Lampiran 1 Tabel Hasil Kajian

Penulis (Tahun)	Bahasa	Sumber Artikel	Tujuan	Metode Penelitian	Hasil/Temuan
(Achmad *et al.*, 2017)	Inggris	Google scholar	Mengetahui angka prevalensi karies gigi pada anak *medically compromised*.	Kualitatif	Terdapat hubungan prevalensi karies dengan kondisi penyakit sistemik.
(Alamoudi *et al.*, 2018)	Inggris	Google scholar	Menginvestigasi gen IRF6 memiliki pengaruh terhadap terjadinya kasus CBL/P-NS di Saudi Arabia.	Kualitatif	Gen IRF6 memiliki peran terhadap terjadinya kasus CBL/P-NS di Saudi Arabia.
(Alexander *et al.*, 2017)	Inggris	Google scholar	Menjelaskan macam-macam etiopatogenesis terjadinya CBL/P-NS.	*Literature review*	Gen IRF6 memiliki peran terhadap terjadinya kasus CBL/P-NS
(Almaeeni and Hassan, 2018)	Inggris	Google scholar	Membandingkan sifat fisikokimiawi saliva pada CBL/P-NS dengan non CBL/P-NS.	Kualitatif	Laju alir saliva mengalami penurunan sedangkan pH tidak ada perbedaan dengan kelompok kontrolnya.
(Amalia *et al.*, 2019)	Inggris	Google scholar	Menjelaskan profil *Early Childhood Caries* (ECC) di Indonesia.	*Literature review*	Dari hasil profil data ECC, dapat digunakan untuk menyusun strategi upaya preventif peningkatan ECC.
(Annapoorna and Datta, 2020)	Inggris	Google scholar	Mengevaluasi pengaruh laju alir, kadar pH, kapasitas buffer, dan viskositas saliva terhadap pengalaman karies pada anak sekolah negeri.	Kualitatif	Laju alir, kadar pH, dan kapasitas buffer saliva mengalami penurunan, sementara viskositas meningkat pada anak dengan karies gigi.

Lanjutan Lampiran 1

Penulis (Tahun)	Bahasa	Sumber Artikel	Tujuan	Metode Penelitian	Hasil/Temuan
(Bezamat *et al.*, 2021)	Inggris	PubMed	Mengevaluasi faktor genetik yang menimbulkan *Molah-Incisor Hypomineralization* (MIH).	Kualitatif	TGFα dan IRF6 berperan dalam terjadinya MIH.
(Bezerra *et al.*, 2020)	Inggris	PubMed	Menginvestigasi hubungan IRF6 dengan terjadinya kasus CBL/P-NS di Brazil.	Kualitatif	Terdapat hubungan mengenai IRF6 dengan terjadinya kasus CBL/P-NS di Brazil.
(Biggs *et al.*, 2015)	Inggris	Google scholar	Menginformasi temuan mekanisme molekuler pada palatogenesis.	*Literature review*	Menjelaskan proses palatogenesis.
(Chaudhari *et al.*, 2020)	Inggris	PubMed	Menganalisis faktor pelindung karies, parameter saliva, serta perhitungan mikroba pada anak resiko tinggi karies dengan CBL.	Kualitatif	Anak dengan CBL memiliki kapasitas buffer saliva yang rendah dan tangka mikroba rongga mulut yang tinggi.
(Chowdhury *et al.*, 2017)	Inggris	Google scholar	Menjelaskan status kesehatan gigi dan mulut pada kasus CBL/P-NS di India.	Kualitatif	Didapatkan status angka DMFT dengan keadaan resiko sedang.
(Deshpande and Goudy, 2019)	Inggris	PubMed	Menjelaskan mekansime seluler dan molekuler CBL/P-NS.	*Literature review*	IRF6 memiliki hubungan dengan terjadinya CBL/P-NS.
(Durhan *et al.*, 2019)	Inggris	PubMed	Menjelaskan perubahan-perubahan mikrobiologi dan karies gigi anak usia 0-3 tahun pada kasus CBL/P-NS.	Kualitatif	Anak dengan kasus CBL/P-NS memiliki resiko karies yang tinggi.
(Gomes *et al.*, 2020)	Inggris	PubMed	Evaluasi sifat fenotip biomekanis mastikasi pada subyek atipikal dengan *Down Syndrome*.	Kualitatif	Adanya penurunan laju alir dan perubahan kapasitas buffer pada kasus *Down Syndrome*.

Lanjutan Lampiran 1

Penulis (Tahun)	Bahasa	Sumber Artikel	Tujuan	Metode Penelitian	Hasil/Temuan
(Hauser and Hoffman, 2015)	Inggris	PubMed	Menjelaskan proses organogenesis kelenjar saliva.	*Literature review*	Organogenesis kelenjar saliva memiliki etiologi yang kompleks dalam prosesnya.
(Howe *et al.*, 2017)	Inggris	PubMed	Menjelaskan status angka resiko karies gigi pada kasus CBL/P-NS.	Kualitatif	Angka DMFT pada kasus CBL/P-NS tinggi.
(Kiranahayu *et al.*, 2020)	Inggris	Google scholar	Menganalisis polimorfis BMP2 dan hubungannya dengan terjadinya kasus CBL di Indonesia.	Kualitatif	Adanya hubungan yang kuat antara BMP2 dan CBL di Indonesia.
(Lertsirivorakul *et al.*, 2017)	Inggris	Google scholar	Menjelaskan angka resiko karies gigi pada kasus CBL/P-NS di Thailand.	Kualitatif	Angka resiko karies gigi pada kasus CBL/P-NS tinggi.
(Lin-Shiao *et al.*, 2019)	Inggris	PubMed	Menginvestigasi peran gen p63 terhadap terjadinya kasus CBL/P-NS.	*Literature review*	Gen p63 memiliki peran terhadap terjadinya kasus CBL/P-NS.
(Liu *et al.*, 2018)	Inggris	PubMed	Menjelaskan interaksi gen yang berperan terhadap kasus CBL/P-NS di Cina.	Kualitatif	Beberapa interaksi gen berpengaruh terhadap terjadinya kasus CBL/P-NS di Cina.
(Lubis and Prakas, 2019)	Inggris	Google scholar	Mengetahui pengaruh viskositas dan kapasitas buffer saliva terhadap derajat karies gigi pada pasien *Diabetes Mellitus*.	Kualitatif	Perubahan viskositas dan kapasitas buffer saliva mempengaruhi terjadinya karies gigi pada pasien *Diabetes Mellitus*.
(Maili *et al.*, 2020)	Inggris	PubMed	Menjelaskan jalur gen yang berpengaruh terhadap terjadinya kasus CBL/P-NS.	Kualitatif	Jalur gen IRF6 memiliki peran terhadap terjadinya kasus CBL/P-NS.

Lanjutan Lampiran 1

Penulis (Tahun)	Bahasa	Sumber Artikel	Tujuan	Metode Penelitian	Hasil/Temuan
(Martinelli *et al.*, 2020)	Inggris	PubMed	Menjelaskan etiologi terjadinya kasus CBL/P-NS.	*Literature review*	Didapati banyak gen-gen yang berpengaruh terhadap terjadinya kasus CBL/P-NS.
(Mattingly *et al.*, 2015)	Inggris	PubMed	Menjelaskan proses perkembangan kelenjar saliva dan kelainan-kelainannya.	*Literature review*	Terdapat penjelasan mengenai faktor-faktor genetic apa saja yang mempengaruhi kelainan perkembangan kelenjar saliva.
(Mazaheri *et al.*, 2017)	Inggris	Google scholar	Membandingkan karies gigi, status *oral hygiene*, kadar pH saliva, serta perhitungan *S. Mutans* di plak gigi dan saliva pada kasus ALL.	Kualitatif	Adanya penurunan kadar pH dan peningkatan karies gigi pada kasus ALL.
(Metwalli *et al.*, 2018)	Inggris	PubMed	Menjelaskan peran gen IRF6 terhadap perkembangan kelenjar saliva.	Kualitatif	IRF6 mempengaruhi perkembangan kelenjar saliva.
(Min *et al.*, 2020)	Inggris	PubMed	Menjelaskan peran gen p63 terhadap perkembangan kelenjar saliva.	*Literature review*	Gen p63 memiliki peran terhadap proses perkembangan kelenjar saliva.
(Mohanan *et al.*, 2019)	Inggris	Google scholar	Menilai laju alir saliva dan total antioksidan di saliva pada kasus ED.	Kualitatif	Adanya penurunan laju alir pada kasus ED.
(Parada-Sanchez *et al.*, 2017)	Inggris	PubMed	Menjelaskan pengaruh mutasi gen IRF6 terhadap kelainan perkembangan kelenjar saliva.	Kualitatif	Mutasi gen IRF6 memiliki pengaruh terhadap terjadinya kelainan perkembangan kelenjar saliva.
(de Paula *et al.*, 2017)	Inggris	PubMed	Menjelaskan proses pembentukan kelenjar saliva.	*Literature review*	Menjelaskan proses pembentukan kelenjar saliva.

Lanjutan Lampiran 1

Penulis (Tahun)	Bahasa	Sumber Artikel	Tujuan	Metode Penelitian	Hasil/Temuan
(Porcheri and Mitsiadis, 2019)	Inggris	PubMed	Menjelaskan proses pembentukan kelenjar saliva.	*Literature review*	Menjelaskan proses pembentukan kelenjar saliva.
(Prasanth *et al.*, 2019)	Inggris	Google scholar	Menjelaskan saliva sebagai *biomarkers* karies gigi.	*Literature review*	Menjelaskan saliva sebagai *biomarkers* karies gigi.
(Rochmah *et al.*, 2018)	Inggris	Google scholar	Menginvestigasi *polymorphism* dari MTHFR C677T, A1298C and sebagai faktor dari terjadinya CBL/P-NS di Suku Sasak, Lombok Indonesia.	Kualitatif	Terdapat peningkatan *polymorphism* MTHFR A1298C pada kasus CBL/P-NS di Suku Sasak, Lombok, Indonesia.
(Romanos *et al.*, 2015)	Inggris	PubMed	Mengevaluasi hubungan polimorfis BMP2, BMP4, dan BMP7 dengan kejadian karies dan sifat *microhardness* enamel gigi.	Kualitatif	BMP2 berhubungan dengan terjadinya karies gigi desidui.
(Saleem *et al.*, 2019)	Inggris	PubMed	Menjelaskan gen-gen yang berpengaruh terhadap terjadinya kasus CBL/P-NS.	*Literature review*	Gen IRF6 memiliki peran terhadap terjadinya kasus CBL/P-NS.
(Seymen *et al.*, 2016)	Inggris	PubMed	Mengidentifikasi etiologi genetik dari kasus ALSG.	Kualitatif	Haploinsufisien dari FGF10 menimbulkan terjadinya kasus ALSG.
(Shaffer *et al.*, 2015)	Inggris	PubMed	Mengobservasi pengaruh kromosom X pada terjadinya karies gigi.	Kualitatif	Adanya perbedaan peningkatan karies gigi pada pria dan wanita.
(Shashni *et al.*, 2015)	Inggris	ScienceDirect	Membandingkan resiko karies gigi pada kasus CBL/P-NS dengan kelompok non CBL/P-NS.	Kualitatif	Pada kelompok CBL/P-NS didapati angka karies yang lebih tinggi dibanding dengan kelompok non CBL/P-NS.

Lanjutan Lampiran 1

Penulis (Tahun)	Bahasa	Sumber Artikel	Tujuan	Metode Penelitian	Hasil/Temuan
(Skare *et al.*, 2018)	Inggris	PubMed	Menganalisis pengaruh kromosom X pada kasus CBL di asia dan eropa.	Kualitatif	Adanya hubungan FGF13 dan EGF16 dengan terjadinya kasus CBL.
(Smallridge *et al.*, 2017)	Inggris	ScienceDirect	Menjelaskan perawatan gigi pada kasus CBL/P-NS di Inggris.	*Literature review*	Menjelaskan perawatan gigi pada kasus CBL/P-NS di Inggris.
(Suazo *et al.*, 2020)	Inggris	PubMed	Menjelaskan peran IRF6 terhadap terjadinya CBL/P-NS di Chile.	Kualitatif	Menjelaskan peran IRF6 terhadap terjadinya CBL/P-NS di Chile.
(Sundell *et al.*, 2015)	Inggris	PubMed	Membandingkan profil resiko karies kelompok CBL dan kontrol di usia yang sama menggunakan model penilaian resiko karies yang terkomputerisasi.	Kualitatif	Kelompok CBL menunjukan resiko karies yang tinggi dengan *oral hygiene* yang rendah dan peningkatan mikroba saliva.
(Sunderji *et al.*, 2017)	Inggris	PubMed	Menjelaskan angka kejadian karies gigi pada kasus CBL/P-NS.	*Literature review*	Angka karies pada kasus CBL/P-NS lebih tinggi dibanding kelompok non CBL/P-NS.
(Tamasas and Cox, 2017)	Inggris	PubMed	Menjelaskan peran gen IRF6 terhadap angka terjadinya karies kasus CBL/P-NS.	Kualitatif	Didapatkan angka karies tinggi pada kasus CBL/P-NS.
(Tikhonova *et al.*, 2018)	Inggris	PubMed	Menjelaskan asosiasi stress terhadap terjadinya karies gigi.	*Literatur review*	Stres berpengaruh terhadap peningkatan karies gigi.

Lanjutan Lampiran 1

Penulis (Tahun)	Bahasa	Sumber Artikel	Tujuan	Metode Penelitian	Hasil/Temuan
(Tuaño-Cabrera *et al.*, 2017)	Inggris	Google Scholar	Menjelaskan angka kejadian karies pada kasus CBL/P-NS di Filipina.	*Literatur review*	Angka kejadian karies pada kasus CBL/P-NS di Filipina tinggi.
(Worth *et al.*, 2017)	Inggris	PubMed	Menginvestigasi tingginya faktor resiko karies pada kasus CBL/P-NS.	*Literature review*	Pada kasus CBL/P-NS memiliki faktor resiko terjadinya karies yang tinggi.
(Wu *et al.*, 2016)	Inggris	Google scholar	Mengivestigasi *Single Nucleotid Polymorphisms* dari IRF6 pada kasus CBL di provinsi Guangdong.	Kualitatif	Adanya hubungan antara IRF6 dengan terjadinya kasus CBL/P-NS.
(Wu-Chou *et al.*, 2018)	Inggris	PubMed	Menjelaskan hubungan IRF6 & TP63 terhadap terjadinya kasus CBL/P-NS.	Kualitatif	IRF6 & TP63 memiliki peran terhadap terjadinya kasus CBL/P-NS.
(Xiao *et al.*, 2015)	Inggris	PubMed	Menunjukan prevalensi karies gigi pada kasus CBL/P-NS di Cina.	Kualitatif	Pada kasus CBL/NS angka karies tinggi.
(Xing *et al.*, 2019)	Inggris	PubMed	Menjelaskan hubungan gen IRF6 terhadap terjadinya kasus CBL/P-NS.	Kualitatif	Gen IRF6 berpengaruh terhadap faktor resiko terjadinya kasus CBL/P-NS.
(Xu *et al.*, 2016)	Inggris	PubMed	Menjelaskan hubungan gen IRF6 terhadap terjadinya kasus CBL/P-NS di Cina.	Kualitatif	Gen IRF6 berpengaruh terhadap faktor resiko terjadinya kasus CBL/P-NS di Cina.

