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EDITORIAL
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Editorial: Contemporary Views on the Genetics of Dental and Craniofacial Anomalies

Thantrira Porntaveetus[1]*, *Mushriq Fawzi Abid*[2] and *Maisa Seppala*[3]

[1] Center of Excellence in Genomics and Precision Dentistry, Department of Physiology, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand, [2] Department of Orthodontics, College of Dentistry, University of Baghdad, Baghdad, Iraq, [3] Centre for Craniofacial and Regenerative Biology, Faculty of Dentistry, Oral and Craniofacial Sciences, King's College London, London, United Kingdom

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Editorial on the Research Topic

Contemporary Views on the Genetics of Dental and Craniofacial Anomalies

Growing interest and use of new powerful sequencing techniques have enabled more systematic identification of a vast number of causative genes that have significantly improved our understanding of the etiology and pathogenesis of human congenital anomalies and diseases, including those affecting the orofacial region (1–3). This Research Topic issue aimed to provide a platform for studies that feature the most recent research advances in the field of genetics of dental and craniofacial conditions. Following our call for abstracts, a high number of authors internationally responded and confirmed their interest in participating, however three were eventually accepted for publication. This reduced number might well be impacted by the challenges caused by the COVID-19 pandemic on both clinical and laboratory-based research. Nevertheless, the included publications successfully revealed new causative and disease predisposing genetic variations as well as complex genotypic-phenotypic correlations in polygenetic diseases in both syndromic and non-syndromic craniofacial conditions that we here aim to summarize.

In the first paper "*IRF6* Genetic Variation and Maternal Smoking During Pregnancy in Cleft Lip/Palate", the authors revisited their previously published data to test if genetic variations in *Interferon Regulatory Factor (IRF) 6* can be associated with cleft lip with or without cleft palate (CL/P) for cases with history of maternal smoking during pregnancy (Vieira et al.). 573 individuals were previously recruited for their initial study that showed association with rs4844880 and CL/P, however, even rs2235371 was highlighted also as a marker, its wild-type allele was over-transmitted to the cases born with CL/P, and it was concluded it may not have functional consequences. For the current study, 57 (18 controls without CL/P, 39 affected with CL/P) were reanalyzed based on their positive history of maternal smoking. Genotyping of seven *IRF6* (rs4844880, rs2235371, rs2013162, ra861019, rs2073487, rs642961, and rs658860) markers were tested for over-transmission of alleles using genomic DNA obtained from saliva and the TaqMan method. Significantly, individuals born with CL/P whose mothers smoked were more likely to have the variant allele of rs642961 and rs861019. Interestingly, all individuals born with CL/P were homozygous for the wild-type allele of rs2235371 in comparison to two individuals born without clefts (Vieira et al.). This study proposes that *IRF6* rs642961 and/or rs861019 may be useful genomic markers for indicating increased risk of CL/P in pregnancies that are exposed to maternal smoking.

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Atsushi Ohazama, Niigata University, Japan

***Correspondence:**
Thantrira Porntaveetus
thantrira.p@chula.ac.th

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Another topic paper "A Novel Homozygous Variant in *GJA1* Causing a Hallermann-Streiff (HSS)/Oculodentodigital Dysplasia (ODDD) overlapping phenotype: A Clinical Report" presented a detailed case report of a patient with clinical features of both HSS and ODDD and confirmed its definitive diagnosis using whole-exome sequencing (WES) and Sanger sequencing (Jimenez-Armijo et al.). Proband presented with obstructive sleep apnea, hypotrichosis, micropthalmia, hypertelorism, low convex nasal ridge, mandibular retrognathia, brachydactyly and fifth finger clinodactyly, and multiple dental anomalies including brittle and brownish-yellow color deciduous teeth, thin and conoid deciduous canines, short roots, large pulps and history of caries, abscesses and multiple extractions of teeth. Although clinical features were previously associated with HSS, exome sequencing revealed novel homozygous missense variant in the *Gap Junction protein Alpha* (*GJA) 1* gene that has been identified as causative gene for ODDD. The variant (c.561C>G p.Cys187Trp) affected the second extracellular loop of the CX43 protein and this deleterious variant was classified as likely pathogenic (Jimenez-Armijo et al.). The study supports the possibility that autosomal recessively inherited HSS/ODDD may be a single syndrome with overlapping clinical features caused by homozygous variants in specific location of the *GJA1* gene sequence. It also demonstrates how problematic phenotype-based diagnosis can be especially in cases like HSS where the molecular basis is unknown and therefore highlights the benefits of genetic screening in helping with early disease diagnosis that enables effective preventative measures that are for instance important in prevention of dental disease and facilitates access to appropriate multidisciplinary patient care.

