

Epidemiological and Genetic Determinants of Nonsyndromic Orofacial Clefts: Etiology, Consanguinity, and Oncogenic Susceptibility

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ABSTRACT

Nonsyndromic orofacial clefts, comprising cleft lip with or without cleft palate, represent the most frequent craniofacial malformations globally. Understanding their complex etiology requires analyzing both genetic markers and socio-demographic risk factors within clinical populations.

This descriptive analytical study investigated a hospital-based cohort to assess phenotypic distributions and evaluate parental consanguinity and familial clustering. To broaden the clinical utility of the findings, a systematic appraisal of underlying susceptibility loci was conducted, examining genetic links to both craniofacial disruptions and broad cellular overgrowth mechanisms.

Phenotypic analysis revealed a distinct predominance of unilateral cleft lip and palate over isolated cleft palate, with a pronounced variance based on sex and parental kinship structures. Consanguineous unions significantly elevated the recurrence risks within families. Theoretical assessment of susceptibility regions confirmed that risk clusters on chromosomes 1, 2, 8, 17, and 19 exhibit dual functionality, modulating both palatal shelf fusion and cell proliferation pathways.

The inheritance patterns of orofacial clefts conform to a multifactorial threshold model. Effective long-term prevention and management necessitate integrated clinical strategies that fuse genetic counseling with personalized, patient-centric health coaching models.

Keywords: Orofacial Clefts, Etiological Factors, Consanguinity, Genome-Wide Association Studies, Multifactorial Inheritance, Health Coaching.

1. Introduction

Modern Congenital anomalies involving the craniofacial architecture represent a profound challenge to global public health systems, clinical genetics, and reconstructive surgery. Among these malformations, orofacial clefts stand out as the most common structural defects affecting the face and oral cavity. These conditions present primarily as cleft lip, cleft palate, or a combined manifestation of both cleft lip and palate. The structural divergence of these anomalies is rooted deeply in embryological development, where the failure of facial primordia to fuse correctly between the fourth and twelfth weeks of gestation results in permanent structural divisions. Beyond the immediate physical presentation, these defects impose a substantial lifetime burden on affected individuals, their families, and healthcare infrastructures. The clinical journey for an individual born with an orofacial cleft is prolonged and complex, frequently requiring a highly coordinated, multidisciplinary sequence of interventions. These include primary surgical repairs, secondary bone graftings, extensive orthodontic realignments, speech-language therapy, audiological monitoring, and psychosocial

counseling.

To properly contextualize the structural and biological impacts of these anomalies, it is useful to examine the broad epidemiological metrics that define their presence globally. Large-scale public health evaluations indicate that congenital structural anomalies remain a primary contributor to early-life morbidity and structural disability worldwide (Naghavi et al., 2024). Within this global distribution, orofacial clefts exhibit a complex, highly variable pattern of occurrence that is heavily influenced by geographic region, ethnic background, and socio-demographic factors (Putri et al., 2024). Epidemiological surveys consistently demonstrate that the highest rates of orofacial clefts are observed in Asian and Native American populations, where the prevalence can approach one in every five hundred live births. Conversely, European and Caucasian populations exhibit intermediate rates, typically hovering around one in every seven hundred to one thousand live births. The lowest baseline rates are documented within African and African-descent populations, where the prevalence often falls below one in every two thousand live births (Butali et al., 2014; Eshete et al., 2017).

However, looking purely at baseline occurrence numbers obscures the significant local variations observed within specific clinical contexts. Hospital-based populations, particularly in developing or middle-income regions, frequently present with phenotypic distributions and severity levels that differ markedly from broad national registries (Albalawi et al., 2023). These discrepancies often stem from localized genetic architectures, regional environmental exposures, and disparate access to prenatal and specialty healthcare. For instance, in many regions across the African continent and the Middle East, the documented prevalence of oral diseases and congenital craniofacial malformations reflects a critical intersection of unmet surgical needs and limited epidemiological reporting (Abid et al., 2015). Consequently, localized descriptive analytical studies are essential for capturing the true clinical landscape of orofacial clefts within specific populations. They provide the precise, contextual data necessary to design targeted public health interventions and optimize the allocation of specialized surgical and therapeutic resources.

The fundamental biological challenge in studying orofacial clefts lies in their dual clinical classification: syndromic and nonsyndromic. Syndromic orofacial clefts occur in the presence of additional major structural, developmental, or cognitive anomalies, or as part of a recognized genetic syndrome such as Van der Woude, Pierre Robin, or Stickler syndrome. These syndromic presentations account for roughly thirty percent of all orofacial cleft cases and typically follow classic Mendelian inheritance patterns driven by highly penetrant mutations in single genes. In sharp contrast, the remaining seventy percent of cases are classified as nonsyndromic orofacial clefts. These individuals present with a cleft lip and/or palate in total isolation, without any other detectable physical or cognitive delays.

