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Cleft Lip and Cleft Palate

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Glossary

d0005 **Diploid cell** A cell with a nucleus that contains paired chromosomes, one from each parent; human somatic cells have 23 pairs of chromosomes; human gametes (egg or sperm) contain a single set of 23 chromosomes, the haploid number.

d0010 **Epigenetic factors** Factors which change the state or function of a gene without changing the DNA sequence of the gene, and result in altered phenotypic consequences of that gene's function (e.g., DNA methylation and imprinting).

d0015 **Fraser–Juriloff paradigm** A proposition put forth by geneticists F. Clarke Fraser and Diana Juriloff that, during development, emerging anatomic structures have varying susceptibility to environmental insults depending upon the genetically controlled variability of the intrinsic growth of that structure; for example, slower-growing paired palatal shelves have greater susceptibility to corticosteroid-induced failure to merge (cleft palate) than faster-growing paired palatal shelves.

d0020 **Mendel, Gregor (1822–84)** Father of modern genetics, Mendel was an ethnic German born in Austrian Silesia. After his studies at the University of Vienna, he took residence at the Abby of St. Thomas in Brno (now Czech Republic) as an Augustinian priest. Studies in the monastery's two hectare experimental garden allowed Mendel to induce that the inheritance of specific traits in pea plants followed specific laws (later termed 'Mendel's Laws of Segregation and Independent Assortment'). Mendel's seminal paper, published in 1866, was ignored by Charles Darwin and nearly all other biologists, and then rediscovered in the early years of the twentieth century by Hugo de Vries and others.

d0025 **Philtrum** The infranasal depression (vertical groove) in the central upper lip formed where the medial and maxillary processes merge, both on the left and right sides; Greek *philtron*, from *philein* (to love; to kiss), believed to be one of the most erogenous anatomic sites on the human body.

d0030 **Syndromic versus nonsyndromic oral clefts** Those patients who exhibit one or more major malformations and/or three or more minor malformations in addition to the oral cleft are said to have syndromic oral clefting; all others are considered nonsyndromic.

d0035 **Teratogen** An environmental agent which is demonstrated to have a statistically significant, nonrandom association with a particular congenital malformation or set of malformations (e.g., chemicals, drugs, radiation, viruses).

p0040 Oral clefts are a major public health problem worldwide (Table 1). Nonsyndromic cleft lip with or without cleft palate (CL ± P) has an incidence at birth of about 1 in 500–1000 that varies by population; persons of Asian descent are often at higher risk than those of European or African descent. These geographic differences result from the environmental and/or genetic heterogeneity among different populations. In all populations there are significantly more males born with CL ± P than females. The incidence at birth for nonsyndromic cleft palate alone (CP) is relatively uniform across populations at about 1 in 2000; significantly more females are born with CP than males. It has been clearly established that CL ± P and CP are etiologically distinct. Persons with CL ± P very rarely have relatives with CP and vice versa. What CL ± P and CP do share is that their etiologies are complex and their pathogenesis is only superficially gleaned.

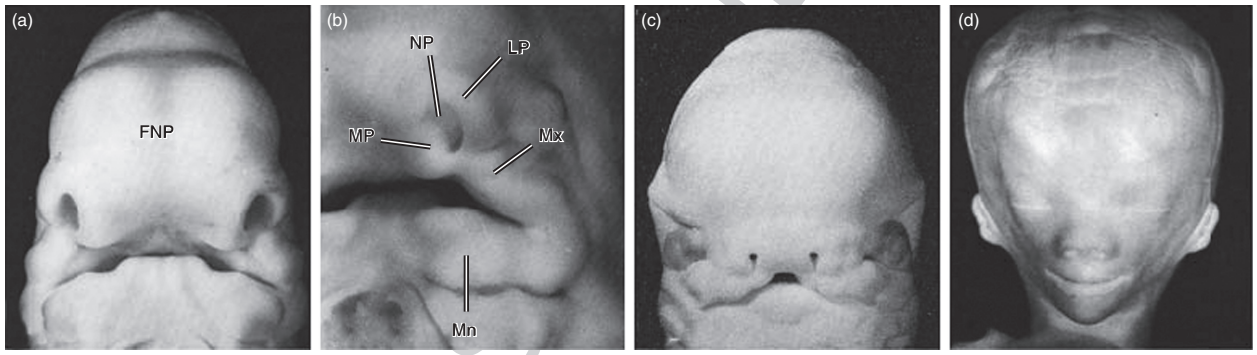
s0005 Normal and Abnormal Lip and Palate Morphogenesis

p0045 In human lip development, by 5 weeks the nasal pit is deep and prominently bounded by the medial and lateral nasal processes; the maxillary processes have rapidly grown by this time and approach each other and the medial processes (Figures 1(a) and 1(b)). The human lip forms at the bottom of the nasal pit with the meeting of the medial surface of the maxillary process and the lateral surface of the medial process. This is soon followed by fusion of the lateral processes, more superiorly and anteriorly, with the medial process. All this occurs between the 40th and 48th days of embryonic life (Figure 1(c)). At the same time the medial processes merge with each other to form the intermaxillary segment. This segment gives rise to the philtrum of the lip and the primary palate, an area of the palate bounded by two lines from the incisive foramen to the alveolar bone between the lateral incisor and canine on each side. The lateral parts of the upper lip, the maxilla, and the secondary palate are formed from the maxillary process. By the 10th week of development, the facial harmony of proportion is largely complete, and continues minor remodeling over the next 4 weeks (Figure 1(d)).

