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Review article

The role of family history as a risk factor for non-syndromic cleft lip and/or palate with multifactorial inheritance

Agung Sosiawan[1], Mala Kurniati[2], Coen Pramono Danudiningrat[3], Dian Agustin Wahjuningrum[4] and Indra Mulyawan[3]
[1]Department of Dental Public Health, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Biology, Faculty of Medicine, Universitas Malahayati, Lampung, Indonesia.
[3]Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.
[4]Department of Conservative Dentistry, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.

ABSTRACT

Background: *Cleft lip with or without cleft palate (CL/P) is a facial growth 'disorder that occurs during gestation and has multifactorial causes owing to both genetic and environmental factors. Several factors can increase the likelihood of CL/P, and one of them is family history. Differences in results obtained from studies conducted across several countries concerning family history as a risk factor for CL/P suggest there is no consensus on how the condition is inherited.* ***Purpose:*** *This study aims to review the literature on the role of family history as a risk factor contributing to the incidence of non-syndromic CL/P (NSCL/P).* ***Review:*** *This review discusses the etiology of CL/P and the risk factors influencing the incidence of CL/P. The review also examines the criteria for inheriting multifactorial disorders to calculate the risks involved should there be a recurrence of the condition based on family history.* ***Conclusion:*** *CL/P is a type of multifactorial disorder with unclear etiology. Therefore, it is important to investigate the risk factors stemming from family history (which play an important role) related to the recurrence risk. Additionally, there should be focus on increasing genetic education and offering counselling to parents and pregnant women.*

Keywords: *cleft lip with or without cleft palate (CL/P); family history; multifactorial; recurrence*

Correspondence: Agung Sosiawan, Department of Dental Public Health, Faculty of Dental Medicine, Universitas Airlangga. Jl. Mayjen Prof. Dr. Moestopo No. 47, Surabaya, 60132 Indonesia. Email: agung-s@fkg.unair.ac.id

INTRODUCTION

Cleft lip with or without cleft palate (CL/P) is a facial growth disorder that occurs during gestation and has multifactorial causes owing to both genetic and environmental factors.[1–3] CL/P has been the subject of many genetic studies, but there has been no consensus on how the condition is inherited.[4] CL/P disorders can interfere with speech, nutrition, hearing, and psychological development.[5,6] The prevalence of CL/P cases varies according to ethnicity and region[7] and is estimated at 1/600 births worldwide. Differences in race, geographical origin, and gender, including the impact of genetic factors, influence the prevalence of CL/P.[8,9] The highest prevalence is observed in Asian populations (1/500 births), and the lowest prevalence is observed in African populations (1/2,500 births). The prevalence of CL/P in the Caucasian race is 1/1,000 births.[10,11]

Family history as a risk factor with the potential to cause CL/P is an interesting area of study. Calculating the recurrence risk in CL/P patients having a family history of CL/P concerns multifactorial inheritance, which is different from the Mendelian inheritance pattern (single gene), because CL/P is a multifactorial and polygenic disorder. Until now, the genes involved in causing CL/P continue to be studied; however, researchers have not found the dominant gene responsible for causing CL/P. Therefore, the authors are interested in studying the literature on the role of family history in increasing the risk of CL/P, especially from the perspective of multifactorial inheritance.

Epidemiology

The prevalence of CL/P worldwide is 1/500–1/2,500 births, with the highest incidence in Asian races at 1/500 births.[12] The ratio of occurrence of CL/P in men and women is 1:2;

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more women suffer from this disorder than men.[3] A study conducted in North America reported a prevalence rate of between 0.6 and 3.92 per 1,000 births. Studies conducted in Europe reported prevalence rates ranging from 1.02 to 1.94 per 1,000 births. Studies carried out in Oceania reported prevalence rates in White people ranging from 1.21 to 1.73 per 1,000 births Many low-income countries do not have a birth control system yet and a system to register birth defects, especially CL/P. This prevalence is indicated in Table 1. International collaborative research on craniofacial malformations in developing countries, under the World Health Organization (WHO), is currently being carried out. Cases of CL/P are also being recorded in these studies.[13]