Lampiran 2 (Achmad et al., 2017)

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Prevalence of Medically Compromised Children Regarding Dental Caries and Treatment Needs in Wahidin Sudirohusodo Hospital

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Abstract

The main problem of oral cavity among children in Indonesia is dental caries. Risk of caries on children with systemic diseases will be different with children without systemic diseases. Children with high caries risk should be given special care by doing intensive treatment to remove caries or decrease the caries risk.

To determine the prevalence of dental caries and treatment needs among medically compromised children in Wahidin Sudirohusodo Hospital.

Cross-sectional study and descriptive-observational approache. A total of 53 patients of Wahidin Sudirohusodo hospital were included in this study as a sample of accidental sampling method. Caries status of patientsmeasure using DMF-T index, and treatment need status measure (using TNI/UTN index) were recorded by clinical observation.

Prevalence of dental caries among medically compromised children, in this cases is thalassemia diseases, is high (57,1%) with caries status is poor (based on WHO scores) and treatment needs status is moderate which need restoration treament about one or two surfaces.

There is a relationship between caries prevalence and systemic diseases.

Clinical article (J Int Dent Med Res 2017; 10(3): pp. 915-920)

Keywords: Medically compromised, dental caries, treatment needs.

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Lampiran 3 (Alamoudi et al., 2018)

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Research Article Open Access

Interferon Regulatory Factor 6 (IRF6) and Gene – Environment Interactions in Non-Syndromic Orofacial Cleft Cases in Saudi Arabia-A Case Control Study

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Abstract

The association between interferon regulatory factor 6 (*IRF6*) and nonsyndromic orofacial cleft (NSOFC) is affected by ethnicity. Also, gene-environment interactions (GEI) may play an important role in its etiology.

Objectives: This case-control study investigated whether *IRF6* gene variants were associated with NSOFC in Saudi Arabian population and whether the gene was affected by maternal environmental exposures.

Methods: We extracted DNA from saliva samples obtained from 171 infant–parent triad cases and 189 matched controls (age, gender, and location) from January 2010–December 2011; this study included a total of 11 referral hospitals in Saudi Arabia. *IRF6* (rs2013162, rs2235375, and rs2235371) polymorphisms were genotyped using restriction-digestion polymerase chain reaction. Data on environmental exposures, for GEI analyses, were collected through questionnaire-led interviews with parents.

Results: We found statistically significant over transmission of the common *IRF6* rs2013162 allele among cleft lip with or without palate CL(P) cases. No associations were found for either of the other two *IRF6* SNPs. Maternal exposure to antipyretics, folic acid, fever, antibiotics, illnesses, common cold/flu, paternal water pipe smoking, stress, x-rays, and/or chemicals could significantly interact with the maternal *IRF6* (rs2013162 and rs2235375) gene variants, affecting the likelihood of having an offspring with NSOFC.

Conclusion: The common allele at *IRF6* rs2013162 was significantly over transmitted among CL(P) cases. This study provides hypotheses for future investigations into genetic and environmental factors and their interaction in the etiology of NSOFC.

Lampiran 4 (Alexander et al., 2017)

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Research Article

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CLEFT LIP AND PALATE-AN OVERVIEW ON ITS COMPLEX ETIOPATHOGENESIS

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Abstract

Cleft lip and or palate (CLP) are birth defects affecting the lip and palate caused by both genetic and environmental factors. CLP can occur as part of a broad range of Mendelian,chromosomal and teratogenic syndromes. The CLP can occur in various forms ranging from a simple bifid uvula or isolated clefts of lip to extensive defects involving bilateral clefts of lip, palate and alveolar mucosaThe ethnic and sex differences support the genetic etiology of these disorders. A combination of epidemiologic, phenotypic and genome wide association studies and animal models have helped to extrapolate several genes involved in CLP.The genetic background will help a long way in providing patients' genetic counseling and developing future preventive measures.

Key Words: Cleft lip, cleft palate, etiopathogenesis

Lampiran 5 (Almaeeni and Hassan, 2018)

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Selected Salivary Physicochemical Properties among Cleft Lip and Palate Children in Iraq

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ABSTRACT

Objective: *To investigate selected salivary properties in children with cleft lip and palate and to compare them with non-cleft children.* ***Setting:*** *The study was conducted in Dentistry College, University of Baghdad and Alwasity and Ghazi Alhareery Teaching Hospitals, Baghdad, Iraq.* ***Patients and methods:*** *A total of 36 children with non-syndromic repaired cleft lip and palate, aged 4 to 10 years, and a total of 37 non-cleft children were investigated for flow rate, pH, total antioxidant, uric acid, and total proteins.* ***Results:*** *Salivary total antioxidant capacity and total protein were significantly different between cleft lip and palate children and non-cleft children, while for salivary flow rate and total antioxidant were significantly lower in children with cleft lip and palate than in non-cleft children. Concerning pH and uric acid, there were no significant differences.* ***Conclusion:*** *Some salivary chemical constituents and some physical parameters deviated from the norm in children with cleft lip and palate.*

Keywords: Cleft lip and palate, Salivary flow rate, pH, Total antioxidant, Uric acid, Total proteins

Lampiran 6 (Amalia et al., 2019)

frontiers in Public Health

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Indonesia: Epidemiological Profiles of Early Childhood Caries

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The Indonesia government has succeeded in achieving national health development targets and has invested heavily in public health. Many positive results have been achieved, which indicate an increasing number of school-aged children free of caries and a decrease in caries experience scores. However, result of previous studies on early childhood caries (ECC) in pre-school children showed high prevalence and severity. Understanding the link between the epidemiology of the ECC and components of health development is critical for formulating appropriate actions. The purpose of this study is to provide a comprehensive review of the epidemiology of ECC in Indonesia based on the results of the national basic health surveys. The complementary data describes access, utilization and profile of oral health personnel in Indonesia.

OPEN ACCESS

Keywords: early childhood caries, Indonesia, caries, policy, children

Lampiran 7 (Annapoorna and Datta, 2020)

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Original Research Article

Effects of the salivary flow rate, pH, viscosity and buffering capacity on dental caries experience in government school children in Bangalore city

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ABSTRACT

Background: The present study was undertaken to evaluate effect of the salivary flow rate, pH, viscosity and buffering capacity on caries experience in government school children.
Methods: This case-control study was conducted amongst the Government school children of Bangalore city aged 6-14 years. A total of 180 school children were selected out of what 90 were selected for the test group based on the presence of one or more active dental caries and another 90 were selected for the control group who were free of dental caries at the time of examination. Saliva samples were collected from all subjects and were estimated for flow rate, pH, viscosity and buffering capacity.
Results: Mean salivary flow rate, pH and buffer capacity have been found to be significantly lower and mean salivary viscosity has been found to be significantly higher among children with dental caries.
Conclusions: The physical and biochemical properties of saliva, such as salivary flow rate, pH, buffering capacity and viscosity are significantly related with the caries experience in children.

Keywords: Salivary flow rate, Salivary pH, Salivary buffering capacity, Salivary viscosity, Caries experience

Lampiran 8 (Bezamat et al., 2021)

PLOS ONE

RESEARCH ARTICLE

Gene-environment interaction in molar-incisor hypomineralization

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Abstract

Molar incisor hypomineralization (MIH) is an enamel condition characterized by lesions ranging in color from white to brown which present rapid caries progression, and mainly affects permanent first molars and incisors. These enamel defects usually occur when there are disturbances during the mineralization or maturation stage of amelogenesis. Both genetic and environmental factors have been suggested to play roles in MIH's development, but no conclusive risk factors have shown the source of the disease. During head and neck development, the interferon regulatory factor 6 (*IRF6*) gene is involved in the structure formation of the oral and maxillofacial regions, and the transforming growth factor alpha (*TGFA*) is an essential cell regulator, acting during proliferation, differentiation, migration and apoptosis. In this present study, it was hypothesized that these genes interact and contribute to predisposition of MIH. Environmental factors affecting children that were 3 years of age or older were also hypothesized to play a role in the disease etiology. Those factors included respiratory issues, malnutrition, food intolerance, infection of any sort and medication intake. A total of 1,065 salivary samples from four different cohorts were obtained, and DNA was extracted from each sample and genotyped for nine different single nucleotide polymorphisms. Association tests and logistic regression implemented in PLINK were used for analyses. A potential interaction between *TGFA* rs930655 with all markers tested in the cohort from Turkey was identified. These interactions were not identified in the remaining cohorts. Associations ($p<0.05$) between the use of medication after three years of age and

Lampiran 9 (Bezerra et al., 2020)

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ORIGINAL ARTICLE

IRF6 polymorphisms in Brazilian patients with non-syndromic cleft lip with or without palate☆

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KEYWORDS
Nonsyndromic orofacial clefts;
Etiology;
IRF6;
Single nucleotide polymorphism

Abstract
Introduction: Non-syndromic orofacial clefts have a complex etiology due to the contribution from both genetic and environmental risk factors, as well as the interaction between them. Among the more than 15 susceptibility loci for non-syndromic orofacial clefts with considerable statistical and biological support, the IRF6 is the most validated gene by the majority of studies. Nonetheless, in genetically heterogeneous populations such as Brazilian, the confirmation of association between non-syndromic orofacial clefts and IRF6 common variants is not a consolidated fact and unrecognized IRF6 variants are poorly investigated.
Objective: The aim of this study was to investigate the association of IRF6 polymorphisms with non-syndromic orofacial clefts development in a population from northeast Brazil.
Methods: Blood samples of 186 non-syndromic orofacial clefts patients and 182 controls from Rio Grande do Norte, Brazil, were obtained to analyze IRF6 polymorphisms (rs2235371, rs642961, rs2236907, rs861019, and rs1044516) by real-time polymerase chain reaction. Non-syndromic orofacial clefts patients were classified in cleft lip and palate, cleft palate only and cleft lip only groups.

Lampiran 10 (Biggs et al., 2015)

DEVELOPMENTAL DYNAMICS 244:289–310, 2015
DOI: 10.1002/DVDY.24224

REVIEWS

Palatogenesis and Cutaneous Repair: A Two-Headed Coin

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Background: The reparative mechanism that operates following post-natal cutaneous injury is a fundamental survival function that requires a well-orchestrated series of molecular and cellular events. At the end, the body will have closed the hole using processes like cellular proliferation, migration, differentiation and fusion. **Results:** These processes are similar to those occurring during embryogenesis and tissue morphogenesis. Palatogenesis, the formation of the palate from two independent palatal shelves growing towards each other and fusing, intuitively, shares many similarities with the closure of a cutaneous wound from the two migrating epithelial fronts. **Conclusions:** In this review, we summarize the current information on cutaneous development, wound healing, palatogenesis and orofacial clefting and propose that orofacial clefting and wound healing are conserved processes that share common pathways and gene regulatory networks. *Developmental Dynamics 244:289–310, 2015.*

Key words: wound healing; palatogenesis; orofacial clefting

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Lampiran 11 (Chaudhari et al., 2020)

American Cleft Palate–Craniofacial Association

Original Article

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Factors Affecting High Caries Risk in Children With and Without Cleft Lip and/or Palate: A Cross-Sectional Study

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Abstract

Objective: The aim of the study was to analyze the caries protective factors, salivary parameters, and microbial counts in high caries risk children with cleft lip and/or palate (CL/P).

Design: This was a cross-sectional study.

Setting: This study was conducted in a tertiary health care teaching hospital in New Delhi, India.

Participants: The study was conducted in 40 children, 20 with CL/P and 20 without aged between 5 and 12 years.

Methods: Children with 2 or more caries lesions in both groups were included in this study. Demographic details, dental caries of affected teeth (World Health Organization criteria for Decayed Missing Filled Teeth [WHO-DMFT] and International Caries Detection and Assessment System [ICDAS II]), caries protective factors, salivary parameters, and microbial counts were recorded by one calibrated investigator.

Main Outcome Measures: Caries protective factors, salivary parameters, and microbial profile.

Results: The Chi-square (χ^2) test and Pearson correlation were used for statistical analysis. All the children participating in the study brushed their teeth only once in a day and consumed sweets more than twice a day. None of the children had ever received fluoride varnish. Resting saliva had a low buffering capacity in 80% of children with CL/P and 95% of children without CL/P. Microbial assessment of stimulated saliva showed that with the increases in the numbers (DMFT scores $\geq$4) and severity (ICDAS codes from 1-2 to 5-6) of caries lesions, both *Streptococci* and *Lactobacilli* counts were $\geq 10^5$ colony-forming units/mL of saliva in the both groups.

Conclusions: Children with CL/P showed limited access to caries protective measures and low buffering capacity in resting saliva, along with elevated levels of salivary *Streptococci* and *Lactobacilli* in stimulated saliva.

