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Epidemiology of Cleft Lip and Palate

Mairaj K. Ahmed, Anthony H. Bui and Emanuela Taioli

Abstract

Orofacial cleft (OFC) anomalies are amongst the most common congenital anomalies and the most common craniofacial anomalies. Despite their poorly characterized etiologies, cases of OFC are usually grouped by epidemiological studies as cleft lip, with or without cleft palate (CL/P), and cleft palate alone (CPO). Incidence of CL/P and CPO differs according to gender and ancestry and may vary widely across studies. Cases of OFC are characterized as either “syndromic” or “nonsyndromic,” with further classification of nonsyndromic cases into isolated cases and cases that present with additional malformations. The genetic bases for many syndromic cases of OFC have been previously elucidated. Genetic associations have been described for nonsyndromic OFC as well. Importantly, etiology of OFC is known to involve interaction between genetic and environmental factors, including maternal nutrition and exposure to teratogenic agents. Furthermore, evidence points toward epigenetic as well as genetic factors influencing OFC etiology. Recent studies have begun to explore the association between CL/P and cancer. These studies report higher incidence of cancer among patients with CL/P and their family members as well as identification of common genetic markers mediating this increased risk, although much remains unknown about this link.

Keywords: cleft, epidemiology, etiology, genetics, epigenetics, environmental risk factors, cancer

1. Introduction

Orofacial cleft (OFC) anomalies may be unilateral or bilateral and involve the lip, the palate, or both. Due to similar phenotypic overlap and resulting health care needs of these patients, epidemiological studies usually group cleft lip, with or without cleft palate (CL/P), and cleft
palate alone (CPO) even though the etiology of each may be unique. Whether or not CL/P and CPO have distinct etiology and should be combined in investigations is under debate.

It is often found in epidemiological studies that CL/P and CPO is considered underneath the umbrella of either “syndromic” or “nonsyndromic.” Furthermore, “nonsyndromic” CL/P and CPO cases can be subgrouped into those that are isolated or those that have additional malformations that do not form a recognizable syndrome. Relatively, the etiology of nonsyndromic cases of CL/P and CPO is lesser known compared to those found identified with a syndrome. Due to the poorly characterized etiology of CL/P and CPO, in general, there is still debate for the best method of grouping CL/P and CPO in epidemiological studies, but the most common current classifications are used to help determine associations and thus help the clinician with their diagnosis and subsequent treatment.

The genetic basis for many syndromic cases of CL/P and CPO are well-described. Evidence for genetic factors underlying nonsyndromic CL/P and CPO has begun to materialize as well. While less well-described, it is also known that epigenetic modifications can play a role in the development of CL/P and CPO. Recently, the association between OFC and cancer has been explored, with evidence suggesting existence of a link between the presence of OFC in patients and risk of cancer in these patients and/or their families.

2. Descriptive epidemiology

2.1. Prevalence

The overall prevalence of OFC is estimated to be approximately 1 in 700 live births, accounting for nearly one half of all craniofacial anomalies [1, 2]. As reported by the World Health Organization (WHO), the prevalence at birth of OFC varies worldwide, ranging 3.4–22.9 per 10,000 births for CL/P, and 1.3–25.3 per 10,000 births for CPO [3]. The incidence of CL/P and CPO can vary greatly between studies. The inclusion criteria, case definition, data sources, and selection bias contribute to the varying incidence estimates. Even though there are many different variables regarding the inclusion or exclusion criteria of in studies, the majority report a higher incidence of CL/P compared to CPO.

Prevalence has been found to vary based on ancestry, with the highest incidence rates observed amongst Asian populations (0.82–4.04 per 1000 live births), intermediate rates amongst Caucasians (0.9–2.69 per 1000 live births), and the lowest rates amongst African populations (0.18–1.67 per 1000 live births) [1, 4]. Prevalence has also been found to vary further by subgroup, for example, with one study reporting lower rates of OFC amongst Far East Asians compared to Filipinos [5].