Etiology of CL/P

The underlying etiology of CL/P is unknown. However, the complex embryogenesis of the lips and palate makes the tissue surrounding these areas susceptible to various disorders that can potentially cause malformations during the developmental stage. As shown in Figure 1, the etiology of CL/P is a complex and multifactorial interaction, involving various genetic and environmental factors and gene–environment interactions.[4,10,14,15]

From a genetic perspective, the etiology of CL/P has been studied for many years. A literature study reveals that the heritability of non-syndromic cleft lip with or without cleft palate (NSCL/P) is 70%.[16] Studies conducted on twins followed by further segregation analysis confirmed the role of genetics in the etiology of CL/P.[2,17] The risk of CL/P increases when there is a family history of CL/P. Parents with CL/P disorders can have children facing a 3–5% risk of having CL/P.[16] The role of environmental factors leading to CL/P is very influential. Previous studies have revealed the increasing prevalence of CL/P in patients whose mothers smoked, consumed alcohol, were administered antiepileptic drugs and corticosteroids, had nutritional deficiencies (folic acid), and were afflicted with infectious diseases during pregnancy.All of these factors affected the intrauterine environment.[18] These environmental factors were found to increase the risk of NSCL/P. Recent studies have shown that maternal diseases (e.g. hyperthermia, parental occupation, diabetes mellitus, and obesity) present risk factors for CL/P.[19] It is vital to examine the interaction and understand the nature of relationship between genes and the environment because CL/P occurs due to the involvement of many genes and environmental factors. Maternal smoking and folic acid deficiency are two factors that can increase the genetic risk of developing CL/P. A study has suggested that there is a gene–environment interaction taking place between mothers who smoke and changes in genetic variants of the growth factor gene, the muscle segment homeobox, and the retinoic acid receptor gene.[20,21]

Table 1. Geographical variation in birth prevalence of orofacial clefts as per continent.[13]

Continent (Location)	Numbers of CL/P	Number of live births	Birth prevalence (per 1,000 live births)	95% Confidence Interval
Asia	15,646	9,965,084	1.57	1.54–1.60
North America	18,276	11,728,914	1.56	1.53–1.59
Europe	5,028	3,236,253	1.55	1.52–1.58
Oceania	2,822	2,125,912	1.33	1.30–1.36
South America	3,205	3,229,179	0.99	0.96–1.02
Africa	216	380,273	0.57	0.54–0.60
Total	45,193	30,665,615	1.47	1.44–1.50

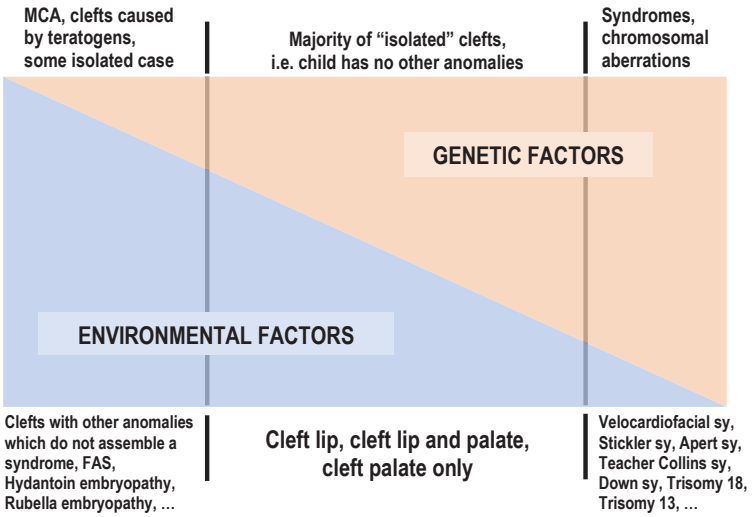

Figure 1. Etiology of CL/P.[15]

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Risk factors involved in the occurrence of CL/P

