”.[3,4]

Precision dentistry is aligned with the precision medicine initiative—a contemporary approach in healthcare that takes into account individual differences due to people’s genetic makeups, environments and lifestyles. Initially, precision medicine was introduced in the context of cancer treatment but its longer-term aim is to inform healthcare, including health promotion, as well as prevention and treatment of chronic disease.[5] Although the concept is not fundamentally new (e.g., blood typing is a simple yet long-established practice) it has the potential to bring about catalytic changes in healthcare if informed by recent advances in genomics and other ‘omics applications. The demands for “more and better data” to support these initiatives are higher than ever, with the need for million-participant cohorts[6] and “deep” phenotyping[7] frequently articulated. Such biologically-informed data from population-based cohorts are still scant in the oral health domain, with few recent examples in periodontal research.[8,9] Early molecular evidence exists, however, to support individual differences to caries susceptibility and fluoride exposure[10] and predisposition to dental fear and anxiety;[11] both of which could inform the customized oral health care (e.g., periodic recall frequency and preventive care plans).

In the pediatric oral health domain, early childhood caries (ECC) persists as the most common chronic childhood disease with substantial human, economic and societal impacts.[12] The disease disproportionately affects minorities and socioeconomically disadvantaged families, who also face barriers of access to care. The problem of high disease burden combined with inadequate opportunities for prevention and treatment, referred to as a “twin disparity”,[13] has substantial social and economic implications, and directly impacts children’s oral health outcomes as well as the quality of their health care. It is unsurprising that despite decreases in the disease prevalence among other age groups, ECC rates have remained high. The overwhelming influence of social determinants of health is an undeniable reason for this trend.[2] With that important backdrop, other possible explanations for the persistence of this early-onset, aggressive form of childhood dental caries must look beyond established behavioral, environmental, and societal risk factors, and consider biological ones.

The heritability of ECC and genetic studies to-date

The notion of a genetic basis of oral traits and dental diseases including dental caries is not new. Early evidence from early twin studies[14,15] supports the heritability of dental caries, while more recent estimates of heritable variance in childhood caries explained by genetics are in the range of 40–70%;[16–19] and this susceptibility appears to be independent of sweetness preference heritability.[20] Despite an understanding of the importance of genomics for ECC, our knowledge on specific ECC risk-conferring polymorphisms is limited. Initial results from candidate-gene studies have highlighted genes involved in amelogenesis, immunity and sweet taste preference;[21–23] nevertheless, none of these early findings has been validated and replicated as a robust, risk polymorphism for dental caries or ECC, specifically. This is not surprising given the small sample sizes of most studies to date, the

fact that candidate-gene results tend to show very low replication rates in subsequent genome-wide scans, and other common research design limitations.[24,25]

Recent genome-wide association evidence

Genome-wide association studies (GWAS) offer an improvement over conventional candidate-gene studies— they entail the simultaneous interrogation (i.e., association testing with a trait of interest) of millions of single nucleotide polymorphisms (SNPs; variable areas of the genome) without being limited to specific areas of the genome due to prior hypotheses.[26,27] GWAS are not meant to provide answers regarding causal evidence or mechanistic explanations in complex diseases, but can highlight areas of the genome (i.e., loci) that offer promising candidates for further experimentation. The first-ever genome-wide association study (GWAS) of primary dentition caries (children ages 3–12) discovered suggestive evidence of association for 7 genetic loci,[28] two of which (*MPPED2* and *ACTN2*) were replicated in a subsequent investigation.[29] Additional key findings from this new line of research utilizing the GWAS methodology, is that genetic influences on dental caries may differ between the primary and the permanent dentition,[30] as well as between tooth surfaces (i.e., smooth versus pits and fissures).[31] Although these results will require further validation and replication, they may reflect different biological pathways in play, different interaction patterns with environmental exposures like fluoride and diet, or other unknown or unmeasured factors. In sum, this line of research so far underscores the importance of considering the intra-oral heterogeneity of dental caries susceptibility in the context of precision dentistry.[3]

It must be acknowledged that these early findings have been generated from non-minority populations (i.e., mainly of European descent) whereas only few children under the age of 6 (the upper age limit for ECC) have been included in the analytical samples. Although validated and replicated loci and genetic pathways for ECC remain largely elusive, the knowledge base of oral health genomics in early childhood is rapidly expanding and holds substantial promise. As the evidence base on the genomics of ECC widens, it is foreseeable that risk loci (i.e., gene polymorphisms, regulatory areas, or other functional elements of the human genome) will be discovered and validated as contributors to ECC—given the multifactorial nature and high prevalence of the disease, one may anticipate that a large number of loci each contribute to a small degrees to ECC resistance of development, according to the paradigm of Manolio et al.[32] The introduction and consideration of more biologically-informed endophenotypes and biological proximates[3,33] of ECC (e.g., microbial plaque metabolome and transcriptome, salivary proteome) in the GWAS context will help further elucidate the molecular basis of the disease pathogenesis, a necessary piece of the precision dentistry puzzle.