The etiology of nonsyndromic orofacial clefts is robustly recognized as multifactorial, representing a intricate interplay between polygenic susceptibility networks and a vast array of maternal environmental triggers. This etiology does not conform to straightforward Mendelian laws; rather, it adheres to a multifactorial threshold model of inheritance. This model posits that an individual accumulates a certain degree of genetic vulnerability and environmental insult up to a critical point-the threshold of liability-beyond which the normal processes of embryological facial fusion are disrupted, resulting in a cleft presentation (Grosen et al., 2010).

From an embryological perspective, the formation of the human face is a marvel of spatial and temporal precision. It requires the perfectly timed migration, proliferation, and differentiation of cranial neural crest cells into the primary facial processes: the frontonasal prominence, the paired maxillary prominences, and the paired mandibular prominences. Cleft lip, with or without cleft palate,

typically arises from a failure of the maxillary prominence to fuse adequately with the medial nasal prominence on one or both sides during the sixth week of embryonic development. Isolated cleft palate, on the other hand, represents a distinct developmental failure occurring later in embryogenesis, specifically between the eighth and eleventh weeks. This involves the failure of the secondary palatal shelves to elevate from a vertical position alongside the tongue, rotate to a horizontal position above the tongue, meet at the midline, and fuse smoothly with one another and the nasal septum. Because the primary lip and the secondary palate develop at distinct chronological points and involve different cellular mechanisms, researchers have traditionally viewed them as separate etiological entities. However, modern genetic mapping has increasingly revealed a significant overlap in the genetic risk loci that sensitize an embryo to both forms of clefting (Tanaka et al., 2012).

The genetic architecture of nonsyndromic orofacial clefts has been extensively mapped over the last two decades through high-throughput genomic technologies, including genome-wide association studies, meta-analyses, and next-generation whole-genome sequencing. These intensive research efforts have successfully unmasked several critical chromosomal regions and specific susceptibility genes that play foundational roles in craniofacial morphogenesis. Among the most pivotal discoveries was the identification of a powerful susceptibility locus on chromosome 8q24, which has been consistently replicated across diverse ethnic populations as a major driver of cleft risk (Birnbaum et al., 2009). Subsequent large-scale genome-wide association studies rapidly expanded this genetic map, identifying further high-impact susceptibility loci at regions such as 10q25 and 13q31 (Mangold et al., 2009).

As genomic consortia grew more inclusive and statistically powerful, meta-analyses began pooling data from thousands of cases worldwide. This led to the discovery of multiple novel risk loci, reinforcing the understanding that the genetic liability for clefting is distributed across a broad array of chromosomal regions, each contributing small to moderate effects on the overall risk profile (Ludwig et al., 2012). Furthermore, exploring diverse global populations has proved indispensable for discovering novel genetic variants. While early genomic studies were heavily skewed toward cohorts of European ancestry, multi-ethnic genome-wide association studies successfully highlighted novel risk loci on chromosomes 2p24.2, 17q23, and 19q31, proving that different populations possess unique genetic risk signatures (Leslie et al., 2016). Similarly, targeted genomic analyses within previously understudied populations, such as various African cohorts, revealed entirely novel risk loci specifically tied to isolated cleft palate, further underscoring the genetic heterogeneity of the condition (Butali et al., 2019). Most recently, the application of high-depth whole-genome sequencing has enabled researchers to look past common variants and identify rare, de-novo mutations that disrupt crucial developmental signaling cascades, providing a

granular look at the extreme end of genetic liability (Awotoye et al., 2022).

While these genetic discoveries have dramatically advanced our biological understanding, they must be interpreted alongside deep-seated socio-cultural and demographic realities that alter genetic dynamics on the ground. Chief among these factors is parental consanguinity. In many global regions, particularly across parts of North Africa, the Middle East, and South Asia, consanguineous marriages-most frequently between first cousins-are deeply embedded cultural traditions. From a genetic standpoint, consanguinity increases genomic homozygosity, significantly raising the probability that a child will inherit identical copies of a deleterious recessive allele from a common ancestor. Rigorous systematic reviews and comprehensive meta-analyses have firmly established a potent, quantifiable association between parental consanguinity and a heightened risk of a child developing a nonsyndromic orofacial cleft (Sabbagh et al., 2014). This reality complicates the multifactorial threshold model by accelerating the accumulation of genetic liability within specific families, leading to distinct recurrence patterns and higher localized prevalence rates that demand tailored clinical counseling.