Keywords

dental caries, cleft lip and/or palate, stimulated and unstimulated saliva, salivary buffering capacity, microbial assessment, *Streptococci*, *Lactobacilli*

Lampiran 12 (Chowdhury et al., 2017)

Original Article

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Oral health status among cleft lip and palate patients in South India: A profile

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ABSTRACT

Background: Cleft lip and palate (CLP) is one of the identified anomalies in India. Many of the CLP cases have compromised oral health status which relates to their quality of life (QoL). Therefore, it is a need to assess their oral health status in terms of dental caries, periodontal disease, hypodontia, malocclusions, etc. Hence, the objective of this study is to investigate the oral health status among CLP cases. **Material and Methods:** A questionnaire survey was designed for a total of 300 CLP cases that came to the Nitte Meenakshi Institute of Craniofacial Surgery of Nitte University, India, were included in the study. A questionnaire was designed and pretested, and informed consent from the cases and carers was taken. **Results:** The average mean age of the patients with CLP was 17.48 (3–47). There were 47% males (n = 141) and 53% females (n = 159). 63% (n = 170) of them came from low socioeconomic background. Out of 300 cases, 31.0% (n = 90) had cleft lip; 1.0% (n = 3) had cleft palate, and 67.8% (n = 196) of them had both CLP. Most of the cases, i.e., 65.4% (n = 196) were unilateral CLP and 52.7% (n = 158) had right-sided clefts. The literacy status of the parents, their socioeconomic status, and occupation had a significant interrelation for the occurrence of CLP ($P < 0.05$). Similarly, diminutive or peg-shaped tooth, hypodontia, facial profile, and absence of lateral incisors in the line of cleft showed a significant association of this CLP condition. There was also strong interrelation between the presence of postoperative intraoral scarring in patients affected with the CLP ($P < 0.05$). The score for decayed missing and filled teeth (DMFT/dmft) was 5.16 for 6–12 years old and >9 in >13 years old, community periodontal index was between 0 and 2, and the simplified oral hygiene index was 0.9–1.41. There were cases of AQ3 hypodontia, hypomineralization, and malocclusion. The statistical test was performed using ANOVA. **Conclusion:** We conclude that, there was a moderate dental caries risk. The periodontal status was fair. There was association of occurrence of hypodontia and malocclusions in craniofacial anomalies. This affects their QoL.

Key words: Key words: Cleft lip, cleft palate, oral health status, quality of life

INTRODUCTION

Orofacial cleft is the most common anomaly occurring in the craniofacial region. The estimated prevalence is 1.7 in 1000 live births in India.[1] The incidence of cleft lip and palate (CLP) in India ranges between 0.25 and 2.29 per 1000 births. Thirty-five thousand new cleft patients are born in India every year and 1 million cases remain untreated.[2] The data from international registries between 1993 and 1998 suggest that a variation in prevalence of cleft lip with or without cleft palate (CL ± P) is 3.4–22.9 per 10,000 births and an even more pronounced variation for isolated cleft palate (CP) with the prevalence of 1.3–25.3 per 10,000 births.[2]

Dental caries is found to be most prevalent oral ailments among CLP cases; gingivitis, periodontal disease, hypodontia, hypoplasia, and maintenance of poor oral hygiene are also prevalent among CLP cases.[3-7] The prevalence of associated systemic diseases and those are detected postnatally is 25% among CLP and CL ± P.[8] Several studies have found that the CP also associated

Lampiran 13 (Deshpande and Goudy, 2019)

Laryngoscope Investigative Otolaryngology

Cellular and Molecular Mechanisms of Cleft Palate Development

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Abstract: Cleft lip and palate are common craniofacial deformities. The etiology underlying these deformities is complex and multifactorial and they can occur as part of one of many chromosomal syndromes, Mendelian single gene disorders, teratogenic effects, and as yet uncharacterized syndromes. Our paper will provide an overview of the multiple genes and molecular pathways that have been implicated in palatal fusion. We believe that understanding the molecular mechanisms of cleft formation can help clinicians anticipate which patients may have difficulties healing and in the future allow them to make surgical and medical treatment decisions based on genetic information.
Key Words: Cleft lip, cleft palate, genetics, molecular pathways, embryology.

INTRODUCTION

Cleft lip and cleft palate are common congenital deformities resulting from failure of the facial processes to grow or fuse appropriately during early embryologic development (fourth through 12th weeks of gestation). The incidence of cleft lip and palate (CLP) varies based on race, with a review article analyzing incidence rate of CLP within livebirths, stillbirths, and abortions finding the following data: Asian and American Indian populations have the highest incidence with 0.79 to 4.04 per 1000, Caucasian populations have an intermediate incidence with 0.91 to 2.69 per 1000, and African populations have the lowest incidence at 0.18 to 1.67 per 1000.[1] The etiology of CLP is multifactorial and complex and includes both genetic and environmental factors. Orofacial clefting can be classified as nonsyndromic, or found as an isolated defect, which occurs in about 85% of cleft lip with or without cleft palate and about 45% of cleft palate alone.[2] Syndromic clefting can be further subdivided as occurring in over 150 chromosomal syndromes, such as van der Woude syndrome, and velocardiofacial syndrome[3,4]; over 300 Mendelian single gene disorders; effects of teratogens, such as alcohol, tobacco smoke, antiepileptic drugs, and organic solvents[5]; and as yet uncategorized syndromes.

CLP are classified by laterality and completeness, with this classification scheme based on embryologic development. Cleft lips can be unilateral or bilateral; complete, in which the cleft involves the entire thickness of the upper lip and in which the alveolar ridge is often cleft as well; or incomplete, in which there is a variable continuous segment across the cleft. A Simonart band is a band of lip tissue bridging the cleft region (Fig. 1). Cleft palates are also described as being unilateral or bilateral and as complete or incomplete (Fig. 2). However, they are also further classified based on the location of the cleft with respect to the incisive foramen, with clefts of the primary palate occurring anterior to the incisive foramen and those of the secondary palate occurring posterior. Cleft of the soft palate alone may also occur.

FACIAL DEVELOPMENT

The development of the human face takes place between the fourth and 10th weeks of gestation by rapid delamination and migration of the cranial neural crest cells (CNC) from the neural placode. Migration and proliferation of the CNC leads to growth and fusion of paired maxillary prominences growing from the lateral sides towards the midline to join the frontonasal prominence, which descends in the midline from the forebrain, and concomitant development of paired mandibular prominences. Helms et al. have published a thorough review of the molecular mechanisms involved in neural crest migration.[6] A pair of thickened ectodermal nasal placodes develop on either side of the frontonasal prominence. When these invaginate to form nasal pits during the fifth week of development, the frontonasal prominence becomes divided into the medial and lateral nasal processes. The medial nasal processes fuse to create the philtrum, medial upper lip, nasal tip, columella, and primary palate, and the lateral nasal processes fuse to create the lateral aspect of the nose. The maxillary processes give rise to the cheeks and lateral upper lip. Palatogenesis occurs during weeks five through 12 of development. The primary palate, which includes the central maxillary alveolar arch with the four incisor teeth and the hard palate anterior to the incisive foramen, develops first from the rapid expansion of the frontonasal prominence and fusion of the medial nasal prominences. The secondary palate then develops from the fusion of the palatine shelves which elongate adjacent to the tongue, and as the

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Conflict of Interest: None.

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Lampiran 14 (Durhan et al., 2019)

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Microbial Profile and Dental Caries in Cleft Lip and Palate Babies Between 0 and 3 Years Old

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Abstract

Objective: The aim of this study was to examine the microbiological changes in newborn babies with cleft lip palate from birth up to age 3 and to correlate them with their caries levels and mothers' microbiological data and to compare with normal infants.

Basic Research Design: Prospective.

Settings: Marmara University, Faculty of Dentistry, Pediatric Dentistry Clinic, and Şişli Hamidiye Etfal Education and Research Hospital New Born Clinic.

Patients/Participants: Cleft lip palate (n = 21) and healthy (n = 13) newborns and their mothers.

Material and Methods: Intraoral samples were taken from babies in each group at least 3 times over the 3 years. Saliva samples of the mothers were collected just after the birth of the babies and examined microbiologically. Dental caries was noted as either present or absent.

Results: The most frequent microorganisms were candida, found at birth (n = 9, 42%) in cleft palate with or without cleft lip (CP ± L) group. The number of babies infected with *Lactobacilli* were found to be significantly higher in the CP ± L group than in the control group at birth ($P = .029$) and after eruption of the first primary tooth ($P = .030$). *Mutans Streptococci* were found in 10% of babies with CP ± L at birth. Initial caries was identified in 20% of the babies with an oral cleft compared with 0% of the controls after eruption of the first primary incisors.

Conclusion: The results show that the CP ± L babies must be considered as a group with an increased caries risk.

Keywords
dental health, microbiology, maternal factors

Lampiran 15 (Gomes et al., 2020)

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ORIGINAL ARTICLE

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Evaluation of the masticatory biomechanical function in Down syndrome and its Influence on sleep disorders, body adiposity and salivary parameters

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Abstract

Objective: To evaluate the phenotypic features of the masticatory biomechanics in atypical subjects with Down syndrome (DS). Its influence was analysed on sleep disorders, body adiposity and its risks, and some physicochemical properties of saliva.

Methods: Seventy subjects were enrolled to assess masticatory biomechanical function and divided into two groups: DS and control groups. Electrical activities of the masseter and temporal muscles (at rest and in maximum voluntary clench-MVC), maximum bite force-MBF and maximum mouth opening-MMO were investigated. Among the atypical subjects, just 24 participants underwent the anthropometry, the polysomnography II and the saliva testing (salivary flow rate-SFR, buffer capacity-BC and salivary cortisol levels, morning/SC-AM and night/SC-PM).

Results: MVC and MBF values showed high statistical significance in the control group ($P < .001$) than in the DS group of 35. MMO values were slightly increased in the DS group in relation to the control group. Overweight and obesity were found in both genders. Atypical women showed higher risk to develop cardiovascular-metabolic diseases than in atypical men. OSA severe was 20% for atypical women and 42.8% for atypical men, whereas snoring index was present in all genders. SFR was reduced in 100% of atypical subjects (hyposalivation in 10% women and 28.5% men). Furthermore, 100% BC, 66.6% SC-AM and 91.6% SC-PM showed normal patterns.

Conclusion: Masseter and temporal muscle hypotonia was found in all atypical subjects with DS. This muscle dysfunction strongly was related to overweight/obesity,

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Lampiran 16 (Hauser and Hoffman, 2015)

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Regulatory Mechanisms Driving Salivary Gland Organogenesis

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Abstract

Salivary glands develop as highly branched structures designed to produce and secrete saliva. Advances in mouse genetics, stem cell biology and regenerative medicine are having a tremendous impact on our understanding of salivary gland organogenesis. Understanding how SMG initiation, branching morphogenesis and cell differentiation occur, as well as defining the progenitor/stem cells and cell and tissue interactions that drive SMG development will help guide regenerative approaches for patients suffering from loss of salivary gland function. This review focuses on recent literature from the past 5 years investigating the regulatory mechanisms driving submandibular gland (SMG) organogenesis.

Lampiran 17 (Howe et al., 2017)

Research Reports: Clinical

Dental Decay Phenotype in Nonsyndromic Orofacial Clefting

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Abstract

Although children with oral clefts have a higher risk for dental anomalies when compared with the general population, prior studies have shown conflicting results regarding their dental decay risk. Also, few studies have assessed dental decay risk in unaffected relatives of children with clefts. Thus, the question of increased risk of dental decay in individuals with oral clefts or their unaffected relatives is still open for empirical investigation. This study characterizes dental decay in the largest international cohort to date of children with nonsyndromic clefts and their relatives, as compared with controls, and it addresses whether families with oral clefts have a significantly increased risk for dental decay versus the general population. A total of 3,326 subjects were included: 639 case probands, 1,549 unaffected relatives, and 1,138 controls. Decay was identified from in-person dental examinations or intraoral photographs. Case-control differences were tested with regression analysis. No significant differences were shown in percentage decayed and filled teeth and decayed teeth in the primary dentition (dft, dt) and permanent dentition (DFT, DT) in cases versus controls. In the cleft region, no significant differences were seen in primary or permanent decay (dt, DT) when compared with controls. No difference was found with regard to cleft type and percentage dft, dt, DFT, and DT in case probands. Nonsignificant differences were found in unaffected siblings and parents versus controls (primary and permanent dentitions). Collectively, these findings indicate that individuals with nonsyndromic oral clefts and their families do not have a higher dental decay risk as compared with the general population. These results suggest that either genetic or environmental factors underlying a higher susceptibility for dental anomalies do not increase caries risk or that the seemingly higher risk for dental decay associated with increased dental anomalies in case probands may be superseded by possible greater access to dental care.

Keywords: dental caries susceptibility, craniofacial, oral health, genetic susceptibility, primary dentition, permanent dentition

Lampiran 18 (Kiranahayu et al., 2020)

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Association of rs235768 A>T polymorphism of the bone morphogenetic protein 2 gene on non-syndromic orofacial cleft in an Indonesian population

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ABSTRACT

Introduction: Orofacial cleft is one of the many congenital malformations that often occur in human, leaving it at the fourth level of the most common orofacial birth defect findings. The incident rate is one in 700-1000 deliveries, where without therapeutic and surgical interventions, children with an orofacial cleft may have problems with speech, nutrition intake, and growth. Bone morphogenetic protein 2 (BMP-2) gene play essential roles in the migration and proliferation of neural crest cell of the early head formation and regulate mineralised tissues such as maxillary, mandible, palate and teeth. This study was aimed to analyse the BMP-2 polymorphism and its potential association with orofacial cleft in an Indonesian population. **Methods:** Cross-sectional study was conducted towards 128 samples, 32 samples of orofacial cleft patients and 96 samples of control. Extracted genotype and allele was determined with PCR-RFLP method using stored DNA samples from 32 orofacial cleft patients, and 96 healthy control. **Results:** The TT genotype was showing the p-value = 0.001, OR = 2.43% in orofacial samples (71.4%), which was significantly higher than in control groups (28.6%). The allele distribution was also considered statistically significant (p = 0.036, OR = 1.89%. **Conclusion:** There is a significant association of rs235768 A>T polymorphism of the BMP-2 gene on non-syndromic orofacial cleft patients in Indonesia.

Keywords: Bone morphogenetic protein 2 (BMP-2), polymorphism, non-syndromic orofacial cleft, Indonesia.