2.2. Gender ratio

Prevalence of OFC additionally varies according to gender and cleft pattern. Male predominance has been consistently identified in CLP, with a male/female sex ratio of 1.81 (CI 95%:
1.75–1.86). For CP, the opposite has been shown, with a reported sex ratio of 0.93 (CI 95%: 0.89–0.96) [3]; however, this may be due in part to sampling bias, as one Danish study could not find a significant predominance of females in individuals with CP after combining both surgically treated and nonsurgically treated cases [6].

2.3. Laterality

OFC may be unilateral or bilateral. According to the International Perinatal Database of Typical Orofacial Clefts (IPDTOC) working group, the proportion of bilateral cases is 10.3% for cleft lip without palate (CL) and 30.2% for cleft lip with palate (CLP). Amongst unilateral cases, 36.9% of CL and 41.1% of CLP occur on the right side, suggesting that unilateral cases of CL/P occur more frequently on the left [7].

3. Classification

It is often found in epidemiological studies that CL/P and CPO are classified as either “syndromic” or “nonsyndromic.” Cases of “nonsyndromic” CL/P and CPO are further categorized as isolated—those without an underlying syndrome or additional, nonsecondary malformations—or multiple—those that have additional malformations that do not form a recognizable syndrome. These distinctions are important epidemiologically, for identifying homogenous subgroups of cases, and clinically, for informing prognosis, recurrence risk, diagnosis, and treatment plan.

3.1. Syndromic

Individuals with “syndromic” CL/P or CP present with patterns of malformations and/or symptomatology that form a recognizable syndrome of known or unknown origin; hence, the CL/P or CP is part of a syndrome. Recognition of these syndromes is essential for assessing the risks faced by the child, providing the necessary treatment, and counseling the parents. Because the prevalence of associated anomalies varies across different populations of individuals with OFC, better understanding of the epidemiology of these anomalies could aid in the proper identification and characterization of the syndrome, leading to better care for the individual. Syndromes associated with OFC for which the underlying cause is known include chromosomal abnormalities, such as trisomy 13 or 18, Mendelian disorders such as Van der Woude Syndrome and teratogenic exposure.

A guideline for identifying syndromes in individuals with CL/P or CP is outlined by Venkatesh as follows [8]:

- Thorough clinical examination, preferably by geneticist or dysmorphologist.
- Comprehensive medical history: description of the cleft, antenatal history, birth history, developmental history, and family history.
- Physical examination: measurement of weight, length or height, and occipitofrontal circumference, identification of anomalies of eyes, ears, heart, extremities, and also to look for associated preauricular tags, lip pits, and epicanthal folds.

- Documentation by photographs of all affected individuals and first-degree relatives.

- Necessary laboratory and radiological evaluations.

3.2. Multiple

The multiple subset of CL/P and CPO includes those cases that are not a part of a recognizable syndrome and have major other malformations which may involve, but are not limited to, the eye, ear, head, neck, respiratory tract, gastrointestinal tract, and musculoskeletal system [5, 9]. Cases of “multiple nonsyndromic” CL/P and CPO may be classified as such simply by virtue of unrecognized syndromes or undocumented teratogenic exposures. Furthermore, wide variation exists in the classification of associated anomalies in cases of OFC [10].

3.3. Isolated

Cases of CL/P and CPO that are classified as “isolated” do not have an underlying syndrome or other secondary malformations. Most epidemiological studies of CL/P and CPO focus on those cases that are isolated in hopes to further gain insight into associations.

4. Etiology

Development of the head and face represents one of the most intricate events during embryonic development, synchronized by a network of transcription factors and signaling molecules together with proteins conferring cell polarity and cell-cell interactions. In mammals, the facial region develops from the facial primordia, which consists of the lateral and medial nasal prominences arising from the frontonasal process and the maxillary and mandibular processes arising from the first branchial arch. As demonstrated in Figure 1, fusion of medial nasal and maxillary prominences gives rise to the lip and primary palate, while fusion of separate palatal processes arising from the maxillary prominence gives rise to the secondary palate and occurs later during embryogenesis. These processes are known to be dependent, in part, on the migration and differentiation of neural crest cells from the neuroectoderm into the branchial arches [11].