An intriguing and rapidly expanding frontier in craniofacial research is the biological link between the genetic pathways that govern embryonic development and those that regulate adult oncogenesis. Accumulating epidemiological and molecular evidence suggests that individuals with orofacial clefts, as well as their first-degree relatives, may exhibit altered long-term risks for various forms of cancer. Population-based cohort studies utilizing extensive national registries have demonstrated elevated cancer risks in individuals carrying oral clefts, suggesting a shared underlying vulnerability to disrupted cellular mechanisms (Bille et al., 2005).

At the center of this connection are specific genes that exhibit dual functionality, operating as crucial regulators of embryogenesis while concurrently acting as proto-oncogenes or tumor suppressors in adult tissues. For example, mutations in the *AXIN2* gene have been directly linked to both the development of orofacial clefts and a pronounced positive family history of colon cancer and other malignancies (Menezes et al., 2009). Systematic reviews focusing on nonsyndromic oral clefts and cancer risk have further substantiated this link, suggesting that the underlying genetic instability or signaling dysregulation that causes a facial cleft may also predispose an individual to uncontrolled cellular overgrowth later in life (Popoff et al., 2013).

This biological intersection is visible across several specific cancer types. Epidemiological evaluations have noted an unexpected clustering of orofacial cleft history within families affected by hematological malignancies, such as

leukemia (J A and V Ar, 2012). Similarly, broader familial surveys have revealed a significant prevalence of cleft lip and palate among the family members of cancer survivors across various tissue types, pointing toward a systemic familial liability to genetic disruption (T E et al., 2010). Large nationwide studies have extended this query to the parents of children born with congenital malformations, examining whether the birth of a child with a structural defect like a cleft reflects an underlying parental genetic environment that carries an elevated risk for malignancy (Zhu et al., 2002).

Specific organ systems show particularly tightly linked pathways; for instance, families displaying a history of clefting have demonstrated altered risk profiles for hormone-driven malignancies, including breast cancer (D A et al., 2012). To unravel these complex, multi-system connections, major public health initiatives have established comprehensive biobanks, such as the AGORA data- and biobank. These repositories link detailed birth defect registries with long-term childhood cancer data, providing the large-scale, high-quality biosamples required to map overlapping etiology (van Rooij et al., 2016).

At the molecular level, these epidemiological links are supported by the behavior of highly conserved signaling pathways. The fibroblast growth factor receptor family, including *FGFR2* and *FGFR3*, is essential for the proliferation and migration of cranial neural crest cells during palatal shelf elevation and fusion. Crucially, somatic and germline mutations in these identical genes are heavily implicated in the pathogenesis of gastric, colorectal, and sporadic postmenopausal breast cancers, demonstrating that a single pathway controls both structural morphogenesis and tumor suppression (Jang et al., 2001; Hunter et al., 2007). Similarly, the *CDH1* gene, which encodes the cell-adhesion molecule E-cadherin, is essential for maintaining epithelial integrity during the fusion of the facial processes. Mutations in *CDH1* have been directly identified in families presenting with a combination of hereditary diffuse gastric cancer and cleft lip and palate, proving that a single genetic lesion can manifest as an embryonic structural defect or an aggressive adult malignancy depending on the cellular context (Frebourg et al., 2006; O F et al., 2019).

The long-term impact of an orofacial cleft extends far beyond early childhood surgical interventions, profoundly affecting an individual's chronic health status and quality of life across their entire lifespan. Scoping reviews investigating young children with cleft lip and palate highlight severe, early-stage disruptions in infant feeding, nutritional intake, and early communication development, which can permanently alter early childhood growth trajectories (Yusof and Mohd Ibrahim, 2023). As these children progress into adolescence and adulthood, the persistent aesthetic and functional differences frequently lead to compromised psychological well-being, social anxiety, and a diminished quality of life.

Furthermore, managing a congenital condition requires

continuous engagement with healthcare systems, demanding high levels of patient and parental compliance with prolonged therapeutic regimens. This reality underscores the need for modern, complementary healthcare delivery models that move past traditional, paternalistic clinical interactions. Health coaching has emerged as a powerful, evidence-based strategy in chronic disease management, utilizing patient-centered behavior modification to improve clinical compliance, self-efficacy, and long-term health outcomes (Cinar et al., 2018). Integrating behavioral health coaching into the long-term management plans for individuals with orofacial clefts and their families represents a promising approach to bridging the gap between complex genetic risks and successful lifelong health outcomes.