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Lampiran 19 (Lertsirivorakul et al., 2017)

Dental Caries Experience, Treatment Needs, Dental Anomalies and Malocclusion in Preschool Children with Cleft Lip and/or Palate

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Background: *At present, little is known about the difference in caries experience in preschoolers with cleft lip/palate compared with the non-cleft children. Moreover, the studies regarding dental treatment needs, dental anomalies and malocclusion in these children are scarce.*
Objective: *To examine dental caries experience, treatment needs, dental anomalies, tooth malalignment and malocclusion in preschool children with cleft lip and/or palate at the Tawanchai Center of Cleft Lip-Cleft Palate and Craniofacial Deformities, Faculty of Medicine, Khon Kaen University.*
Material and Method: *Data were obtained from oral examination and medical records. Caries was diagnosed as decayed, missing, and filled primary teeth using the criteria of the World Health Organization with no radiographs. Type of dental treatment needs, dental anomalies, tooth malalignment and malocclusion were assessed.*
Results: *One hundred and twenty children whose mean age of 3.4 years fulfilled the inclusion criteria. There were 71 boys (59.2%) and 49 girls (40.8%). Majority (70%) of the children had cleft lip and palate. The caries prevalence was 83.3% with the mean decayed, missing, and filled teeth of 8.78. There were 98 children (81.7%) who needed some types of invasive dental treatment. High prevalence of dental anomalies, malalignment and malocclusion were also found in 24.2%, 58.3% and 86.7% of the sample, respectively. The children in cleft lip and palate group exhibited significant higher prevalence of caries experience (86.9% vs. 78.9%, 70.6%), and malocclusion (94.0% vs. 68.4%, 70.6%) and required more treatment needs (85.7% vs. 78.9%, 64.7%) than children in cleft palate and cleft lip groups.*
Conclusion: *This study indicates that cleft children have high caries prevalence and highly required dental treatment which greatly increase in prevalence and complexity after 2 years of age. Moreover, they also presented high prevalence of dental anomalies, tooth malalignment and malocclusion. Therefore, oral health promotion, prevention and early intervention are of importance and should be established at an early age.*

Keywords: *Cleft lip and/or palate, Dental caries, Treatment needs, Dental anomalies, Malocclusion*

J Med Assoc Thai 2017; 100 (Suppl. 6): S109-S116
Full text. e-Journal: *http://www.jmatonline.com*

Lampiran 20 (Lin-Shiao et al., 2019)

SCIENCE ADVANCES | RESEARCH ARTICLE

GENETICS

p63 establishes epithelial enhancers at critical craniofacial development genes

Enrique Lin-Shiao[1,2], Yemin Lan[1], Julia Welzenbach[3], Katherine A. Alexander[1], Zhen Zhang[1], Michael Knapp[4], Elisabeth Mangold[3], Morgan Sammons[1]*, Kerstin U. Ludwig[3], Shelley L. Berger[1†]

The transcription factor p63 is a key mediator of epidermal development. Point mutations in p63 in patients lead to developmental defects, including orofacial clefting. To date, knowledge on how pivotal the role of p63 is in human craniofacial development is limited. Using an inducible transdifferentiation model, combined with epigenomic sequencing and multicohort meta-analysis of genome-wide association studies data, we show that p63 establishes enhancers at craniofacial development genes to modulate their transcription. Disease-specific substitution mutation in the DNA binding domain or sterile alpha motif protein interaction domain of p63, respectively, eliminates or reduces establishment of these enhancers. We show that enhancers established by p63 are highly enriched for single-nucleotide polymorphisms associated with nonsyndromic cleft lip ± cleft palate (CL/P). These orthogonal approaches indicate a strong molecular link between p63 enhancer function and CL/P, illuminating molecular mechanisms underlying this developmental defect and revealing vital regulatory elements and new candidate causative genes.

Lampiran 21 (Liu et al., 2018)

DOI: 10.1002/mgg3.872

ORIGINAL ARTICLE

Molecular Genetics & Genomic Medicine Open Access WILEY

Gene–gene interaction among cell adhesion genes and risk of nonsyndromic cleft lip with or without cleft palate in Chinese case-parent trios

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Funding information
The study was supported by the National Institute for Dental and Craniofacial Research through U01-DE-018993; "International Consortium to Identify Genes &Interactions Controlling Oral Clefts", 2007–2009. This research was also supported by the National Natural Science

Abstract

Background: Nonsyndromic cleft lip with or without cleft palate (NSCL/P) is a common birth defect with complex etiology. One strategy for studying the genetic risk factors of NSCL/P is to consider gene–gene interaction (G × G) among gene pathways having a role in craniofacial development. The present study aimed to investigate the G × G among cell adhesion gene pathway.

Methods: We carried out an interaction analysis of eight genes involved in cell adherens junctions among 806 NSCL/P Chinese case-parent trios originally recruited for a genome-wide association study (GWAS). Regression-based approach was used to test for two-way G × G interaction, while machine learning algorithm was run for exploring both two-way and multi-way interaction that may affect the risk of NSCL/P.

Results: A two-way *ACTN1* × *CTNNB1* interaction reached the adjusted significance level. The single nucleotide polymorphisms pair composed of rs17252114 (*CTNNB1*) and rs1274944 (*ACTN1*) yielded a *p* value of .0002, and this interaction was also supported by the logic regression algorithm. Higher order interactions involving *ACTN1*, *CTNNB1*, and *CDH1* were picked out by logic regression, suggesting a potential role in NSCL/P risk.

Conclusion: This study suggests for the first time evidence of both two-way and multi-way G × G interactions among cell adhesion genes contributing to the NSCL/P risk.

KEYWORDS

Lampiran 22 (Lubis and Prakas, 2019)

The Effect of Viscosity and Saliva Buffer in Diabetes Melitus Patients on the Dental Caries

Pengaruh Visikositas dan Buffer Saliva Terhadap Terjadinya Karies Gigi Pada Pasien Diabetes Melitus

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Abstract

Oral complications will occur in the form of dental caries when Diabetes Mellitus (DM)is not controlled. The purpose of this study was to determine the effect of viscosity and salivary buffer on the severity of dental caries in DM patients. This research was an analytic survey with cross sectional approach involving 61 subjects (42 women and 19 men) who were patients with type II DM in Dr. Pirngadi Hospital Endocrine Clinic Medan. This research was conducted by carrying out an oral examination to calculate the DMF-T index and checking the viscosity of the saliva visually and salivary buffer is measured by using buffer test strip.The results obtained from this study showed that there are 77.0% DM patients who experienced dental caries and 23.0% DM patients who did not experience dental caries. Based on saliva viscosity, subjects had poor saliva viscosity (80.3%). This study also showed that salivary buffer in DM patients was low (67.2%). Data were analysed by chi-square test showed significant results ($p < 0.05$) with a significant value of $p = 0,000$. The significance value of the effect of salivary buffer on DM patients with the occurrence of dental caries is $p = 0.02$. Based on these results, it can be concluded that there is a significant effect between viscosity and salivary buffer with the occurrence of dental caries.

Keywords: Diabetes Mellitus, saliva viscosity, salivary buffer, caries

Abstrak

Diabetes Melitus (DM) yang tidak terkontrol akan terjadi komplikasi oral berupa karies gigi. Tujuan Penelitian ini adalah untuk mengetahui bagaimana pengaruh viskositas dan buffer saliva terhadap derajat karies gigi pada pasien DM. Jenis penelitian ini adalah survey analitik dengan pendekatan *cross sectional* dengan melibatkan 61 subjek (42 orang perempuan dan 19 orang laki-laki) yang merupakan pasien DM tipe II di Poli Endokrin RSU Dr. Pirngadi Medan. Penelitian ini dilakukan dengan melakukan pemeriksaan klinis intra oral untuk menghitung indeks DMF-T kemudian diukur viskositas saliva secara visual dan buffer saliva diukur dengan menggunkan *buffer test strip*. Hasil yang diperoleh dari penelitian ini menunjukkan pasien DM yang mengalami karies gigi 77,0% dan pasien DM yang tidak mengalami karies gigi 23,0%. Berdasarkan viskositas saliva, subjek mempunyai viskositas saliva buruk (80,3%). Penelitian ini juga menunjukkan bahwa buffer saliva pada pasien DM rendah (67,2%). Data dianalisa dengan uji *chi-square*. menunjukkan hasil yang signifikan ($p < 0,05$) yaitu dengan nilai signifikan $p = 0,000$. Nilai signifikansi dari pengaruh buffer saliva pada pasien DM dengan terjadinya karies gigiadalah $p = 0,02$. Berdasarkan hasil tersebut, dapat disimpulkan bahwa adanya pengaruh yang signifikan antara viskositas dan buffer saliva dengan terjadinya karies gigi.

Kata kunci: Diabetes Melitus, viskositas saliva, buffer saliva, karies

Lampiran 23 (Maili et al., 2020)

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PBX-WNT-P63-IRF6 pathway in nonsyndromic cleft lip and palate

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Abstract

Nonsyndromic cleft lip and palate (NSCLP) is one of the most common craniofacial anomalies in humans, affecting more than 135,000 newborns worldwide. NSCLP has a multifactorial etiology with more than 50 genes postulated to play an etiologic role. The genetic pathway comprised of *Pbx-Wnt-p63-Irf6* genes was shown to control facial morphogenesis in mice and proposed as a regulatory pathway for NSCLP. Based on these findings, we investigated whether variation in *PBX1*, *PBX2*, and *TP63*, and their proposed interactions were associated with NSCLP. Fourteen single nucleotide variants (SNVs) in/nearby *PBX1*, *PBX2*, and *TP63* were genotyped in 780 NSCLP families of nonHispanic white (NHW) and Hispanic ethnicities. Family-based association tests were performed for individual SNVs stratified by ethnicity and family history of NSCLP.

Lampiran 24 (Martinelli et al., 2020)

frontiers in Cell and Developmental Biology

REVIEW
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Non-syndromic Cleft Palate: An Overview on Human Genetic and Environmental Risk Factors

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The epithelial and mesenchymal cells involved in early embryonic facial development are guided by complex regulatory mechanisms. Any factor perturbing the growth, approach and fusion of the frontonasal and maxillary processes could result in orofacial clefts that represent the most common craniofacial malformations in humans. The rarest and, probably for this reason, the least studied form of cleft involves only the secondary palate, which is posterior to the incisive foramen. The etiology of cleft palate only is multifactorial and involves both genetic and environmental risk factors. The intention of this review is to give the reader an overview of the efforts made by researchers to shed light on the underlying causes of this birth defect. Most of the scientific papers suggesting potential environmental and genetic causes of non-syndromic cleft palate are summarized in this review, including genome-wide association and gene–environment interaction studies.

OPEN ACCESS

Edited by:
Erika Kuchler,

Lampiran 25 (Mattingly et al., 2015)

Advanced Review

Salivary gland development and disease

Aaron Mattingly, Jennifer K. Finley and Sarah M. Knox*

Mammalian salivary glands synthesize and secrete saliva via a vast interconnected network of epithelial tubes attached to secretory end units. The extensive morphogenesis required to establish this organ is dependent on interactions between multiple cell types (epithelial, mesenchymal, endothelial, and neuronal) and the engagement of a wide range of signaling pathways. Here we describe critical regulators of salivary gland development and discuss how mutations in these impact human organogenesis. In particular, we explore the genetic contribution of growth factor pathways, nerve-derived factors and extracellular matrix molecules to salivary gland formation in mice and humans.

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Lampiran 26 (Mazaheri et al., 2017)

Dental Research Journal

Original Article

Oral health status, salivary pH status, and *Streptococcus mutans* counts in dental plaques and saliva of children with acute lymphoblastic leukemia

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ABSTRACT

Background: Acute lymphoblastic leukemia (ALL), accounting for 23% of all malignancies in children, is the most prevalent pediatric malignancy. This study compared dental caries, oral hygiene status, salivary pH, and *Streptococcus mutans* counts in dental plaques and saliva of children with leukemia with those of healthy controls.

Materials and Methods: This case–control cross-sectional study assessed 32 children with ALL and 32 healthy children (4–9-year-old) for gingival bleeding index (GBI), decayed, missing, and filled/decayed, missing, and filled surfaces (DMF/dmfs), and plaque index (PI). Sampling was performed to determine salivary pH and *S. mutans* counts of the participants. The two groups matched in terms of age, gender, and socioeconomic status. The groups were compared using independent t-test, Mann–Whitney test, Chi-square test, and Spearman's and Pearson's correlation analyses.

Results: The mean DMF/dmfs and GBI were significantly higher in the ALL group ($P_{DMF/dmfs}$ = 0.03; P_{GBI} = 0.04). However, the two groups were not significantly different in the mean PI values (P = 0.47). The mean *S. mutans* counts in dental plaques and saliva of the children with leukemia were significantly lower than the healthy controls (P < 0.01). Moreover, the mean salivary pH was significantly lower in the ALL group compared to the control group (P < 0.01).

Conclusion: Higher caries and gingival bleeding rates, higher dental plaque accumulation in children with ALL, decreased salivary pH, and cumulative effects of other risk factors highlight the significance of oral hygiene training programs (for the parents of these children) and regular dental examinations for these children.

Key Words: Acute lymphoblastic leukemia, caries, children, dental plaque, gingival health, *Streptococcus mutans*

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INTRODUCTION

Acute lymphoblastic leukemia (ALL), the most prevalent malignancy in children, accounts for 23% of all malignancies in children younger than 15 years of age worldwide. While advances in the treatment of ALL have increased the 5-year survival rate for all children with the disease to over 85%,[1] various types of infection have been suggested to be responsible for

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Lampiran 27 (Metwalli et al., 2018)

Research Reports: Biological

Interferon Regulatory Factor 6 Is Necessary for Salivary Glands and Pancreas Development

Journal of Dental Research
2018, Vol. 97(2) 226–236

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Abstract

Interferon regulatory factor 6 (*IRF6*) acts as a tumor suppressor and controls cell differentiation in ectodermal and craniofacial tissues by regulating expression of target genes. Haploinsufficiency of *IRF6* causes Van der Woude and popliteal pterygium syndrome, 2 syndromic forms of cleft lip and palate. Around 85% of patients with Van der Woude express pits on the lower lip that continuously or intermittently drain saliva, and patients with the common cleft lip and palate have a higher prevalence of dental caries and gingivitis. This study aims to identify the role of IRF6 in development of exocrine glands, specifically the major salivary glands. Our transgenic mouse model that expresses *LacZ* reporter under the control of the human *IRF6* enhancer element showed high expression of IRF6 in major and minor salivary glands and ducts. Immunostaining data also confirmed the endogenous expression of IRF6 in the developing ductal, serous, and mucous acinar cells of salivary glands. As such, we hypothesized that *Irf6* is important for proper development of salivary glands and potentially other exocrine glands. Loss of *Irf6* in mice causes an increase in the proliferation level of salivary cells, disorganized branching morphogenesis, and a lack of differentiated mucous acinar cells in submandibular and sublingual glands. Expression and localization of the acinar differentiation marker MIST1 were altered in *Irf6*-null salivary gland and pancreas. The RNA-Seq analysis demonstrated that 168 genes are differentially expressed and confer functions associated with transmembrane transporter activity, spliceosome, and transcriptional regulation. Furthermore, expression of genes involved in the EGF pathway—that is, *Ereg*, *Ltbp4*, *Matn1*, *Matn3*, and *Tpo*—was decreased at embryonic day 14.5, while levels of apoptotic proteins were elevated at postnatal day 0. In conclusion, our data report a novel role of *Irf6* in exocrine gland development and support a rationale for performing exocrine functional tests for patients with *IRF6*-damaging mutations.