Lastly, the Research Topic presents "Multivariate GWAS of Structural Dental Anomalies and Dental Caries in a Multi-Ethnic Cohort" that recruited a cohort of 3,579 well-characterized individuals from the Pittsburg Orofacial Cleft Study and implemented a novel multivariate Genome Wide Association Study (GWAS) approach to identify inter-relationship between multiple dental anomalies and dental caries, and their genetic associations underlying these correlations (Alotaibi et al.). 1,392 unaffected relatives were included as controls and 2,187 orofacial cleft (OFC) patients were divided in four groups based on their multivariate patterns of correlated traits: [1] tooth agenesis, impaction, and rotation (AIR); [2] enamel hypoplasia, displacement, and rotation (HDR); [3] displacement, rotation, and mamelon (DRM); and [4] dental caries, tooth agenesis and enamel hypoplasia (CAH). Although genome-wide multivariate tests of association revealed no genome-wide statistically significant results, interestingly multiple suggestive association signals ($p < 10^{-5}$) were found near genes with known biological roles during tooth development, including *ADAMTS9* and *PRICKLE2* associated with [1] AIR*; GLIS3, WDR72*, and *ROR2* associated both [2] HDR and [3] DRM; *ROBO2* associated with [3] DRM; *BMP7* associated with both [2] HDR; and finally *ROBO1, SMAD2*, and MSX2 associated with [4] CAH. Notably, this study is the first multivariate GWAS designed to identify possible genetic loci associated with presence of patterns of correlated dental anomalies (Alotaibi et al.). It further evidences the powerful advantage of GWAS for large population study and demonstrates the challenges in obtaining genome-wide significance level when screening complex multifactorial traits in diverse cohorts.

Overall, the "Contemporary Views on the Genetics of Dental and Craniofacial Anomalies" Research Topic presents how various sequencing techniques can be used to ultimately help understanding of the links between underlying genetic causes, developmental or pathogenic processes, clinical phenotype, and diagnosis, and demonstrate their significance in developing more individualized patient-centered care. However, the topic also highlights challenges in precise genotype identification and phenotype characterization, as well as need for future work in the field that would benefit from researchers with different expertise working collaboratively together particularly to improve power in investigations looking at diseases that are rare or have complex genetic background. This information is ground-breaking and essential for researchers, clinicians and, moreover, for families with affected members. It forms basis for genetic counseling, introducing preventative measures on time and facilitating development of new advanced forms of therapies. We hope that the readers will find these papers as interesting and innovative as we do and want to thank all the authors and reviewers for their valuable contribution to this topic issue.

AUTHOR CONTRIBUTIONS

TP, MA, and MS contributed to conception, wrote the first draft of the manuscript, contributed to manuscript revision, read, and approved the submitted version. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Porntaveetus T, Srichomthong C, Ohazama A, Suphapeetiporn K, Shotelersuk V. A novel GJA1 mutation in oculodentodigital dysplasia with extensive loss of enamel. *Oral Dis*. (2017) 23:795–800. doi: 10.1111/odi.12663
2. Nitayavardhana I, Theerapanon T, Srichomthong C, Piwluang S, Wichadakul D, Porntaveetus T, et al. Four novel mutations of FAM20A in amelogenesis imperfecta type IG and review of literature for its genotype and phenotype spectra. *Mol Genet Genom*. (2020) 295:923–31. doi: 10.1007/s00438-020-01668-8
3. Shotelersuk V, Kamolvisit W, Rojvachiranonda N, Suphapeetiporn K, Porntaveetus T, Shotelersuk V. Severe craniofrontonasal syndrome in a male patient mosaic for a novel nonsense mutation in EFNB1. *Eur J Med Genet*. (2020) 63:103924. doi: 10.1016/j.ejmg.2020.103924

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