Despite the wealth of global literature on this topic, a critical gap remains in combining localized, hospital-based descriptive clinical data with the broader theoretical landscapes of modern genomics and long-term systemic health risks. Many clinical studies focus strictly on the immediate surgical or phenotypic outcomes of a specific cohort, failing to connect these findings to the underlying genetic architectures mapped by large-scale genomic consortia. Conversely, high-level genomic papers often lack the grounded, clinical context of real-world patient populations, particularly regarding the lived impact of socio-cultural variables like consanguinity.

This comprehensive descriptive analytical study addresses this gap by directly evaluating a hospital-based population presenting with orofacial clefts. By synthesizing concrete clinical observations with an exhaustive, multi-layered theoretical analysis of modern genetic susceptibility loci, parental consanguinity dynamics, and shared oncogenic pathways, this paper provides an integrated framework. This approach advances both immediate clinical management and long-term, systemic public health strategy for orofacial clefts.

2. Methodology

The operational framework of this investigation was structured as a hospital-based, descriptive analytical study designed to thoroughly evaluate the clinical, phenotypic, and demographic characteristics of patients presenting with congenital orofacial clefts. The study was situated within a major tertiary care hospital environment, serving as a primary regional referral center with specialized departments in pediatric plastic surgery, clinical genetics, speech therapy, and orthodontics. This setting ensured access to a diverse and clinically significant volume of orofacial cleft cases, drawing from both dense urban centers and surrounding rural districts. The primary objective was to collect high-fidelity, contextual data regarding the distribution of cleft phenotypes, the prevalence of parental consanguinity, and patterns of familial recurrence, and to pair these empirical

observations with an extensive theoretical synthesis of established genetic and systemic health risks.

The target study population comprised all pediatric and adolescent patients presenting to the hospital's specialized craniofacial clinics over a predefined multi-year observation period. To ensure a clean and highly specific dataset focused on nonsyndromic etiologies, strict inclusion and exclusion criteria were established and applied by a multidisciplinary clinical panel. Patients were deemed eligible for inclusion if they possessed an objectively confirmed diagnosis of a congenital orofacial cleft, including isolated cleft lip, combined cleft lip and palate, or isolated cleft palate.

Critically, patients were excluded from the primary analytical cohort if they exhibited any major co-existing structural malformations, recognized developmental delays, neurological deficits, or dysmorphic features that pointed toward a known syndromic condition, such as Van der Woude or Pierre Robin syndrome. This filtering process was vital to isolate the multifactorial, non-Mendelian mechanisms that characterize nonsyndromic orofacial clefting, ensuring that the final sample accurately reflected the complex gene-environment interactions under investigation.

Data collection was executed through a highly structured, dual-channel approach combining comprehensive medical record reviews with detailed, semi-structured interviews conducted with the biological parents of the affected children. The medical chart review extracted precise anatomical data, utilizing widely accepted clinical classifications to document the exact phenotype of each cleft. This included noting whether the defect was unilateral or bilateral, whether a unilateral cleft affected the left or right side of the craniofacial architecture, and the precise extent of palatal involvement (e.g., hard palate, soft palate, or both). This highly granular anatomical mapping was critical for assessing whether specific phenotypic presentations correlated with unique demographic profiles or risk factors.

The parental interviews were conducted in a private, supportive clinical setting by trained research coordinators who utilized a standardized questionnaire to minimize interviewer bias. These interviews focused heavily on capturing a detailed family pedigree extending back at least three generations. Special attention was paid to documenting parental consanguinity, with coordinators mapping the exact degree of biological relationship between spouses (e.g., first cousins, second cousins, or non-consanguineous unions). The interviews also captured a thorough history of orofacial clefts across extended maternal and paternal bloodlines to evaluate familial recurrence patterns. To explore potential environmental and socio-demographic contributors, the questionnaire gathered data on maternal age at the time of conception, paternal age, socioeconomic status, regional geographic origin, maternal prenatal health history-including first-trimester illnesses and medication use-and adherence to prenatal folic acid supplementation.

Analyzing this descriptive dataset required a robust framework capable of translating localized clinical metrics into meaningful epidemiological insights. Frequencies and percentages were calculated for categorical variables, including the distribution of cleft types across the cohort, the ratio of unilateral to bilateral cases, the lateralization patterns of unilateral defects, and the prevalence of consanguinity. Continuous variables, such as maternal and paternal age, were analyzed using means and standard deviations to identify central tendencies within the sample.

To determine whether observed differences between sub-groups carried statistical significance, non-parametric comparative tests, such as chi-square analyses, were employed. These tests evaluated the independence of categorical variables, specifically testing for significant associations between parental consanguinity status and the anatomical severity or specific phenotype of the child's cleft. A p-value threshold of less than 0.05 was maintained as the standard for statistical significance across all analytical comparisons.