Lampiran 28 (Min et al., 2020)

iScience

CellPress
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Article

p63 and Its Target Follistatin Maintain Salivary Gland Stem/Progenitor Cell Function through TGF-β/Activin Signaling

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SUMMARY

Multipotent ΔNp63-positive cells maintain all epithelial cell lineages of the embryonic and adult salivary gland (SG). However, the molecular mechanisms by which ΔNp63 regulates stem/progenitor (SP) cell populations in the SG remains elusive. To understand the role of ΔNp63 in directing cell fate choices in this gland, we have generated ΔNp63-deleted adult mice and primary salivary cell cultures to probe alterations in SP cell differentiation and function. In parallel, we have leveraged RNA-seq and ChIP-seq-based characterization of the ΔNp63-driven cistrome and scRNA-seq analysis to molecularly interrogate altered SG cellular identities and differentiation states dependent on ΔNp63. Our studies reveal that ablation of ΔNp63 results in a loss of the SP cell population and skewed differentiation that is mediated by Follistatin-dependent dysregulated TGF-β/Activin signaling. These findings offer new revelations into the SP cell gene regulatory networks that are likely to be relevant for normal or diseased SG states.

Lampiran 29 (Mohanan et al., 2019)

Original Article

Assessment of Salivary Flow Rate and Antioxidant Levels in Ectodermal Dysplasia Patients: An *In vivo* Study

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Abstract

Aims: To assess the salivary flow rate levels and total antioxidant levels in ectodermal dysplasia (ED) patients and to compare with normal individuals. **Materials and Methods:** Unstimulated saliva sample of control and case were collected from the mouth to a pre-weighed Eppendorf tube using a Pasteur pipette for 4 min. Stimulated saliva of case and control was also collected after chewing paraffin wax for 30 s. Both the Eppendorf tubes were weighed again after collection of both the saliva samples. The flow rate was calculated as difference of weight of the tube divided by time (4 min). Both unstimulated and stimulated saliva was also separately collected for estimation for total antioxidant levels. **Statistical analysis:** For intergroup comparison, Mann–Whitney test was used, and for intragroup comparison, Wilcoxon signed-rank test was used. **Results:** In the intergroup comparison of both the salivary flow rate and total antioxidant levels, there was no statistically significant difference; however, there was statistically significant difference in the intragroup comparison of salivary flow rate and total antioxidant levels in case group. **Conclusions:** There was a diminished unstimulated salivary flow rate in ED group, but stimulated salivary flow rate was significantly high and the total antioxidant levels in unstimulated saliva of the case group were significantly higher than the stimulated antioxidant levels.

Keywords: *Ectodermal dysplasia, salivary flow rate, total antioxidant levels*

Introduction

Ectodermal dysplasias (EDs) are conditions constituting defect of developmental origin affecting two or more ectodermal evolved such as sweat glands, teeth, nails, and hairs. The ED was first published by Thurnam in 1848[1] and it was Weech[2] in 1929 who coined the term. The prevalence of ED has been assessed as between 1:10000 and 1:100000 live male birth.[3,4] To date, more than 192 distinctive ectodermal syndromes have been described.

The most common type of ED is the hypohidrotic ED (HED) and hidrotic ED. ED is constituted by frontal bossing, wrinkled and hyperpigmented skin around the eyes, saddle nose, thick and everted lips, sunken cheeks, and large, low-set ears. Delay in the eruption of permanent teeth, hypodontia, and conical shaped or pegged teeth are some of the dental manifestations.

Saliva depicts an individuals' body health and therefore it is used to keep a check on health and diseased conditions. For the better understanding of involvement of the salivary gland in EDs, Nordgarden *et al.* conducted a study, wherein they found diminished flow of saliva from parotid and/or submandibular gland; moreover, a depleted unstimulated and stimulated salivary flow and submandibular glands is more affected than parotid glands in EDs.[5] Lexner *et al.* investigated female carriers along with genotype and phenotype in males influenced with X-linked HED. They concluded that oligodontia and subnormal saliva flow are strong clinical symptoms for potential female carriers.[6]

Free radicals are harmful for the body, and protection against these is provided by antioxidants which are present in all body fluids and tissues. These antioxidants have been contemplated as one of the vital contributing factors for the oral inflammatory pathologies.

Tulunoglu *et al.* examined saliva collected from caries-active and caries-free children for estimation of flow rates, pH, total proteins, buffer capacity, calcium, and antioxidant status. They could not find any

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Access this article online

Website: www.contempclindent.org

DOI: 10.4103/ccd.ccd_358_18

Quick Response Code:

Lampiran 30 (Parada-Sanchez et al., 2017)

Research Reports: Clinical

Disrupted IRF6-NME1/2 Complexes as a Cause of Cleft Lip/Palate

Journal of Dental Research
2017, Vol. 96(11) 1330–1338

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journals.sagepub.com/home/jdr

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Abstract

Mutations and common polymorphisms in interferon regulatory factor 6 (*IRF6*) are associated with both syndromic and nonsyndromic forms of cleft lip/palate (CLP). To date, much of the focus on this transcription factor has been on identifying its direct targets and the gene regulatory network in which it operates. Notably, however, IRF6 is found predominantly in the cytoplasm, with its import into the nucleus tightly regulated like other members of the IRF family. To provide further insight into the role of IRF6 in the pathogenesis of CLP, we sought to identify direct IRF6 protein interactors using a combination of yeast 2-hybrid screens and co-immunoprecipitation assays. Using this approach, we identified NME1 and NME2, well-known regulators of Rho-type GTPases, E-cadherin endocytosis, and epithelial junctional remodeling, as bona fide IRF6 partner proteins. The NME proteins co-localize with IRF6 in the cytoplasm of primary palatal epithelial cells in vivo, and their interaction with IRF6 is significantly enhanced by phosphorylation of key serine residues in the IRF6 C-terminus. Furthermore, CLP associated *IRF6* missense mutations disrupt the ability of IRF6 to bind the NME proteins and result in elevated activation of Rac1 and RhoA, compared to wild-type IRF6, when ectopically expressed in 293T epithelial cells. Significantly, we also report the identification of 2 unique missense mutations in the NME proteins in patients with CLP (NME1 R18Q in an *IRF6* and *GRHL3* mutation-negative patient with van der Woude syndrome and NME2 G71V in a patient with nonsyndromic CLP). Both variants disrupted the ability of the respective proteins to interact with IRF6. The data presented suggest an important role for cytoplasmic IRF6 in regulating the availability or localization of the NME1/2 complex and thus the dynamic behavior of epithelia during lip/palate development.

Lampiran 31 (de Paula et al., 2017)

THE ANATOMICAL RECORD 300:1180–1188 (2017)

Overview of Human Salivary Glands: Highlights of Morphology and Developing Processes

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ABSTRACT

Salivary glands are essential organs that produce and secrete saliva to the oral cavity. During gland morphogenesis, many developmental processes involve a series of coordinated movements and reciprocal interactions between the epithelium and mesenchyme that generate the ductal system and the secretory units. Recent studies have shown new findings about salivary gland development, particularly regarding lumen formation and expansion, with the involvement of apoptosis and cell polarization, respectively. Moreover, it has been observed that human minor salivary glands start forming earlier than previously published and that distinct apoptotic mediators can trigger duct lumen opening in humans. This review summarizes updated morphological and cellular features of human salivary glands and also explores new aspects of the human developmental process. Anat Rec, 300:1180–1188, 2017.

Lampiran 32 (Porcheri and Mitsiadis, 2019)

cells

MDPI

Review

Physiology, Pathology and Regeneration of Salivary Glands

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Abstract: Salivary glands are essential structures in the oral cavity. A variety of diseases, such as cancer, autoimmune diseases, infections and physical traumas, can alter the functionality of these glands, greatly impacting the quality of life of patients. To date, no definitive therapeutic approach can compensate the impairment of salivary glands, and treatment are purely symptomatic. Understanding the cellular and molecular control of salivary glands function is, therefore, highly relevant for therapeutic purposes. In this review, we provide a starting platform for future studies in basic biology and clinical research, reporting classical ideas on salivary gland physiology and recently developed technology to guide regeneration, reconstruction and substitution of the functional organs.

Keywords: salivary glands; oral epithelium; xerostomia; exocrine glands; salivary gland-resident stem cells

1. Introduction

Structures secreting fluid to facilitate feeding emerge progressively throughout evolution and can be found in very simple organisms (e.g., *Caenorhabditis elegans*) and more complex species (e.g., *Drosophila melanogaster*, placental mammals). In humans, major and minor salivary glands produce and secrete digestive fluids or protein-rich fluids. The three pairs of major salivary glands (i.e., parotid, submandibular and sublingual glands) are responsible for the production and secretion of saliva in the oral cavity, whose moisturizing effect preserves oral hygiene and allows taste, speech and mastication [1].

The parotid gland (PG) is mainly composed of serous acini-secreting α-amylase-rich saliva [2]. The sublingual gland (SL) secretes mucous, a viscous solution rich in mucins [3–5]. The submandibular gland (SMG) is composed by a mixed population of acini with a mucous and serous function [1,4,6]. These three major salivary glands account for more than 90% of salivary secretion. Minor salivary glands are distributed throughout the oral cavity, specifically in the labial and lingual mucosa, as well as palate and floor of the mouth.

Saliva is an essential fluid for oral cavity maintenance and functionality. Digestive enzymes within saliva initiate the digestion process, and at the same time, saliva acts as a lubricant of solid nutrition, thus helping its passage through the esophagus. By moisturizing the tongue and other tissues of the oral cavity, saliva has an essential role in speech and taste sensitivity [7]. It also balances the pH of the mouth, thus protecting the soft oral tissues and teeth from an extended exposure to an acidic environment. Saliva contains several signalling molecules, such as EGF, FGF, NGF and TGF-α, that are essential for the regeneration of oral and oesophageal mucosa. Finally, the antibacterial and antifungal components of the saliva, such as lysozymes, immunoglobulins and lactoferrin, inhibit the progression of bacterial infection and dental caries.

Physiological functions and the histological appearance of salivary glands are rather conserved between species and individuals, but clear distinctions exist in terms of anatomical position and

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Salivary Biomarkers for Dental Caries – A Review

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ABSTRACT: Dental caries (tooth decay) is a highly prevalent multifactorial infectious disease that afflicts a large proportion of the world's population. Dental caries is caused by cariogenic microorganisms in the biofilm (dental plaque), which ferment dietary carbohydrates to produce acid, leading to mineral loss from tooth hard tissues and subsequently the destruction of tooth structures. The interaction of microorganisms, diet and host determines the occurance of dental caries. The constituents and properties of saliva plays an essential role in the occurrence and progression of dental caries. Saliva may protect teeth through several mechanisms, such as clearance of food debris and sugar, aggregation and elimination of microorganisms, buffering actions to neutralize acid, maintaining supersaturation with respect to tooth mineral, participating in acquired enamel pellicle formation (which slows down demineralization during acid attack) and antimicrobial defense. Saliva is composed of 99% water and less than 1% solid (mainly electrolytes and proteins). Although salivary electrolytes and proteins account for only a small proportion of saliva, they play various important roles to maintain the oral health and integrity of teeth.Many measurable characteristics of saliva arepotential biomarkers for dental caries. These salivarybiomarkers may be exploited for the prediction, diagnosis,prognosis and management of dental caries, aswell as for evaluating the outcome of therapeutic regimens. This narrative review aims to provide an overview of the current understanding of salivary biomarkers associated with dental caries.

Keywords: Biomarkers, protiens, electrolytes, microorganisms,

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Maternal Polymorphism MTHFR A1298C not C677T and MSX1 as the Risk Factors of Non-syndrome Cleft Lips /Palate in Sasak Tribe Indonesia

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Abstract

The etiology of orofacial cleft as Non-syndromic cleft lips with or without palate (NSCL/P) are complex which including genetic and environmental factors.

To investigate maternal polymorphism of MTHFR C677T, A1298C and MSX1as the risk factor of NSCL/P in Sasak Tribe, Lombok Indonesia.

The study was a case control study involving 148 subjects from Sasak Tribe, consisting of 35 children with NSCL/P-mother pairs and 39 healthy children-mother pairs as controls. EDTA blood was drawn from all subjects. Molecular analyses of MTHFR C677T, A1298C and MSX1 polymorphisms were done using PCR-RFLP. The risk factors were analyzed statistically using OR and Chi square test.

Children with at least one copy of the MTHFR 1298C allele had a higher risk of NSCL/P (p=0.036, OR 2.7, 95% CI (1.1-7.0)). Maternal polymorphisms MTHFR C677T and MSX1 were not found to be risk factors of NSCL/P (p>0.05). New sequence variation of c.469 + 12G>A was found near the splice site region of exon 1 MSX1 in an affected child.

MTHFR A1298C polymorphism increases the risk of NSCL/P in Sasak Tribe, Lombok, Indonesia. A novel sequenceof MSX1 c.469 + 12G>A was found. Further study with higher sample size to fullfill minimum number of subjects for genetic study may found more new novel polymorphisms.

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Keywords: MTHFR C677T, MTHFR A1298, MSX1, Orofacial cleft.

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Original Paper

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BMP2 Is Associated with Caries Experience in Primary Teeth

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Ticiana de Medeiros Sabóia[a] Patricia Nivoloni Tannure[b] Andrea Lips[c]
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Key Words
Early childhood caries · Epidemiology · Genetics

Abstract
Bone morphogenetic proteins (BMPs) play an important role during the initial process of enamel development and therefore may play a role in caries susceptibility. The purpose of this study was to evaluate the association between the polymorphisms in the *BMP2*, *BMP4* and *BMP7* genes and their association with caries experience and primary enamel microhardness characteristics. DNA from buccal cells as well as clinical and demographic information from 1,731 subjects from three different data sets from Brazil were included. Polymorphisms in *BMP2*, *BMP4* and *BMP7* were analyzed by real-time polymerase chain reaction from genomic DNA. Association between caries experience, genotype, and allele distribution in both cohorts was evaluated using χ^2 and logistic regression analyses. In the family-based set, the association between caries experience and alleles was tested using the transmission disequilibrium test. In the Rio de Janeiro cohort, microhardness data on 108 exfoliated primary teeth before and after demineralization and remineralization challenges was included. Associations between microhardness values and genotype and allele distribution were evaluated using χ^2 and logistic regression analyses. Differences between caries experience and some risk factors were statistically significant. In the cohort from Nova Friburgo, *BMP2* was associated with caries experience in primary dentition during logistic regression analysis ($p = 0.023$; OR = 2.58; 95% CI 1.13–5.86). There was no association between genotype and allele distribution for *BMP* polymorphisms and primary enamel microhardness alterations. Our result suggests that *BMP2* may be involved in caries experience in primary dentition from a Nova Friburgo cohort.