Many factors are associated with the occurrence of CL/P, but the susceptibility of CL/P can increase if triggered at the right time, place, and moment of morphogenesis and facial formation.[19] Risk factors that can cause CL/P disorders include geographic location, family history, alcohol and tobacco consumption, inadequate nutrition, drug intake during pregnancy, miscellaneous infections, and occupational hazards affecting pregnant women. The first set of factors responsible for the occurrence of CL/P are the geographical location, the climate and the continental differences in the world. Asian races are at the greatest risk marked at 14 cases in 10,000 births. This is followed by the Caucasian race, who face a risk of 10 cases in 10,000 births. Finally, the African Americans face a risk of 4 cases in 10,000 births.[19] The second risk factor is family history. Family members with CL/P are at a greater risk of transmitting the condition to their offspring.[22] Therefore, clinicians and parents should realise the importance of genetic counselling. The third factor leading to CL/P is consuming alcohol during pregnancy. When alcohol is combined with other factors (e.g. consumption of tobacco and drugs, along with other socio-geographical factors), the risk of developing CL/P is extremely high.[23,24]

The fourth factor leading to the occurrence of CL/P is nutrition. Folic acid, vitamins, zinc, and other micro elements create a great impact on pregnancy. Several studies have shown that consuming soda and tea can influence pregnancy.[25,26] The fifth factor leading to the occurrence of CL/P is the consumption of certain drugs during pregnancy. Drugs, corticosteroids, antibiotics, and local and general agents administered during pregnancy can strongly influence the occurrence of CL/P.[27,28] The sixth factor that can lead to the occurrence of CL/P, which is quite important, is the health status and the presence of viral infection in pregnant women. Viral infections and diseases associated with an increase in body temperature play a major role in causing hereditary diseases.[29,30] The seventh factor leading to the occurrence of CL/P is the nature of work that pregnant women are involved in. Factors related to work (e.g. radiation, exposure to high temperatures, chemicals, light and electromagnetic fields, and some other elements can affect a women's health in the early stages of pregnancy).[31–33]

DISCUSSION

The etiology of CL/P is multifactorial, involving many unknown genes that have not yet been thoroughly studied. Thus, the possibility of recurrence in a family is based on case experience.[14] An interesting risk factor that can be investigated is the relationship between family history and the occurrence of CL/P. Family history is one of the genetic factors that can increase the occurrence of CL/P and is polygenic or multifactorial. In certain multifactorial disorders, certain phenotypes are passed from one generation to another, indicating intermittent variation (as shown in Figure 2).

Recurrence of CL/P ranges from 1–5%. This disorder usually has an incidence of about 1 per 1,000 live births and involves a single organ system or an embryologically-related organ system. There are several criteria for inheriting polygenic or multifactorial disorders: recurrence risk as a function of relatedness, recurrence risk as a function of prior offspring, recurrence risk by severity, and recurrence risk by sex.[34,35] An individual has two copies of their parent's genes: one from the mother and the

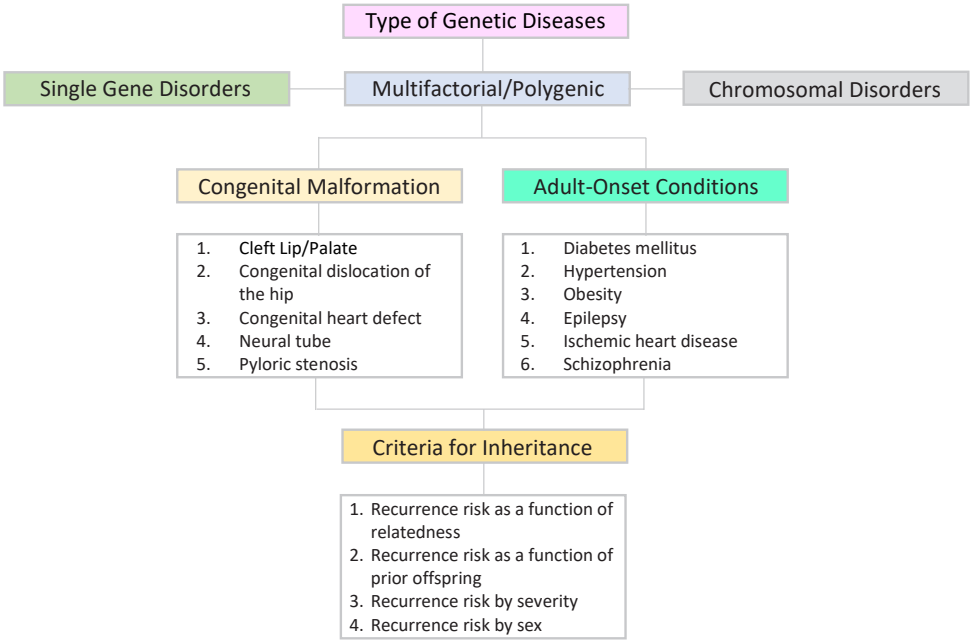

Figure 2. Criteria for polygenic or multifactorial inheritance.