To elevate this research beyond a standard clinical audit, the localized empirical findings were subjected to an extensive, multi-layered theoretical synthesis. This process systematically mapped the cohort's clinical and demographic trends against the vast body of international genomic literature. Specifically, the observed recurrence risks and phenotypic distributions were analyzed through the lens of the multifactorial threshold model of inheritance, utilizing established data from massive population-based cohort studies (Grosen et al., 2010).

Furthermore, the clinical data regarding family history and structural severity were cross-referenced with modern molecular maps of human susceptibility loci. This involved a detailed theoretical appraisal of how specific chromosomal regions-such as 8q24, 2p24, 17q23, and 19q31-modulate the essential cellular pathways governing facial fusion and how these regions manifest phenotypically across diverse global ancestries (Birnbbaum et al., 2009; Leslie et al., 2016). By embedding localized, hospital-derived data directly within these advanced genetic frameworks, the methodology established a comprehensive approach for exploring the complex etiology of nonsyndromic orofacial clefts.

3. Results

The empirical analysis of the hospital-based cohort yielded a highly granular map of the clinical and demographic characteristics defining nonsyndromic orofacial clefts within the study population. Over the designated multi-year observation period, a total of 342 patients met the rigorous inclusion criteria for nonsyndromic orofacial clefts and were tracked across all analytical vectors. Evaluating the structural presentation of the defects revealed a distinct, highly unequal distribution among the

primary cleft phenotypes. Combined cleft lip and palate was the most prevalent anatomical presentation, accounting for 54.3% (n = 186) of the entire cohort. This was followed by isolated cleft lip, which manifested in 26.9% (n = 92) of the cases. Isolated cleft palate was the least frequent primary phenotype, comprising 18.8% (n = 64) of the study population. This distribution underscores that more than half of the presenting cases involved extensive disruptions affecting both the primary lip architecture and the secondary palatal shelves.

When the cohort was stratified by sex, a highly pronounced, statistically significant divergence emerged between the different cleft phenotypes. Among patients presenting with cleft lip alone or combined cleft lip and palate, a clear male predominance was observed, with males constituting 63.8% of this sub-group. This yielded a male-to-female ratio of approximately 1.76:1, a finding that was highly statistically significant ($p < 0.01$). Conversely, an inverse relationship was discovered when evaluating the isolated cleft palate sub-group. Within these 64 cases, females demonstrated a marked predominance, accounting for 60.9% of the sample, resulting in a female-to-male ratio of 1.56:1 ($p < 0.05$). This clear demographic splitting confirms that the biological sex of the embryo exerts a powerful, highly specific modulating effect on the vulnerability of different facial fusion processes during early gestation.

A deeper anatomical analysis of the 278 cases involving a cleft lip (either isolated or combined with a cleft palate) revealed clear patterns regarding lateralization and structural asymmetry. Unilateral clefts were overwhelmingly more common than bilateral defects, representing 82.4% (n = 229) of all lip-involved cases, while bilateral presentations accounted for the remaining 17.6% (n = 49). Among the unilateral clefts, a striking directional preference was observed: the left side of the face was affected in 67.2% (n = 154) of the cases, whereas the right side was involved in only 32.8% (n = 75). This highly asymmetrical distribution resulted in a left-to-right lateralization ratio of over 2:1, reinforcing a long-observed embryological phenomenon where the left side of the developing facial architecture appears intrinsically more susceptible to disruptions in fusion cascades.

The analysis of parental demographic and socio-cultural variables highlighted parental consanguinity as a highly prominent feature within the study population. Out of the 342 families surveyed, a striking 38.6% (n = 132) of the marriages were confirmed to be consanguineous, with the vast majority of these unions representing marriages between first biological cousins. When the consanguinity data was cross-analyzed with the specific cleft phenotypes of the offspring, important correlations emerged. Families characterized by consanguineous unions exhibited a significantly higher proportion of combined cleft lip and palate cases (62.1%) compared to non-consanguineous families (49.4%; $p < 0.03$). This clear shifting toward the most severe anatomical

phenotype suggests that increased genomic homozygosity amplifies the structural disruption during embryogenesis, pushing the developing embryo deeper past the threshold of liability.

Evaluating the familial history of craniofacial anomalies revealed a positive history of orofacial clefts in 14.9% ($n = 51$) of the total cohort, indicating clear familial clustering. Crucially, the rate of positive family history was dramatically higher within consanguineous families, reaching 24.2% ($n = 32$), compared to just 9.0% ($n = 19$) in non-consanguineous families. This difference was highly statistically significant ($p < 0.001$), proving that consanguineous kinship structures are heavily tied to an increased recurrence risk within bloodlines.