Dental caries is one of the most common diseases in oral health and has a significant impact on individuals and society. The etiology of this disease is complex. Three main factors in dental caries have been identified: the in-

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Review article

Assessment of candidate genes and genetic heterogeneity in human non syndromic orofacial clefts specifically non syndromic cleft lip with or without palate

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ABSTRACT

Non syndromic orofacial clefts specifically non-syndromic cleft lip/palate are one of the most common craniofacial malformation among birth defects in human having multifactorial etiology with an incidence of 1:700/1000. On the basis of association with other congenital malformations or their presence as isolated anomaly, OFC can be classified as syndromic (30%) and nonsyndromic (70%) respectively. The major cause of disease demonstrates complex interplay between genetic and environmental factors. The pathogenic mechanism of underlying factors have been provided by different genetic studies on large-scale with significant recent advances in genotyping technologies usually based on linkage or genome wide association studies (GWAS). On the basis of recent studies, new tools to identify causative genes involved in NSCL/P reported approximately more than 30 genetic risk loci that are responsible for pathogenesis of facial deformation. Despite these findings, it is still uncertain that how much of variance in NSCL/P predisposing factors can be explain by identified risk loci, as they all together accounts for only 20%–25% of NSCL/P heritability. So there is need of further findings about the problem of rare low frequency coding variants and other missing responsive factors or genetic modifiers. This review will described those potential genes and loci reported in different studies whose involvement in pathogenesis of nonsyndromic OFC has wide scientific evidence.

Lampiran 37 (Seymen et al., 2016)

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ORIGINAL ARTICLE

Novel *FGF10* mutation in autosomal dominant aplasia of lacrimal and salivary glands

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Abstract
Objective Aplasia of lacrimal and salivary glands (ALSG) is a rare autosomal dominant inherited disease, characterized by aplasia, atresia, or hypoplasia of the lacrimal and salivary systems with variable expressivity. The purpose of this study was to identify genetic etiology of an ALSG family.
Materials and methods We recruited a Turkish family with ALSG and performed a mutational analysis, based on the candidate gene approach, to clarify the molecular genetic etiology.
Results The candidate gene sequencing of the *FGF10* gene identified a novel heterozygous nonsense mutation (c.237G>A, p.Trp79*) in the exon 1.
Conclusion The identified novel mutation would result in a haploinsufficiency of the FGF10, because of nonsense-mediated mRNA decay caused by a premature stop codon. This report further confirms that ALSG is caused by the haploinsufficiency of functional FGF10.
Clinical relevance Identification of the genetic etiology of the ALSG will help both the family members and dentist understand the nature of the disorder. Therefore, it will positively motivate oral health care to avoid further destraction of the tooth due to the lack of salivary production.

Keywords FGF10 · Aplasia of lacrimal and salivary glands · Lacrimo-auriculo-dento-digital syndrome · Haploinsufficiency · Nonsense mutation

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Introduction

Aplasia of lacrimal and salivary glands (ALSG; OMIM #180920) is a rare autosomal dominant inherited disease with variable expressivity. Affected individuals present with irritation or infection of the eyes, dry mouth, and dental caries due to aplasia, atresia or hypoplasia of the lacrimal and salivary glands [1]. Inactivating mutations in the *FGF10* (p.Arg193* and a deletion of exons 2 and 3) gene have been shown to be associated with ALSG. Furthermore, aplasia of the lacrimal glands and hypoplasia of the salivary glands were observed in the investigation of heterozygous $Fgf10^{+/-}$ knockout mice [2]. Therefore, it has been suggested that the haploinsufficiency of FGF10 underlies ALSG.

Lacrimo-auriculo-dento-digital syndrome (LADD; OMIM #149730) is also an autosomal dominant congenital disease characterized by hearing loss and malformations of the ears and digits in addition to the symptoms of ALSG [3]. Mutational analysis revealed heterozygous mutations in the tyrosine kinase domains of the *FGFR2* and *FGFR3* genes. Further investigation using the candidate gene approach revealed a missense mutation affecting a conserved amino acid

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Genetic Susceptibility to Dental Caries Differs between the Sexes: A Family-based Study

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Abstract

Many of the factors affecting susceptibility to dental caries are likely influenced by genetics. In fact, genetics accounts for up to 65% of inter-individual variation in dental caries experience. Sex differences in dental caries experience has been widely reported, with females usually exhibiting higher prevalence and severity of disease across all ages. The cause for this sex bias is currently uncertain, although may be partly explained by the differential effects of genetic factors between the sexes: gene-by-sex interactions. In this family-based study (N=2,663; 740 families; ages 1–93 years), we assessed dental caries via intra-oral examination and generated six indices of caries experience (DMFS, dfs, and indices of both pit-and-fissure surface caries and smooth surface

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Declaration of Interests
All authors declare no conflicts of interest.

Author contributions: JRS conceived the study, performed the data analysis, and wrote the manuscript; DWM, RJW, RC, and MLM conceived the COHRA1 initiative; JRS, XW, DWM, RJW, RC, and MLM interpreted the results, and edited and approved the manuscript.

Lampiran 39 (Shashni et al., 2015)

Comparison of risk indicators of dental caries in children with and without cleft lip and palate deformities

Rubina Shashni, Ashima Goyal[1], Krishan Gauba[1], Ashok Kumar Utreja[2], Pallab Ray[3], Ashok Kumar Jena[4]

Abstract

Objective: To test the hypothesis that there are no differences in various risk factors of dental caries among children with cleft lip and palate when compared to non-cleft high caries risk and non-cleft caries free children. **Design:** Seventy-three children in the age range of 4–9 years comprised three groups; Group-I ($n = 23$, children with cleft lip and palate), Group-II ($n = 25$, non-cleft high caries risk children) and Group-III ($n = 25$, non-cleft caries free children). Various risk factors for dental caries like type of oral hygiene practice, sugar exposures/day, developmental defects of enamel, caries activity, salivary streptococci mutans levels and lactobacilli levels were evaluated and compared among the three groups of children. **Results:** The mean deft score among Group-II children was significantly more ($P < 0.01$) as compared to the Group-I children. The mean deft + DMFT score among Group-I and Group-II children was comparable ($P = 0.149$). Developmental enamel defects were more among Group-I children as compared to Group-II and Group-III children ($P < 0.01$). Hypoplasia of the maxillary anterior teeth was more common among Group-I children as compared to Group-II ($P < 0.05$) and Group-III children ($P < 0.001$). The association between hypoplastic teeth and dental caries was significant ($P < 0.05$). The salivary acidogenic potential as evaluated by Snyder test was comparable among Group-I and Group-II children. The salivary streptococcus mutans levels in Group-I and Group-II children were higher when compared to lactobacillus counts. **Conclusion:** The risk factors of dental caries among children with cleft lip and palate were more as compared to non-cleft high caries risk and non-cleft caries free children.

Keywords: Cleft lip and palate, dental caries, risk factors

Lampiran 40 (Skare et al., 2018)

frontiers in Genetics

ORIGINAL RESEARCH
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Analysis of Parent-of-Origin Effects on the X Chromosome in Asian and European Orofacial Cleft Triads Identifies Associations with *DMD*, *FGF13*, *EGFL6,* and Additional Loci at Xp22.2

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Background: Although both the mother's and father's alleles are present in the offspring, they may not operate at the same level. These parent-of-origin (PoO) effects have not yet been explored on the X chromosome, which motivated us to develop new methods for detecting such effects. Orofacial clefts (OFCs) exhibit sex-specific differences in prevalence and are examples of traits where a search for various types of effects on the X chromosome might be relevant.

Materials and Methods: We upgraded our R-package Haplin to enable genome-wide analyses of PoO effects, as well as power simulations for different statistical models. 14,486 X-chromosome SNPs in 1,291 Asian and 1,118 European case-parent triads of isolated OFCs were available from a previous GWAS. For each ethnicity, cleft lip with or without cleft palate (CL/P) and cleft palate only (CPO) were analyzed separately using two X-inactivation models and a sliding-window approach to haplotype analysis. In addition, we performed analyses restricted to female offspring.

Results: Associations were identified in "Dystrophin" (*DMD*, Xp21.2-p21.1), "Fibroblast growth factor 13" (*FGF13*, Xq26.3-q27.1) and "EGF-like domain multiple 6" (*EGFL6*, Xp22.2), with biologically plausible links to OFCs. Unlike *EGFL6*, the other associations on chromosomal region Xp22.2 had no apparent connections to OFCs. However, the Xp22.2 region itself is of potential interest because it contains genes for clefting syndromes [for example, "Oral-facial-digital syndrome 1" (*OFD1*) and "Midline 1" (*MID1*)]. Overall, the identified associations were highly specific for ethnicity, cleft subtype and X-inactivation model, except for *DMD* in which associations were identified in both CPO and CL/P, in the model with X-inactivation and in Europeans only.

Discussion/Conclusion: The specificity of the associations for ethnicity, cleft subtype and X-inactivation model underscores the utility of conducting subanalyses, despite the

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ORIGINAL ARTICLE

WILEY

Centre-level variation in dental treatment and oral health and individual- and area-level predictors of oral health in 5-year-old children with non-syndromic unilateral cleft lip and palate: the Cleft Care UK study. Part 3

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Structured Abstract

Objectives: To explore centre-level variation in fluoride treatment and oral health outcomes and to examine the association of individual- and area-level risk factors with dental decay in Cleft Care UK (CCUK).

Setting: Two hundred and sixty-eight 5-year-old British children with non-syndromic unilateral cleft lip and palate (UCLP).

Materials and Methods: Data on caries and developmental defects of enamel (DDE) were collected. The child's history of fluoride ingestion and postcode was used to assess exposure to fluoridated water. Centre-level variation in fluoride exposure and caries was examined using hierarchical regression. Poisson regression was used to estimate the association between individual- and area-level fluoride exposures and outcome.

Results: Children had high levels of caries, rampant caries and DDE. There was no evidence of variation between centres in the number of children with caries or rampant decay. There was evidence of variation in prescription of fluoride tablets and varnish and the type of toothpaste used. Area level of deprivation was associated with a higher risk of dental caries—risk ratio (RR) in the lowest quartile versus the rest was 1.43 (95% CI 1.13 to 1.81). Use of fluoride tablets and varnish was associated with higher risk of caries—RR 1.73 (95% CI 1.29 to 2.32) and RR 1.33 (95% CI 1.04 to 1.70), respectively, adjusted for age, sex and deprivation.

Conclusion: The association with use of fluoride tablets and varnish probably reflects reverse causality but indicates the need for early preventative interventions in children with UCLP.

Lampiran 42 (Suazo et al., 2020)

Reproductive Sciences
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ORIGINAL ARTICLE

Association Between *IRF6* Variants and Nonsyndromic Cleft Lip With or Without Cleft Palate in Chile

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Abstract
The aim of this study was to assess the association between *IRF6* single nucleotide polymorphisms and nonsyndromic cleft lip, with or without cleft palate (NSCL/P), in a Chilean population, based on a case-control sample and confirmed in a case-parent trio population. In a sample of 150 Chilean case-parent trios and 164 controls (cohort 1), we evaluated the association between three common *IRF6* variants (rs764093, rs2236909, rs2235375) and NSCL/P using odds ratio (OR) for case-control and case-parent trios and in a combined OR of both designs. To confirm associations from the cohort 1, we increased the sample size to 215 triads and 320 controls (cohort 1 + cohort 2). The combined OR for the cohort 1 reveals that the rs2235375 C allele is associated with NSCL/P in Chile (OR 1.34; $p = 0.013$), which was supported by the results for the two cohorts (OR 1.29; $p = 0.006$). Bioinformatic prediction showed that this variant, located 27 bp downstream from *IRF6* exon 6, potentially alters the splicing process and based on functional annotations is associated with a decrease of gene expression. We propose that the C allele of rs2235375 from *IRF6* gene seems to be a risk factor for NSCL/P in a Chilean population. However, we cannot discard a population stratification bias in our findings. On the other hand, further studies are necessary to confirm the biological role of rs2235375 in *IRF6* function at craniofacial development level.

Keywords Nonsyndromic cleft lip with or without cleft palate · *IRF6* · Case-control · Case-parent trios

Lampiran 43 (Sundell et al., 2015)

Sundell et al. BMC Oral Health (2015) 15:85
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BMC Oral Health

RESEARCH ARTICLE Open Access

Comparing caries risk profiles between 5- and 10- year-old children with cleft lip and/or palate and non-cleft controls

Anna Lena Sundell[1*], Christer Ullbro[2], Agneta Marcusson[3] and Svante Twetman[4]

Abstract

Background: Previous studies have suggested that children with oral clefts may have higher caries prevalence in comparison with non-cleft controls but the relative importance of the potential risk factors is not clear. The aim of this study was to compare the caries risk profiles in a group of cleft lip and/or palate (CL(P)) children with non-cleft controls in the same age using a computerized caries risk assessment model.

Methods: The study group consisted of 133 children with CL(P) (77 subjects aged 5 years and 56 aged 10 years) and 297 non-cleft controls (133 aged 5 years and 164 aged 10 years). A questionnaire was used to collect data concerning the child's oral hygiene routines, dietary habits and fluoride exposure. Oral hygiene was assessed using Quigley-Hein plaque Index and the caries prevalence and frequency was scored according to the International Caries Detection and Assessment System. Whole saliva samples were analyzed for mutans streptococci, lactobacilli, buffering capacity and secretion rate. The risk factors and risk profiles were compared between the groups with aid of Cariogram and the estimated risk for future caries was categorized as "high" or "low".