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second from the father.[27] Genetic variation occurs due to gene interactions (not spontaneously) and is passed down from generation to generation.[36] The incidence of CL/P does not involve only one hereditary factor arising from one or both parents. CL/P is a concurrent condition.[28] This explains why the probability of passing down CL/P to subsequent offspring is relatively low. The probability that the next child will also inherit the same combination of several genes and be exposed to certain environmental factors ranges from 3 to 5%.[37,38] It can be concluded that if the prevalence of the condition in a population is A, the recurrence risk in offspring and siblings is the root of A ($\sqrt{A}$).[34,35]

In polygenic or multifactorial inheritance, the concordance rate of monozygotic twins with CL/P disorders is higher (40–60%) than in dizygotic (DZ) twins (3–5%). In DZ and non-twin siblings, the recurrence risk can be approximated through the square root of incidence in a population.[39] In contrast to Mendelian inheritance, the recurrence risk increases empirically after more than one offspring has the disorder. The risk rarely approaches the expected 25% for the recessive trait and the expected 50% for the dominant trait. However, the risk is extremely high (15–20%) after three offspring are affected.[34] The study conducted by Sivertsen et al.[37] found a strong specificity of recurrence risk for two main types of clefts, suggesting that they had different causes. The risk is similar among children of affected fathers, children of affected mothers, and affected siblings. This pattern suggests that autosomal fetal genes play a major role in risk recurrence, with a small additional contribution from the inherited aspects of the maternal phenotype.[38,40]

The study carried out by Martelli et al.[38] in Brazil aimed to determine the incidence of family NSCL/P. The results revealed that there were differences observed between the types of CL/P disorders and family history in 185 patients ($p<0.001$).[38] Jamilian et al.[28] conducted a study with a sample size of 187 people with the aim of understanding the link between parental risk factors and the incidence of malformations (CL/P). The results revealed that the risk factors involved when considering family history variables were an odds ratio of 7.4 and a 95% confidence interval and an odds ratio of 3.2 and a 95% confidence interval in consanguineous marriages. These factors increased the incidence of CL/P.[28] Acuña-González et al.[41] conducted a study with the aim of understanding the relationship between family history and socio-demographic risk factors in the incidence of NSCL/P. The results indicated that the risk factors associated with family history and those associated with the incidence of CL/P were 1) the occurrence of past NSCL/P cases in the father's or mother's family and 2) having a sibling with CL/P.[41]

Complex inherited diseases can be influenced by interactions between the influence of one or several genes that increase or decrease susceptibility to a disease combined with triggers (e.g. environmental exposure) that can accelerate, exacerbate, or protect an individual against a disease. The new paradigm of genetic engineering today has brought freshness in diagnosing and analysing congenital disorders. Previously, the Mendel's Law theory was applied to estimate the risk of recurrence in single-gene diseases. However, in multifactorial diseases, chromosomal disorders, and diseases whose etiology is unknown, the empirical method of calculating the recurrence risk is an important tool for evaluating multifactorial disorders. Although, in general, the empirical recurrence risk can be inaccurate (either due to differences in gene frequency and environmental factors among populations or due to the heterogeneity of a disease), population studies of family history, computer programmes, genotyping technology, genome-wide association studies, and single nucleotide polymorphisms can be employed to estimate the recurrence risk of multifactorial disorders.[42]

It is important to emphasise the need to enhance our knowledge about the potential risk factors that can lead to the occurrence of CL/P, especially genetic education and counselling to parents and mothers regarding the right behavioural lifestyle to follow before and during pregnancy. There is a potential to reduce the incidence of CL/P by spreading awareness and educating people. There are several criteria that lead to the high recurrence risk of CL/P, especially in multifactorial inherited diseases (including CL/P): 1) more than one family member is affected with CL/P; (2) the disease expression in the proband is more severe; (3) the proband belongs to the less commonly affected gender; and (4) the recurrence risk usually decreases rapidly in more distant relatives.

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