Disturbance of this closely controlled cascade can result in a facial cleft where these facial primordia ultimately fail to meet and fuse or form the proper structures. Historically, OFCs have been classified as either CL/P or CPO [13, 14]. This broad subdivision is consistent with both the distinct developmental origins of the lip/primary palate and the secondary palate and the distinct cellular and genetic etiologies described for CL/P and CPO; cleft palate may occur secondary to or independently from cleft lip. However, there is some epidemiologic
Evidence suggesting that cleft lip only has distinct etiologic features from cleft lip with palate and should be classified accordingly [15, 16].

5. Genetics

Both genetic and environmental factors have been shown to influence the risk of CL/P and CPO. Approximately 70% of all cases of CL/P and 50% of cases of CPO are designated as nonsyndromic [17], with the rest comprised of a wide range of malformation syndromes with known genetic and/or cellular etiologies. A summary of syndromic forms of CL/O and CPO in which the underlying genetic mutation has been elucidated is provided by Dixon et al. (Table 1; see original article for references) [18].

Figure 1. Schematic diagrams depicting human craniofacial development and formation of the secondary palate [12].
(a) By the fourth week of embryonic development, neural crest cells have migrated into the craniofacial region to form the frontonasal prominence, paired maxillary processes and the paired mandibular processes. (b) Formation of the nasal pits by the fifth week of embryogenesis divides the frontonasal prominence into paired medial and lateral nasal processes. (c) By the end of the sixth week of embryonic development, the medial nasal processes have merged with one another and with the maxillary processes to form the upper lip and primary palate, whereas the lateral nasal processes form the alae of the nose. The mandibular processes fuse together to form the lower jaw. (d) The secondary palate develops from the maxillary processes as bilateral outgrowths which grow vertically down the side of the tongue during the sixth week of embryogenesis. (e) During the seventh week of embryonic development, the palatal shelves elevate to a horizontal position above the tongue, make contact with one another and begin to fuse. (f) Fusion of the secondary palatal shelves with one another and with the primary palate and nasal septum is completed by the tenth week of embryogenesis. Figure is adapted from [12] © (2009) John Wiley and Sons Ltd.
<table>
<thead>
<tr>
<th>Cleft type</th>
<th>Syndrome</th>
<th>Gene</th>
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<td>ACTB</td>
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<td>Familial gastric cancer and CLP</td>
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<td>Tetra-amelia with CLP</td>
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<td>Larsen syndrome; atelosteogenesis</td>
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<td>Hereditary lymphedema-distichiasis</td>
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In contrast, nonsyndromic CL/P is complex and multifactorial in origin. Both genetic and environmental risk factors have been shown to influence the probability of occurrence. Furthermore, there is evidence that the presence of environmental factors—in particular, maternal smoking—modulates the risk conferred by genetic factors and vice-versa, complicating the genetic analysis of nonsyndromic forms of CLP [19]. As such, multifactorial models of inheritance which allow for the evaluation of these risk factors both independently and in interaction with each other are preferred.

Association studies such as candidate gene studies, which test correlation between a phenotype and prespecified genes of interest, and genome-wide association studies (GWAS), which identify genetic variations across entire genomes that are associated with a phenotype, have been used to evaluate a variety of genetic polymorphisms associated with nonsyndromic OFC. Genes that have been examined through these studies for associations with nonsyndromic OFC exhibit a range of functions, including growth, DNA transcription, nutrient metabolism, immunity, and oncogenesis. A few such genes are described here.

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<td>Saethre-Chotzen</td>
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<td>Oro-facial-digital type I</td>
<td>OFD1</td>
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Table 1. Clefting syndromes in which the mutated gene has been identified. Adapted from Ref. [18].

In contrast, nonsyndromic CL/P is complex and multifactorial in origin. Both genetic and environmental risk factors have been shown to influence the probability of occurrence. Furthermore, there is evidence that the presence of environmental factors—in particular, maternal smoking—modulates the risk conferred by genetic factors and vice-versa, complicating the genetic analysis of nonsyndromic forms of CLP [19]. As such, multifactorial models of inheritance which allow for the evaluation of these risk factors both independently and in interaction with each other are preferred.
5.1. Growth factors

Transforming growth factor alpha (TGF-α) is a growth factor encoded by the TGFA gene that serves as a ligand for the epidermal growth factor receptor, which is involved in cell proliferation, differentiation, and development [20]. The first association study of genes associated with CL/P found an association with TFGA [21]; however, evidence of this linkage since then has been mixed [22, 23]. TGFA is currently viewed as a modifier, rather than a necessary or sufficient determinant, of risk for OFC.