Results: Children with CL(P) (the entire study group) had significantly higher counts of salivary lactobacilli ($p < 0.05$) and displayed less good oral hygiene ($p < 0.05$). More 10-year-old children in the CL(P) group had low secretion rate but this difference was not significant. The average chance to avoid caries ranged from 59 to 67 % but there were no significant differences between the groups. The odds of being categorized with high caries risk in the CL(P) group was significantly elevated (*OR* = 1.89; 95 % *CI* = 1.25–2.86). In both groups, children in the high risk category had a higher caries experience than those with low risk.

Conclusion: Children with CL(P) displayed increased odds of being categorized at high caries risk with impaired oral hygiene and elevated salivary lactobacilli counts as most influential factors. The results suggest that a caries risk assessment model should be applied in the routine CL(P) care as a basis for the clinical decision-making and implementation of primary and secondary caries prevention.

Keywords: Cleft lip, Cleft palate, Cleft lip and/or palate, Caries risk, Cariogram, Children

Background

Cleft lip and/or palate (CL(P)) is the most common congenital craniofacial deformity, affecting nearly two in every 1.000 newborns in Sweden [1]. The association between CL(P) and dental caries in children is not fully clear but a number of studies indicate a higher caries prevalence in children with different oral clefts in comparison with non-cleft controls [2–6]. Several factors can contribute to this higher susceptibility such as impaired oral hygiene [2, 5, 7, 8], enamel hypoplasia [9, 10] and early colonization of caries-associated microorganisms [11]. Furthermore, parents to children with CL(P) tend to overindulge the children and offer them sucrose-containing food and snacks as a compensation for their medical condition [12, 13]. The prolonged oral clearance time in children with oral clefts may also contribute to a cariogenic environment [14]. The role and relative importance of the potential risk factors are however not

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Lampiran 44 (Sunderji et al., 2017)

PEDIATRIC DENTISTRY / V 39 / NO 5 SEP / OCT 17

CASE CONTROL STUDY

Dental Caries Experience in Texan Children with Cleft Lip and Palate

Sabrina Sunderji, DDS, MScD[1] • Bhavini Acharya, BDS, MPH[2] • Catherine Flaitz, DDS, MS[3] • Brett Chiquet, DDS, PhD[4]

Abstract: ***Purpose:*** *The purpose of this study was to assess the caries experience in the primary dentition of children born with cleft lip and palate (CLP).* ***Methods:*** *A retrospective chart review was conducted on subjects between two and six years old recruited from a university-based pediatric dentistry residency clinic. The number of dental visits and professional fluoride applications, the plaque index and treatment modality, and the presence/location of caries, white spot lesions, and enamel hypoplastic lesions were compared between CLP patients and healthy age- and gender-matched controls. Descriptive statistics, Student's t test, Mann-Whitney U test, and regression analysis were completed.* ***Results:*** *A total of 183 charts were reviewed. Compared to healthy children, CLP children had increases in number of dental visits (P<0.001), decayed-missing-filled surfaces (dmfs; P<0.001), decayed-missing-filled teeth (dmft; P<0.001), enamel hypoplastic lesions (P=0.003), treatment completed under general anesthesia (P<0.001), plaque score (P<0.001), and caries increment between baseline and most recent oral examination (P=0.003). Regression analysis revealed a positive association between age and dmft scores within the CLP group (P=0.018). The caries experience of unilateral and bilateral CLP cases was the same (P>0.05).* ***Conclusions:*** *Children with cleft lip and palate are at a greater risk of enamel hypoplasia and dental caries. No significant caries experience difference was found between unilateral or bilateral CLP cases.* *(Pediatr Dent 2017;39(5)397-402) Received December 12, 2016 / Last Revision May 16, 2017 / Accepted May 21, 2017*

KEYWORDS: CLEFT LIP, CLEFT PALATE, CARIES, PRIMARY TOOTH

Lampiran 45 (Tamasas and Cox, 2017)

Research Reports: Biological

Massively Increased Caries Susceptibility in an *Irf6* Cleft Lip/Palate Model

Journal of Dental Research
2017, Vol. 96(3) 315–322

DOI: 10.1177/0022034516679376
journals.sagepub.com/home/jdr

B. Tamasas[1,2] and T.C. Cox[2,3,4]

Abstract

Patients with cleft lip/palate (CLP) have been reported, in some studies, to exhibit an increased prevalence of caries, although the underlying cause for this increase is unknown. In genetically defined mouse models, studies of postnatal sequelae associated with CLP have been hampered by neonatal lethality. Using a conditional targeting approach, we ablated the major CLP gene *Irf6* only in the late embryonic oral epithelium (*Irf6* cKO), bypassing the role of the gene in lip and palate morphogenesis and thus ensuring survival to adulthood. We report that *Irf6* cKO mice present with 1) dysplastic salivary glands due to disruptions of epithelial junctional complexes, likely secondary to elevated activation of RHO GTPases, and 2) increased salivary cell proliferation. These changes result in significantly reduced saliva flow rate and buffering capacity and increased mucus acidity. A marked decrease in expression of CCL27, one of the major mucosal and skin cytokines, was found that correlated with increased bacterial colonization of the oral cavity with the cariogenic pathogen *Streptococcus mutans* and other bacteria. When placed on a high-sugar diet, *Irf6* cKO mice show a 35-fold increase in presentation and severity of dental caries as compared with wild-type control mice. Strikingly, within the 8-wk test period, many molars extensively dissolved, and there was progressive loss of the alveolar bone, likely as a result of increased colonization of periodontal pathogens. These data provide the first mechanistic insight into the heightened caries susceptibility associated with CLP and indicate a direct role for the major CLP gene *Irf6* in salivary gland development and a significant role in regulating oral immunity. Our data suggest that careful evaluation of salivary gland function and the implementation of early oral health preventive strategies are warranted to reduce the burden of dental care in this at-risk population.

Lampiran 46 (Tikhonova et al., 2018)

Tikhonova *et al. BMC Oral Health* (2018) 18:41
https://doi.org/10.1186/s12903-018-0500-z

BMC Oral Health

RESEARCH ARTICLE Open Access

Investigating the association between stress, saliva and dental caries: a scoping review

Svetlana Tikhonova[1*], Linda Booij[2,3], Violet D'Souza[4], Karla T. B. Crosara[5], Walter L. Siqueira[5] and Elham Emami[4]

Abstract

Background: This scoping review addressed the question 'what do we know about stress-related changes in saliva and dental caries in general population?'

Methods: The review was conducted using electronic searches via Embase, MEDLINE, PsycINFO, CINAHL and WoS. All published human studies with both observational and experimental designs were included. Two reviewers independently reviewed eligible articles and extracted the data. The studies' quality was assessed using the Effective Public Health Practice Project Quality Assessment Tool.

Results: Our search identified 232 reports, of which six were included in this review. All six studies were conducted in children and used salivary cortisol as stress marker. The studies varied by design, types of stressors, children's caries experience, methods of saliva collection. Four studies reported a positive association between saliva cortisol levels and caries ($p < 0.05$) while the other two reported no association ($p > 0.05$). The quality of the included studies was weak to moderate.

Conclusions: There is lack of evidence about an association between stress-related changes in saliva and caries. Well-designed longitudinal studies with rigorous measurement technics for stress, saliva and dental caries are necessary. This will help to generate new insights into the multifactorial etiology of caries and provide evidence for a rational method for its control.

Keywords: Saliva, Dental caries, Psychological stress, Anxiety, Depression

Lampiran 47 (Tuaño-Cabrera et al., 2017)

Caries Experience in Filipino Children with Cleft Lip and/or Palate from the Noordhoff Craniofacial Foundation, Philippines

Cecile Ammeli Tuaño-Cabrera,[1,2] Eula C. Ildefonso[3] and Maria Blanca S. Palabrica[3]

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[2]*Noordhoff Craniofacial Foundation Philippines*
[3]*College of Dentistry, University of the Philippines Manila*

ABSTRACT

Objective. This study aims to provide an overview and statistical data on the prevalence of dental caries and caries index scores in Filipino children from the Noordhoff Craniofacial Foundation Philippines, Incorporated (NCFPI).

Methods. A retrospective quantitative descriptive study was undertaken based on pretreatment records of 332 children aged 2 to12 years, with cleft lip (CL), cleft palate (CP), or cleft lip and palate (CLP).

Results. The prevalence of caries ranged from 81% to 100%. There were significant differences in dmft scores between the 2 to 5 year-olds and the 6 to 9 year-olds ($p<0.0001$), and between the 6 to 9 year-olds and the 10 to 12 year-olds ($p<0.0001$). There were also significant differences between the DMFT scores of the 6 to 9 year-olds and the 10 to 12 year-olds ($p<0.0001$), between the CL and CP groups ($p<0.0001$), and between the CL and CLP groups($p<0.0001$). There were no significant differences in dmft and DMFT scores between the males and females.

Conclusion. There is high caries prevalence in children with CL, CP and CLP. Caries index scores are higher with increasing age. Poor oral hygiene and the presence of other predisposing factors increase their susceptibility to caries.

500 newborns[2] in the country. In a series of epidemiologic studies done from 1989 to 1996 in six sites within the country, the prevalence of cleft lip and palate was 1.94 per 1000 live births.[3] An infant/child with oral cleft endures physical disabilities like speech, hearing, and dental problems.[4] Due to this defect, the child's oral health and function are compromised. Children with CLP have a higher prevalence of dental abnormalities than do children without clefts. Tooth malformations and malpositions, along with problems such as crowding and the presence of fistulas, are among the predisposing factors in the development of dental caries. Due to the presence of these predisposing factors in children with CLP, one can assume for them to have a high caries index.[5]

The prevalence of dental caries in patients with CLP has been researched extensively in different parts of the world.[6–11] However, there is little published research regarding dental caries prevalence and/or incidence in individuals with CLP in the Philippines. On the other hand, the 2006 National Oral Health Survey conducted among the public school population in the Philippines has shown that 6-year-old schoolchildren have 97% overall caries

Lampiran 48 (Worth et al., 2017)

Are people with an orofacial cleft at a higher risk of dental caries? A systematic review and meta-analysis

V. Worth,*[1] R. Perry,[1] T. Ireland,[2] A. K. Wills,[1] J. Sandy[2] and A. Ness[3]

In brief

Highlights that individuals born with a cleft lip and/or palate may face difficulties throughout life which can affect their physical and mental well-being.	Notes that the quality of the papers included in this systematic review and meta-analysis were considered poor due to incomplete descriptions of the participants.	Shows that the CL/P groups had a greater deciduous dmft and permanent DMFT experience than the unaffected controls.

Objective To establish whether children born with an orofacial cleft have a higher risk of dental caries than individuals without cleft. **Design** A systematic review and meta-analysis **Methods** The search strategy was based on the key words 'cleft lip palate' and 'oral hygiene caries decay'. Ten databases were searched from their inception to April 2016 to identify all relevant studies. All data were extracted by two independent reviewers. The primary outcome measure was caries measured by the decayed, missing, filled surfaces/teeth index (dmfs/dmft or DMFS/DMFT). **Results** Twenty-four studies met the selection criteria. All of the studies were observational. Twenty-two studies were suitable for inclusion in the meta-analysis. The overall pooled mean difference in dmft was 0.63 (95% CI: 0.47 to 0.79) and in DMFT was 0.28 (95% CI: 0.22 to 0.34). **Conclusion** Individuals with cleft lip and/or palate have higher caries prevalence, both in the deciduous and the permanent dentitions.

Lampiran 49 (Wu et al., 2016)

Int J Clin Exp Med 2016;9(6):11732-11739
www.ijcem.com /ISSN:1940-5901/IJCEM0024605

Original Article

Association of polymorphisms of *IRF6* to non-syndromic cleft lip with or without palate in a Guangdong population

Wenli Wu[1], Jiansuo Hao[1], Hongtao Wang[1], Liang Hua[2], Fan Li[1], Yiyang Chen[1], Jiayu Liu[1]

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Received January 21, 2016; Accepted May 12, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Non-syndromic cleft lip with or without cleft palate (NSCL/P) is the most common birth defect. The gene interferon regulatory factor 6 (*IRF6*) is the most studied candidate-cause of clefts of the lip, palate, or both. Variations of *IRF6* are associated with ethnicity. We investigated the presence of 8 tag SNPs of *IRF6* in residents of Guangdong province: 126 patients with NSCL/P (29 with cleft lip only [CLO], 45 with cleft palate only [CPO], 52 with cleft lip and palate [CLP]), and 140 healthy individuals. After genotyping, associations between the tag SNPs and NSCL/P were based on results of allele and genotype frequency, multivariate logistic regression, linkage disequilibrium, and haplotype analysis. The *IRF6* polymorphisms rs2236909 T/C, rs2236908 C/G, rs2236907 G/T, rs2235375 C/G, and rs2235373 C/T appeared linked and may belong to the same haplotypes. They may increase risk for NSCL/P but are not linked with risk factor rs2235371 G/A. SNPs rs595918 (C > T) and rs861019 (T > C) are protective against NSCL/P. Thus, these SNPs of *IRF6* are present in residents of Guangdong province and are associated with risk of CLP, CPO and CLO.

Keywords: *IRF6*, polymorphisms, non-syndromic cleft lip with or without cleft palate, Guangdong population, gene type

Lampiran 50 (Wu-Chou et al., 2018)

American Cleft Palate-Craniofacial Association 75th Anniversary

Original Article

The Cleft Palate-Craniofacial Journal
1-8

DOI: 10.1177/1055665618809244
journals.sagepub.com/home/cpc
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Association Studies Between Regulatory Regions of *IRF6*/*TP63* Genes and Nonsyndromic Oral Clefts

Yah-Huei Wu-Chou, PhD[1,2], Yi-Chieh Lu, MS[1,2], Kuo-Ting Philip Chen, MD[2,3], Hsien-Fang Chang, MS[4], Yin-Ting Lin, BS[1,2], and Lun-Jou Lo, MD[2,3,5]

Abstract

Objective: To evaluate genetic variants within the regulatory regions of interferon regulatory factor 6 (*IRF6*) and *TP63* for the etiology of nonsyndromic oral clefts risk factors.

Design: We performed allelic transmission disequilibrium test analysis on 5 eligible single-nucleotide polymorphisms (SNPs) and SNP haplotypes using the Family-Based Association Test.

Participants: The study sample consisted of 334 case–parent trios of nonsyndromic oral clefts from Taiwanese population, separated into nonsyndromic cleft lip/palate (NSCL/P) and nonsyndromic cleft palate only (NSCPO) groups.