Genetic regulation of intermediate characteristics—endophenotypes

Genetic influences may be hard to identify when considering multifactorial clinical dental endpoints (e.g., a decayed, missing due to caries, and restored tooth surfaces index) that are affected by upstream factors, including access to dental care. However, the key regulatory role of the genome on oral and dental traits may be possibly discerned with higher fidelity

when considering more proximal, biological endpoints, often called “endophenotypes”. Such promising targets include dental anatomy, enamel quality, salivary properties, immunity, oral microbiome composition, and others.[3] From a mechanistic standpoint, the regulation of dental tissue (e.g., enamel, dentin, cementum and pulp) formation may be a first-target domain for the study of genetic contributions on both physiologic development and pathology. Accordingly, substantial progress has been made on the genetics front of ectodermal dysplasias and associated dental manifestations, including aberrations in tooth number (e.g., hypodontia and oligodontia), size and shape.[34–36]

Genomic control of odontogenesis

A recent investigation by Hu and colleagues,[37] found that thousands of genes are implicated in amelogenesis and dentinogenesis, with a subset of genes differentially expressed between these two developmental processes. Importantly, enamel is the dental tissue that is first affected by dental caries and one may expect that developmental defects of the enamel may predispose to ECC.[38] Wright and colleagues offer an excellent review[39] of genes and processes involved in enamel formation including cell differentiation, production and processing of extracellular matrix, altering of cell function during different stages of enamel formation, cell movement and attachment, regulation of ion and protein movement, regulation of hydration, pH, and other conditions of the microenvironment, and more. Unraveling the complexity and diversity of molecular pathways involved tooth development is certainly a key for the next steps in personalized, precise dental care—including bioengineering or regenerative dentistry applications,[40] even the prospect of dental rehabilitation via whole tooth regeneration.[41]

The genomic basis of other oral health traits

A model example of another, genetically-controlled condition with important oral health implications is the family of orofacial clefts—these birth defects comprise congenital malformations of the oral cavity and the face. The environmental and genetic underpinning of orofacial clefts has been the focus of major collaborative research efforts.[42] Although a comprehensive characterization of the genetic basis of various subtypes of orofacial clefts has yet to be accomplished, substantial progress has been made in the discovery of implicated genetic loci in diverse ancestral populations, as recently reviewed and reported by Dixon and colleagues.[43] Other conditions include ectodermal dysplasias,[44,45] and other issues related to histodifferentiation, apposition, and mineralization including amelogenesis imperfecta, dentinogenesis imperfecta, and dentin dysplasia—all of these conditions have profound impacts on the oral health functioning and related quality of life of affected individuals and require specialized, precise oral health care.[44]

Necessary steps to advance the science and practice of early childhood oral health care

The need for a solid evidence-base to advance the science and practice of dentistry is undeniable.[45,46] Above and beyond more and better data at all levels (from genes to communities), other features are equally important for an agenda that advances and

promotes oral health in childhood—these include but are not limited to interdisciplinary collaboration to maximize synergies and population impact, understanding the full spectrum of individual, cultural and societal factors impacting oral health and related behaviors, engaging and ultimately empowering communities to take control and create healthy environments, advocating for wellness-promoting and socially-responsible policies at all levels.[13,47,48]

A vision for precision dentistry in pediatric oral health care

Advancements in the science underlying pediatric oral health care will be based upon a thorough understanding of the biology of oral health and disease, including the key orchestrating roles of the genome and the oral microbiome, as well as the science of behavior change, nutrition and specifically sugar-related policies, and technological innovation. The introduction of biosensors is certain to revolutionize oral health self-monitoring at home or remotely, similar to stem cell research transforming dental rehabilitation options. However, the promotion of precision dentistry should not done at the expense of efforts aimed at reducing and ultimately eliminating health disparities via upstream action—at first, it may appear that the two approaches are to some degree antagonistic when research funding decisions or inferences regarding individuals need to be made.[49] In the long run, the translation of precise oral health care into socially-responsible practices, interventions and policies can bring about the desired equitable and sustainable population-level oral health improvements.

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KEY POINTS

- Genomics' role is now well-characterized for rare and penetrant developmental traits of early childhood including craniofacial malformations and developmental defects of dental hard tissues.
- Children have demonstrably varying individual susceptibilities to dental caries; however, specific loci, genes, as well as implicated pathways, functions and environmental interactions remain elusive.
- Dental caries is etiologically heterogeneous but mostly behaviorally-driven—half of its observed variance may be attributable to predisposing genomic factors that interact with common, modifiable risk factors.
- Genomics likely influences early childhood caries susceptibility via control of dental anatomy, enamel quality, salivary properties, immunity, oral microbiome composition, taste preference and other intermediate characteristics.