Proteins in the transforming growth factor beta (TGF-β) family bind various TGF-β receptors leading to recruitment and activation of the SMAD family of transcription factors. TGF-β is involved in processes including apoptosis, modulation of immune cell function, and wound healing; disruption of TGF-β has been implicated in cancer, Loeys-Dietz syndrome, and other conditions [20]. Knockout experiences in mice have shown the TGFB3 gene to be associated with OFC [24, 25], and subsequent association studies have identified these results in humans [26].

5.2. Transcription factors

The MSX1 gene, which is a part of the homeobox gene family, codes for a protein that is involved in transcriptional regulation during embryogenesis as well as limb pattern formation, craniofacial development (in particular odontogenesis), and tumor growth inhibition [20]. This gene has been implicated in the development of cleft in several candidate gene studies, and may even account for 1–2% of all isolated cases of OFC [27].

Interferon regulatory factor 6 (IRF6) is a transcription factor protein that is involved in early development, especially of tissue in the head and face [20]. Mutations of the IRF6 gene at 1q32 causes Van der Woude syndrome, a Mendelian-inherited disorder which induces CL/P or CPO and accounts for about 2% of all CL/P cases [28, 29]. The overlap between phenotypic presentation of Van der Woude syndrome and isolated CL/P motivated further study into the role of IRF6 in development of OFC. Variation at IRF6 has been found to be strongly associated with CL/P and may account for up to 12% of the genetic contribution to CL/P at the population level [30–32]. Furthermore, the discovery of ILF6 as a risk factor for CL/P served as an important example of elucidating genetic variants associated with cases of nonsyndromic OFC, which are often excluded from genetic analyses [33].

5.3. Nutrient metabolism

Deficient maternal folate intake has long been implicated in risk of OFC in children, leading to suggestions that mutations of the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR), which catalyzes the synthesis of 5-methyltetrahydrofolate, play a role in the etiology of cases of nonsyndromic CL/P [34]. However, results from several association studies evaluating the role of MTHFR mutations in CL/P have been conflicting [35–37].

Retinoic acid plays an important role during development. Its functions, mediated by retinoic acid receptor alpha (RAR-α), include regulation of development, differentiation, apoptosis, granulopoeisis, as well as transcription of genes involved in the circadian
rhythm [20]. Transgenic and knockout mice studies have additionally proposed a role in facial development [38]. Mutations of the RARA gene have been associated with development of OFC [39].

6. Epigenetics

Due to the relative lack of success in identifying causal genetic factors involved in OFC despite the numerous association studies that have been performed, recent attention has been directed toward the role of epigenetic programming, or modifications that do not involve DNA sequencing. Commonly studied epigenetic events include histone modification, chromatin remodeling, posttranscriptional gene alteration via noncoding MicroRNAs, and DNA methylation. MicroRNAs and DNA methylation, in particular, have begun to demonstrate distinct roles in etiologies of OFC.

6.1. MicroRNAs

While protein-coding genes make up only about 1.2% of the human genome, recent estimates suggest that up to 93% of the human genome codes for RNA transcripts. MicroRNAs (miRNAs) represent the largest family of such noncoding RNAs in the human genome. They are involved in gene silencing and play important roles in cell and tissue differentiation, including development of the secondary palate [40–43]. miRNAs have been shown to orchestrate many of the processes that are central to palatal morphogenesis, including epithelial-mesenchymal transformation, platelet-derived growth factor (PDGF) and TGF-β signaling, cell migration and proliferation, and collagen synthesis [44–48]. As such, further analysis of miRNA expression and gene networks will be key to elucidating mechanisms of palatal development as well as etiologies of OFC.