Results: We found all 3 selected SNPs of the *IRF6* gene show significant association with nonsyndromic oral clefts (rs2235371, $P = 5.10E-07$; rs642961, $P = .00194$; and rs77542756, $P = 9.08E-07$). Haplotype analyses identified 3 possible SNP combination haplotypes in the *IRF6* gene and found that C-G-G showed significant undertransmission ($P = .058$), whereas 2 other haplotypes, T-G-A and C-A-G ($P = 2.71E-06$ and $P = 5.00E-04$, respectively), were significantly overtransmitted to the NSCL/P children but not to the NSCPO children. For the *TP63* gene, we failed to detect evidence of nonsyndromic oral cleft association in the 2 SNPs within the *TP63* large intron 1 region.

Conclusions: We used a family-based analysis in 334 Taiwanese case–parent trios to evaluate selected SNPs of *IRF6* genes and *TP63* genes for a risk of orofacial clefting. This study provides additional evidence for an association between *IRF6* and NSCL/P, including the genetic variants within the 5′-noncoding region of the gene. We also confirmed that NSCL/P and NSCPO individuals belong to different groups. For the TP63, our data did not favor the direct involvement of TAp63 isoforms during orofacial development.

Lampiran 51 (Xiao et al., 2015)

Int J Clin Exp Med 2015;8(9):16322-16327
www.ijcem.com /ISSN:1940-5901/IJCEM0008794

Original Article

The caries prevalence of oral clefts in eastern China

Wen-Lin Xiao[1,2], Dai-Zun Zhang[1,2], Yao-Xiang Xu[1,2]

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Received April 5, 2015; Accepted September 2, 2015; Epub September 15, 2015; Published September 30, 2015

Abstract: Little information is available concerning the prevalence of caries among patients with oral clefts in Eastern China. Consecutive patients aged 6-18 with oral clefts were recruited. Patients were stratified into 2 groups according to their ages, namely Group I with aged 6-12 and Group II with aged 13-18. For each age group, the children were further divided into three subgroups according to the types of oral clefts they had: cleft lip/cleft lip and alveolus (CL), cleft palate only (CP), and cleft lip and palate (CLP). Dental caries were examined by using the decayed, missing, and filled index for primary teeth (dmft) and Decay, Missing and Filled index for Permanent teeth (DMFT) according to criteria of the World Health Organization. 268 eligible patients with oral clefts were included in the study. The mean DMFT for Group I was 1.77 (SD2.58) while that for Group II was 6.96 (SD4.35). The mean DMFT was statistically significant different between the age group I and age group II ($t=12.21$, $P<0.05$). In Group I, the dmft scores was 4.68 (SD3.67) for CL group, while that for the CP group was 7.36 (SD3.93), and that for the CLP group was 5.72 (SD 3.87). The mean dmft was no statistically significant different among cleft types ($F=3.13$, $P>0.05$). Also in Group I, the mean DMFT was 1.56 (SD2.18) for CL group, while that for the CP group was 1.24 (SD 1.81) and that for the CLP group was 2.08 (SD2.96). There were no statistically significant different in mean DMFT among different cleft types ($F=1.09$, $P>0.05$). In Group II, the mean DMFT was 6.06 (SD3.97) for CL group while that for the CP group was 7.71 (SD 4.94) and that for the CLP group was 7.05 (SD4.32). No significant difference was shown in the mean DMFT among different cleft groups (CL, CP, and CLP) ($F=0.55$, $P>0.05$). During assess the prevalence of dental caries among Eastern Chinese with oral clefts; the study confirmed that the prevalence of caries was increased with increasing age for oral clefts patients. It was also demonstrated that there was no significant difference in the mean dmft/DMFT scores among different cleft types.

Keywords: Dental caries, oral clefts, epidemiology

Lampiran 52 (Xing et al., 2019)

GENETIC TESTING AND MOLECULAR BIOMARKERS
Volume 23, Number 9, 2019

Pp. 1–12
DOI: 10.1089/gtmb.2018.0315

Association Between an Interferon Regulatory Factor 6 Gene Polymorphism and Nonsyndromic Cleft Palate Risk

Yue Xing,[1,2,*] Wancong Zhang,[1,*] Xinhong Wan,[3,*] Zhiqian Hong,[1,*] Hanxing Zhao,[1,2] Weijie Liang,[1,2] Lungang Shi,[1,2] Jiasheng Chen,[1,2] Xiaoping Zhong,[1,2] Jianda Zhou,[4] and Shijie Tang[1]

Background: Involvement of interferon regulatory factor 6 (*IRF6*) gene polymorphisms in nonsyndromic cleft palate (NSCP) risk remains controversial. This investigation was performed to evaluate the relationship between *IRF6* gene polymorphisms and NSCP risk.
Materials and Methods: Two hundred forty-one patients with NSCP (including 103 complete trio families) were recruited, and 242 unaffected individuals were included as controls. Polymorphisms for *IRF6* rs2235371, rs801619, rs642961, rs44844880, and rs8049367 were characterized in both groups. Furthermore, eligible studies were identified from the databases through June 1, 2017, and were recruited and calculated using meta-analysis to enhance the robustness of our conclusions.
Results: The *IRF6* rs2235371 A allele and AA genotype in the case group were found at higher frequencies than in the control group (A allele: $p < 0.0016$; AA genotype: $p < 0.0049$). The *IRF6* rs801619 AA genotype and G allele were associated with NSCP risk (G allele: $p < 0.0061$; AA genotype: $p < 0.0195$). At the *IRF6* rs642961, rs44844880, and rs8049367 loci genotype and allele frequencies were not statistically different between the NSCP group and normal controls. In the meta-analysis, the *IRF6* A/G gene polymorphism (rs2235371) and IRF6 A/G gene polymorphism (rs642961) were associated with NSCP risk in the general population, whereas the *IRF6* A/C gene polymorphism (rs2013162) was not.
Conclusion: *IRF6* A/G gene polymorphisms at rs2235371 and rs642961, but not the *IRF6* A/C gene polymorphism rs2013162, were associated with NSCP risk.

Lampiran 53 (Xu et al., 2016)

Association of single-nucleotide polymorphisms, rs2235371 and rs2013162, in the *IRF6* gene with non-syndromic cleft palate in northeast China

W. Xu[1], W.T. Han[1], Y.P. Lu[1], W.H. Feng[1] and M. Dai[2]

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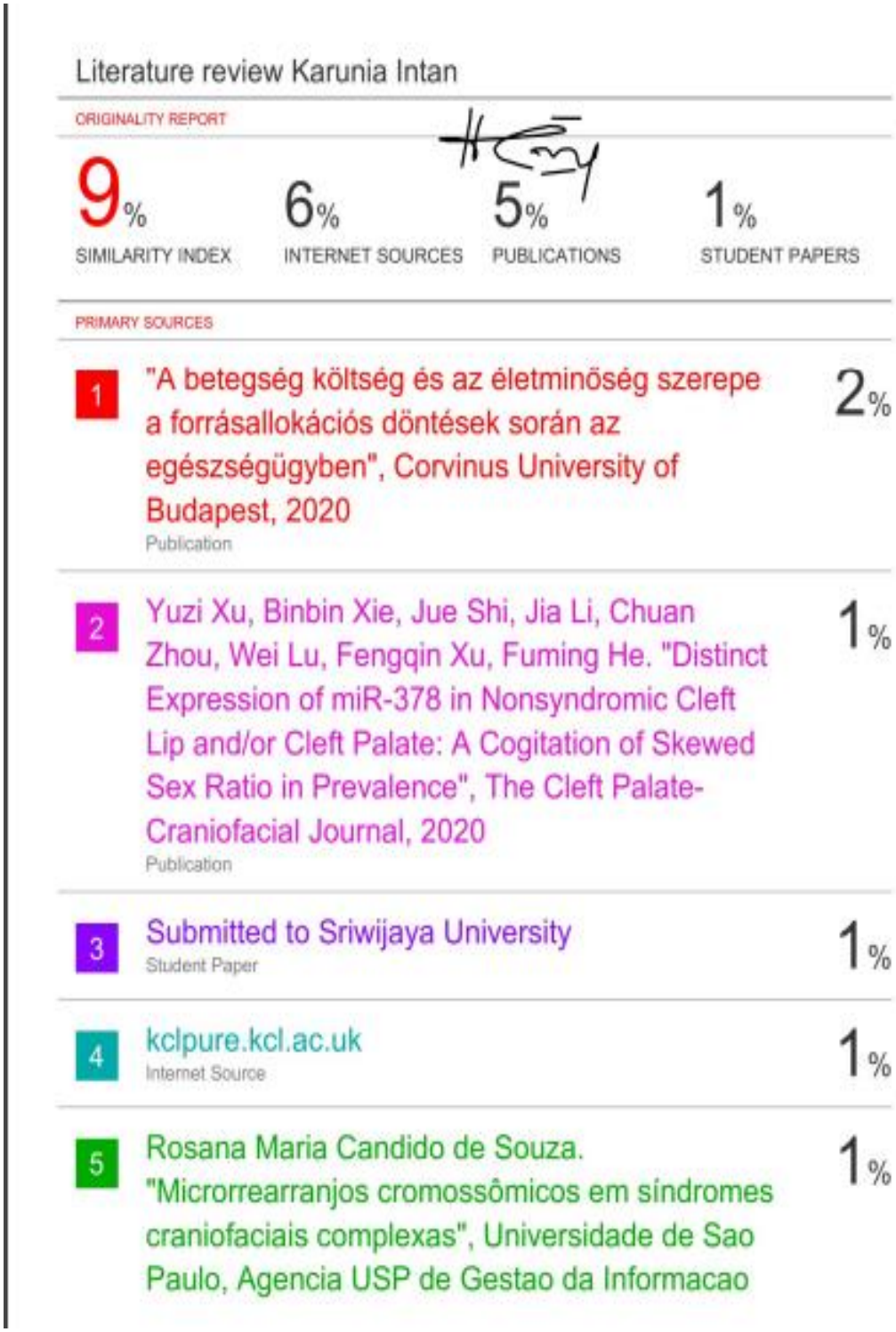
ABSTRACT. The aim of this study was to determine the association between two SNPs (rs2235371 and rs2013162) in the interferon regulatory factor 6 (*IRF6*) gene and non-syndromic cleft palate (NSCP) in northeast China. We genotyped these two SNPs in 104 NSCP cases, as well as in 178 parents and 300 controls. Case-control and case-parent analyses were performed using χ^2 tests and family-based association tests (FBAT). Results indicated that there were significant differences in both genotypic and allelic distributions between patients and controls at rs2235371 and rs2013162 in the *IRF6* gene. Case-parent analysis revealed over-transmission of the C allele in rs2235371 and the A allele in rs2013162. Lastly, FBAT showed over-transmission of the CA haplotype. This study demonstrated that the two SNPs, rs2235371 and

Lampiran 54 Hasil turnitin skripsi



Literature review Karunia Intan

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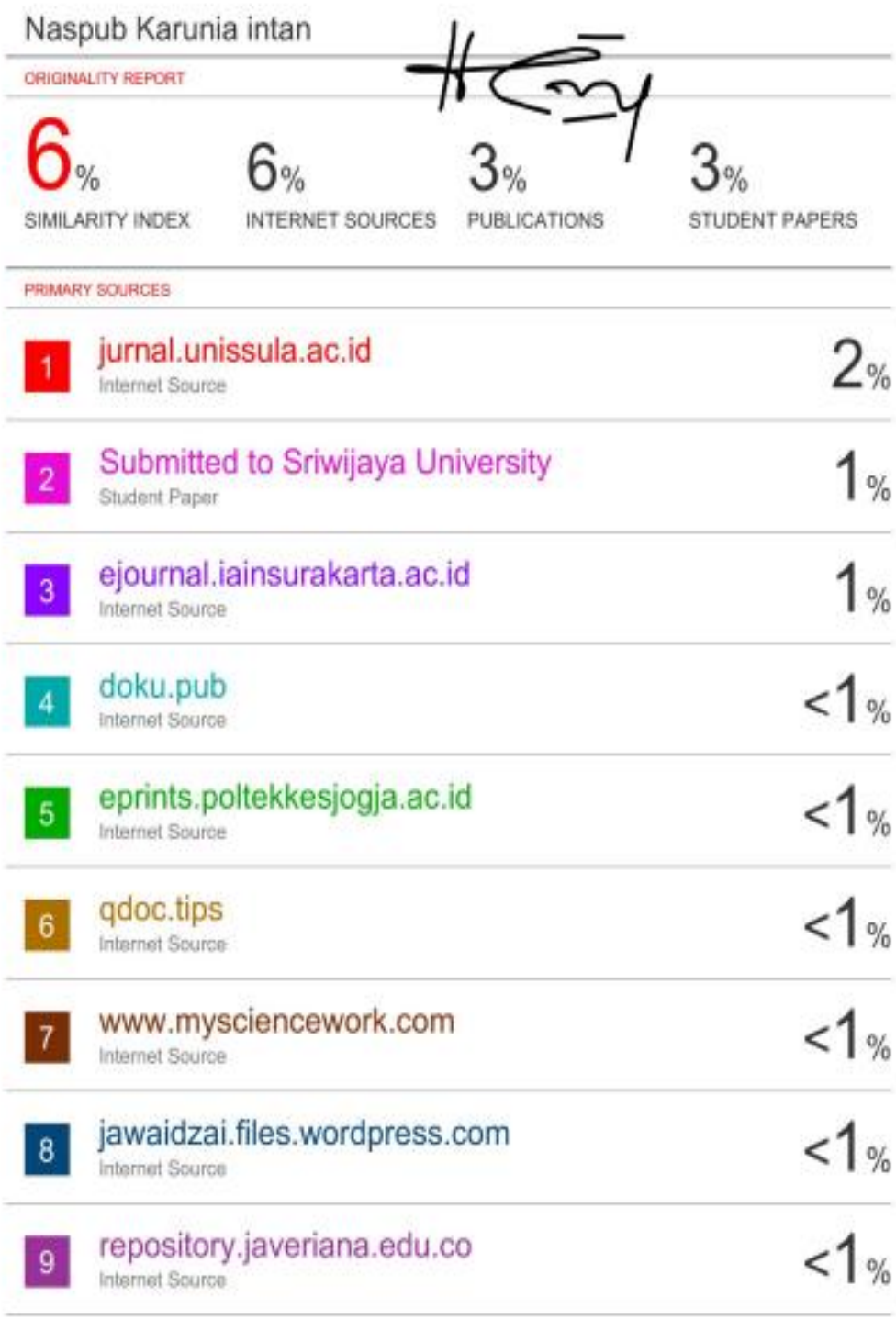

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