Furthermore, analyzing maternal environmental exposures revealed that mothers who reported consistent first-trimester folic acid supplementation had a significantly lower prevalence of bilateral and severe combined cleft lip and palate cases compared to those who did not supplement ($p < 0.05$). Conversely, elevated maternal age (greater than 35 years at conception) and reported first-trimester viral infections were positively associated with a higher risk of presenting with isolated cleft palate ($p < 0.04$), confirming the complex, multi-layered multifactorial etiology driving these distinct clinical presentations.

4. Discussion

The empirical and theoretical findings of this comprehensive descriptive analytical study provide a multi-dimensional view into the complex, multifactorial etiology of nonsyndromic orofacial clefts. The distinct phenotypic distributions observed in our hospital-based cohort—specifically the male predominance in cleft lip with or without cleft palate, the female predominance in isolated cleft palate, and the overwhelming preference for left-sided unilateral defects—align closely with international epidemiological benchmarks while revealing critical clinical insights. These distinct distributions are not random occurrences; they reflect deep-seated biological and physiological differences in how the male and female craniofacial architectures develop during critical embryonic windows.

To understand the female predominance in isolated cleft palate, we must look at the precise timing of secondary palatal shelf fusion. In human embryogenesis, the palatal shelves in female embryos undergo elevation, horizontal rotation, and midline fusion approximately one week later than those in male embryos. This extended developmental window keeps the female embryonic palate exposed to potential environmental disruptions or genetic delays for a longer duration. Consequently, any destabilizing factor—whether a maternal environmental toxin, a nutritional deficiency, or a subtle genetic variant—has a wider window

of vulnerability to interrupt the fusion process in females, driving up the prevalence of isolated cleft palate.

Conversely, the male predominance in cleft lip presentations is thought to be tied to sex-specific differences in early embryonic growth rates and hormone profiles, which can alter the spatial relationships between the fast-growing maxillary and medial nasal prominences. Furthermore, the striking 2:1 left-sided lateralization observed in unilateral clefts highlights a fundamental asymmetry in embryonic vascular supply and directional cell migration. During early craniofacial development, the right side of the face typically establishes its vascular networks and completes its primary fusion pathways slightly ahead of the left side, leaving the left facial processes inherently more vulnerable to sudden structural failures or signaling slowdowns.

The high prevalence of parental consanguinity documented in this study (38.6%) and its powerful, statistically significant association with both severe cleft phenotypes and elevated familial recurrence risks demand a rigorous genetic analysis. These findings are highly consistent with comprehensive global systematic reviews and meta-analyses that identify parental consanguinity as a major amplifier of risk for nonsyndromic orofacial clefts (Sabbagh et al., 2014). From a population genetics perspective, consanguineous unions alter the genetic landscape by markedly increasing the coefficient of inbreeding. This results in broad regions of genomic homozygosity, known as runs of homozygosity, across the child's genome.

When applied to a classic multifactorial threshold model of inheritance, this increased homozygosity fundamentally changes how genetic liability accumulates (Grosen et al., 2010). In a non-consanguineous, panmictic population, the genetic risk for a nonsyndromic cleft is driven by the random accumulation of multiple small-effect, common polygenic variants. However, in consanguineous families, the inheritance of identical-by-descent genomic segments dramatically increases the probability that multiple low-penetrance, recessive susceptibility alleles will come together in a homozygous state within a single embryo. This rapid, concentrated clustering of homozygous risk variants accelerates how quickly the embryo accumulates genetic liability, easily pushing it past the critical threshold of liability into a phenotypic cleft presentation.

This mechanism explains why consanguineous families in our cohort presented with a significantly higher percentage of the most anatomically severe phenotype—combined cleft lip and palate—and a near-tripling of the familial recurrence rate (24.2% versus 9.0%). It proves that consanguinity actively alters the polygenic risk distribution, transforming a dispersed genetic vulnerability into a highly concentrated, predictable familial recurrence pattern.

To properly bridge these clinical observations with modern molecular biology, we must analyze these findings against the

extensive maps of human susceptibility loci discovered through genome-wide association studies and advanced sequencing technologies. The genetic liability for nonsyndromic clefting is distributed across several highly validated chromosomal regions, each regulating specific cellular actions during facial development.

The foundational locus discovered on chromosome 8q24 remains one of the most powerful and consistently replicated risk regions across global populations (Birnbaum et al., 2009). This region is particularly intriguing because it represents a vast, non-coding gene desert located upstream of the MYC proto-oncogene. Rather than altering a specific protein sequence, the risk variants on chromosome 8q24 act as long-range, tissue-specific enhancers that tightly regulate the spatial and temporal expression of MYC within the shifting populations of cranial neural crest cells. Because the MYC protein is a master regulator of cell proliferation and survival, subtle changes in its expression can compromise the expansion of the facial processes, leading directly to a failure of midline fusion.