6.2. DNA methylation

DNA methylation, one of the most important epigenetic modifications in mammalian cells, is a process by which methyl groups are added to DNA in order to regulate gene expression. Methylation generally occurs at cytosines within the context of symmetrical CpG dinucleotide sequences, which are often concentrated in regions known as CpG islands and found in both gene bodies and promoter regions [49, 50]. Classically, methylation of CpG islands at gene promoters is thought to induce silencing of gene transcription; however, positive correlation between gene body methylation and gene expression has been observed [51, 52].

DNA methylation was first identified as a potential mediator of palatal development after a series of studies in which DNA demethylating agents were used to induce cleft palate in mice [53–55]. Since then, failures in DNA methylation demonstrated involvement in craniofacial malformations including cleft palate [56, 57]. Despite the current lack of knowledge regarding the epigenetic mechanisms mediating palatal development, evidence strongly indicates that DNA methylation plays a central role in regulating this process, and may perhaps serve as future risk assessment and therapeutic targets for patients with OFC.
7. Risk factors

The role of environmental factors in the etiology of OFC has been extensively studied. Known and suspected risk factors for CL/P and CP include family history, maternal nutrition, and exposure to teratogenic agents. The upper lip and palate are developed by 7 and 9 weeks after conception, respectively. Therefore, risk factors must be present before these times to influence the risk of CL/P and CPO.

7.1. Heredity

Family history is one of the strongest risk factors for both CL/P and CP. The risk of CL/P and CP has been reported to be increased in the first-, second-, and third-degree relatives and the identical twins of individuals with CL/P and CP, with even nonsyndromic cases of CL/P exhibiting evidence of genetic components [58–61]. However, few cases demonstrate true Mendelian inheritance patterns [62]. Moreover, CL/P and CP are known to be influenced by environmental risk factors. Specifically, there is growing evidence of gene-environment interactions that may influence the risk of these conditions.

7.2. Maternal drug use

Maternal drug use seems to play only a small role for the origin of orofacial clefts, but studies have shown that maternal use of folate antagonists (valproic acid and carbamazepine), dihydrofolate reductase inhibitors (trimethoprim, triamterene, and sulfasalazine), benzodiazepines, nonsteroidal anti-inflammatory drugs, retinoids, and corticosteroids is associated with a marked increase of cleft lip and palate [63–67].

7.3. Maternal diseases

The increased risk of having a child with CL/P or CP in women with nongestational diabetes or maternal hyperthermia is well-characterized [68, 69]. Additionally, a study conducted in Hungary found an increased risk of CL/P for children born to mothers with influenza, common cold, orofacial herpes, and gastroenteritis during pregnancy, posterior CP in mothers with influenza, sinusitis, and bronchitis, and OFC in mothers with epilepsy or angina pectoris [70].

7.4. Nutrition

The role of maternal nutrient intake in the development of congenital malformations in the child has long been studied with the aim of elucidating the etiologies of specific birth defects and informing effective prevention strategies. Evidence indicates that maternal nutrient intake affects the risk of giving birth to a child with CL/P or CP. In particular, a lack of vitamin B9, more commonly known as folate (or its synthetic form, folic acid), in the mother’s diet has long been linked to the risk of congenital malformations. An association between maternal
Folate intake and reduced risk of having a child with CL/P or CP has previously been demonstrated [71]. However, studies have not consistently linked folic acid with OFC as they have with neural tube defects [72, 73].

Previous reports have shown maternal intake of vitamins other than folate, such as other B vitamins (e.g. riboflavin), iron, zinc, and the amino acids choline, methionine, and cysteine, to be associated with reduced risk of having a child with CL/P or CP [72, 74, 75].

Vitamin A is known to play a crucial role in fetal development. Deficient and excessive intakes of vitamin A increase the risk of birth defects, including OFC, in animals as well as humans [76–79], but exact daily intake numbers have not been established [80].

7.5. Maternal exogenous exposures

Most of the CL/P and CPO epidemiologic studies support a role for environmental factors in the etiology of clefting. The most common risk factors reported were maternal exposure to tobacco products [81, 82], alcohols [83], some viral infections [70], pesticides [84], and teratogens in the workplace or at home in early pregnancy [85–87]. Recognized teratogens included rare exposures such as phenytoin, valproic acid, thalidomide, and herbicides such as dioxin. As mentioned previously, risk of CL/P or CPO conferred by these exposures—in particular tobacco—may be modulated by the presence or absence of certain genetic factors [19, 88, 89].