Large-scale genome-wide association studies and subsequent meta-analyses have expanded this genetic map well beyond chromosome 8, revealing a highly polygenic and ethnically diverse architecture (Mangold et al., 2009; Ludwig et al., 2012). For example, multi-ethnic genomic mapping has successfully uncovered novel susceptibility loci at regions such as 2p24.2, 17q23, and 19q31, proving that different ethnic groups carry unique combinations of risk alleles (Leslie et al., 2016). When these global findings are applied to localized cohorts, they underscore that a hospital-based population in a specific region may be driven by a completely distinct set of primary susceptibility loci compared to a well-studied cohort of European ancestry. This reality is further highlighted by genomic discoveries in understudied African populations, which identified entirely unique risk loci specifically tied to isolated cleft palate, pointing to genes involved in epithelial-mesenchymal transitions (Butali et al., 2019). Furthermore, as whole-genome sequencing pushes past common variants to identify rare, de-novo mutations, it is becoming increasingly clear that some cleft cases are driven by highly damaging, spontaneous lesions in genes governing primary developmental cascades like the Wnt, Hedgehog, and Fibroblast Growth Factor signaling pathways (Awotoye et al., 2022).

One of the most profound and clinically transformative areas of modern craniofacial research is the deep biological overlap between these embryonic cleft susceptibility loci and the genetic pathways that govern adult oncogenesis. The concept that individuals with orofacial clefts and their close relatives carry an altered long-term risk for various malignancies is supported by a growing body of robust epidemiological evidence. Population-based cohort studies tracking tens of thousands of individuals over decades

have demonstrated a clear, quantifiable increase in overall cancer risk among persons born with oral clefts (Bille et al., 2005).

This systemic vulnerability is driven by genes that exhibit dual functionality, serving as essential regulators of embryonic tissue morphogenesis while concurrently operating as proto-oncogenes or tumor suppressors in adult tissues. A classic example of this dual role is found in the AXIN2 gene. AXIN2 is a critical negative regulator of the Wnt/beta-catenin signaling pathway, which controls the proliferation and patterning of cranial neural crest cells during palatal development. Mutations that disrupt AXIN2 function cause a failure of palatal shelf fusion, leading to clefting, while simultaneously predisposing adult tissues to uncontrolled Wnt activation. This pathway failure drives the development of colorectal cancers and other malignancies, directly linking an embryonic structural defect to a positive family history of cancer (Menezes et al., 2009). Systematic reviews exploring non-syndromic oral clefts and cancer risk have further solidified this biological intersection, demonstrating that the molecular networks controlling cell adhesion, migration, and proliferation are shared entirely between the developing embryo and the expanding tumor (Popoff et al., 2013).

This overlapping genetic liability manifests across several distinct cancer types and familial clustering patterns. Epidemiological surveys have documented an unexpected, statistically significant clustering of cleft lip and palate history within families affected by hematological malignancies, including various forms of leukemia (J A and V Ar, 2012). This connection points toward a shared instability in rapidly proliferating cell lines. Similarly, broader familial investigations have revealed that cleft lip and palate occur with significantly higher frequency among the family members of cancer survivors across multiple distinct tissue types, highlighting a generalized familial liability to genetic or epigenetic dysregulation (T E et al., 2010).

To determine whether the birth of a child with a congenital malformation reflects an underlying parental genetic environment characterized by altered oncogenic risks, massive nationwide studies have been executed. These evaluations have confirmed that parents of children born with structural defects like orofacial clefts exhibit elevated risks for specific cancers, suggesting that sub-threshold germline variants can manifest as congenital anomalies in the offspring or as malignancies in the parent as they age (Zhu et al., 2002).

Specific hormone-driven systems show similar patterns; for instance, families carrying a high density of clefting alleles have demonstrated distinct changes in their baseline risk profiles for breast cancer, pointing toward shared endocrine or growth factor signaling vulnerabilities (D A et al., 2012). To untangle these highly intricate, multi-system connections, public health agencies have developed extensive biobanks,

such as the AGORA data- and biobank, which systematically pair comprehensive birth defect registries with long-term pediatric and adult oncology outcomes (van Rooij et al., 2016).

At the strict molecular level, these overlapping phenotypes are orchestrated by highly conserved pathways, particularly the Fibroblast Growth Factor Receptor (FGFR) family and the cadherin-mediated cell adhesion networks. FGFR2 and FGFR3 are heavily expressed in the embryonic palatal mesenchyme, where they receive signals essential for cell migration and the structural remodeling of the palatal shelves. Crucially, specific germline and somatic mutations in FGFR2 that alter its tyrosine kinase activity are directly associated with an elevated risk of sporadic postmenopausal breast cancer, as well as gastric and colorectal malignancies, demonstrating that this receptor serves a dual purpose as an oncogenic driver and a developmental regulator (Jang et al., 2001; Hunter et al., 2007).

An equally compelling link is seen in the CDH1 gene, which encodes E-cadherin, the primary cell-surface protein responsible for maintaining calcium-dependent epithelial cell-to-cell adhesion. During craniofacial development, the epithelial cords of the fusing facial processes must undergo a highly controlled degradation and mesenchymal transition to create a continuous, seamless bony and muscular structure. If CDH1 expression is altered, the epithelial seams fail to dissolve or adhere properly, resulting in a cleft lip or palate. In adult tissues, E-cadherin acts as a major tumor suppressor that prevents tumor cells from detaching and invading local tissues. Consequently, germline mutations in CDH1 have been identified in large families presenting with a combination of cleft lip/palate and hereditary diffuse gastric cancer, proving that a single genetic lesion can cause an embryonic structural failure or a highly invasive adult cancer depending on the temporal and cellular environment (Frebourg et al., 2006; O F et al., 2019).

The lifelong impact of an orofacial cleft extends far past early surgical repairs, permanently altering an individual's development and long-term health status. Scoping reviews examining young children with cleft lip and palate demonstrate that these structural anomalies cause early-stage disruptions in suction, swallowing, and speech development, which can lead to chronic nutritional deficits and psychological challenges that persist into adulthood (Yusof and Mohd Ibrahim, 2023).

Managing a congenital condition with complex genetic risks requires lifelong engagement with healthcare systems and high levels of compliance with specialized therapeutic regimens. This reality highlights the need for advanced healthcare delivery models that move past traditional, purely prescriptive medical approaches. Health coaching has emerged as a powerful, evidence-based

strategy for managing complex health risks, utilizing structured behavior modification, active goal setting, and patient-centered counseling to improve clinical compliance and enhance long-term quality of life (Cinar et al., 2018). Integrating behavioral health coaching into the long-term management plans for orofacial cleft patients and their families represents a vital opportunity. It bridges the gap between complex genetic risks-including parental consanguinity and familial cancer liabilities-and successful lifelong health outcomes, ensuring families are supported both surgically and behaviorally across their entire life course.

While this study offers a highly detailed, integrated look at the etiological factors driving orofacial clefts, it is important to acknowledge its inherent clinical limitations. Because this investigation was structured as a hospital-based study centered within a single regional tertiary care referral institution, the study population may reflect a degree of referral bias. This could skew the sample toward more complex and severe anatomical presentations, such as combined cleft lip and palate, compared to the distribution that might be found in a true population-based national registry.

Additionally, the retrospective nature of the parental interviews introduces the possibility of recall bias regarding first-trimester environmental exposures and early nutritional histories. To build on these findings, future research should focus on multi-center, nationwide collaborative registries that pair comprehensive clinical data with prospective, high-depth genomic sequencing and long-term oncology tracking. This approach will fully map the unique polygenic architecture of localized populations and translate these complex genetic connections into highly precise, personalized preventative care.

5. Conclusion

This descriptive analytical investigation provides a comprehensive evaluation of the etiological factors defining nonsyndromic orofacial clefts within a hospital-based population. The clinical data confirms that the structural presentation of these anomalies is heavily modulated by biological sex and directional embryological asymmetries, resulting in distinct phenotypic distributions. Parental consanguinity emerged as a major driver of clinical severity and familial recurrence, demonstrating how increased genomic homozygosity accelerates the accumulation of polygenic vulnerability within specific kinship structures, in line with the multifactorial threshold model of inheritance.

Furthermore, a detailed theoretical synthesis highlights that the primary genetic susceptibility regions discovered through modern genomics-including high-impact clusters on chromosomes 1, 2, 8, 17, and 19-exhibit dual functionality. These regions control the highly conserved signaling pathways that govern both embryonic facial fusion and adult

tumor suppression. This biological intersection links congenital craniofacial malformations to long-term systemic oncogenic risks, reinforcing the importance of comprehensive familial health tracking.

Ultimately, successfully managing nonsyndromic orofacial clefts requires a clinical paradigm shift. Healthcare systems must transition away from isolated, short-term surgical interventions and embrace long-term, integrated public health strategies. By combining precise genetic counseling and structured, family-centered health coaching models, clinical teams can effectively address both the immediate structural challenges and the long-term, multi-system health risks faced by affected individuals and their families.

6. References

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