8. Cleft palate and cancer

Several studies from different countries (USA, Latvia, Denmark, and Brazil) have identified an association between cleft palate and cancer [90–95]. The first epidemiological studies addressed the presence of cancer in cleft lip/palate subjects and their families. Parents of kids with sporadic CL/P have a higher risk of developing cancer than control families [96], and increased risk of cancer in adulthood can be seen in a Danish population-based cohort of CL/P subjects [97]. Such studies suggested that the association was most frequent for breast cancer but also colorectal, gastric, prostate, and uterus cancers. In a large study, 313 families segregating cases of isolated CL/P, including information of 13,879 individuals, were analyzed by Vieira [93]. The study brings further evidence that individuals born with CL/P and their family members have a higher prevalence of cancer than the general population. This risk is three times higher in first- and second-degree relatives and decreases to 1.5 times in third-degree relatives.

A possible genetic link was identified in two families with mutations in the E-cadherin gene CDH1 with CL/P and hereditary diffuse gastric cancer [98]. CDH1 is highly expressed in the palate. Vogelaar et al. also identified germline mutations multiple families with gastric cancer and orofacial clefts [99]. One concern in interpreting these studies is that cleft lip/palate patients tend to have a higher prevalence of behavioral risk factors, such as smoking and drinking because of their limited social interactions as adolescents, thus
are at higher risk of tobacco and alcohol-related cancers independently from their initial malformation.

What is lacking is a study of cancer cases and the risk of cleft palate in their family members. Such studies are limited by the fact that the genetic defect is still a rare event, and the number of cancer cases necessary to address the problem would be extremely large. A study conducted on family members of cancer patients (Taioli et al. [95]) involved an epidemiological questionnaire including family history of cancer and congenital oral cleft malformations that was administered to 168 cancer survivors and a population-based sample of 170 healthy subjects. In the control group, 1.2% reported a family member with CL/P; among cancer survivors, the figure was 4.2% (odds ratio: 3.7; 95% confidence interval: 0.75–17.8; \( p = .07 \)). Among cancer survivors with a family member with CL/P, there was an apparent excess of testicular cancer and melanoma in comparison with the cancer survivors with no family history of CL/P. These preliminary results suggest a common etiologic background for cancer and CL/P.

Taken all together, the data suggest that there are shared environmental and genetic factors in families that predispose to both cleft palate and cancer.

9. Conclusion

OFCs are the most common craniofacial anomalies, and one of the most common congenital anomalies worldwide. OFCs have historically been grouped as CL/P or CPO. However, existing evidence suggests that separate etiologies may exist for cleft lip alone versus cleft lip with palate. CL/P and CPO are classified as syndromic or nonsyndromic; nonsyndromic cases are further subclassified as multiple or isolated.

Both genetic and environmental factors have been implicated in the etiology of OFC. The genes underlying a number of known syndromes associated with OFC have been identified. Furthermore, environmental factors such as alcohol and tobacco have been shown to modulate the risk of OFC conferred by certain genetic factors.

Although nonsyndromic OFCs are not traditionally the subject of genetic analysis, a number of genomic association studies have evaluated the link between genetic variants and nonsyndromic OFC. Examples of genes that have been examined in such studies include those that code for growth factors, transcription factors, and nutrient metabolism proteins. In addition to genetic factors, studies have recently begun to explore the role of epigenetic modifications in palatal ontogeny and etiology of OFC.

A number of environmental and maternal factors that influence the risk of having a child with OFC are well-described. In particular, family history, maternal drug use, nutrition, and exogenous exposures demonstrate strong links with development of OFC in the child.

Several studies have shown a higher incidence of cancer amongst patients with CL/P and their families. Additionally, studies have begun to identify higher rates of CL/P in the families of patients with cancer, although less is known about this. Combined, these suggest that CL/P and cancer may be mediated by shared environmental and genetic etiologies.
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