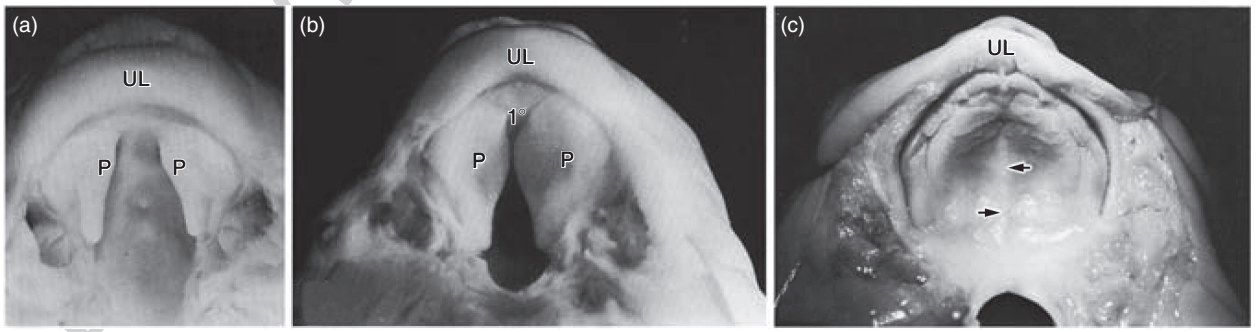
p0050 The human secondary palate derives from two internal projections from the paired maxillary processes, termed 'palatal shelves'. Initially these shelves are vertically positioned on either side of the developing tongue, but as the mandible grows the tongue moves downward and the shelves become more horizontal and grow toward one another (Figure 2(a)). Between the 8th and 9th week of development, the shelves have grown sufficiently large to approximate each other and begin to fuse anteriorly (Figure 2(b)). Fusion is complete by the 12th week of gestation (Figure 2(c)). The shelves also fuse with the primary palate (Figures 2(b) and 2(c)) and nasal septum,

t0005 **Table 1** Cleft lip and/or cleft palate: general population frequencies and male/female sex ratios, worldwide

	General Population Frequency		*Male/Female Sex Ratio of Affected*	
Country	*CL ± P*	*CP*	*CL ± P*	*CP*
Denmark	0.0011	0.00047	2.31	0.75
Sweden	0.0012	0.00051	2.10	0.64
Finland	0.0007	0.00067	2.08	0.77
England	0.0010	0.00046	1.57	0.52
Hungary	0.0010	0.00027	–	–
Iceland	0.0018	0.00073	2.67	0.67
U.S.A.	0.0011	0.00043	1.93	0.82
Australia	0.0009	0.00039	1.67	0.87
Japan	0.0017	0.00036	1.47	0.42
China	0.0013	–	1.67	–



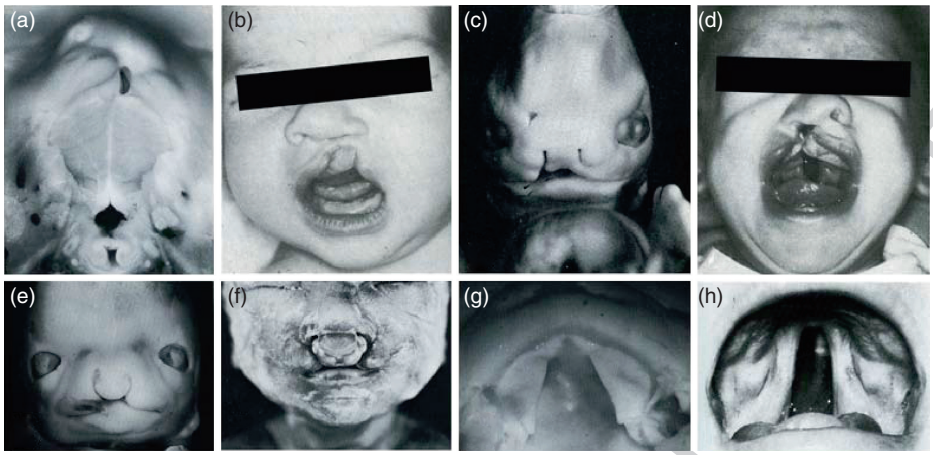
f0005 **Figure 1** (a) Human embryonic face at ~37 days (×17); FNP = frontonasal prominence. (b) Human embryonic face at ~37 days (×20); Mn = mandibular process, Mx = maxillary process, MP = medial nasal process, LP = lateral nasal process, NP = nasal pit. (c) Human embryonic face at ~44 days (×7.5). (d) Human embryonic face ~10 weeks (×2). (a, b) Proximate to the stomodeum, the frontonasal prominence (FNP) gives rise to horseshoe-shaped ridges surrounding deepening nasal pits (NP), the medial and lateral nasal processes (MP; LP). (c) The upper lip is formed bilaterally by the merging of the maxillary processes (Mx) and the medial nasal processes (MP); the lateral nasal processes form the nasal alae. (d) The medial nasal processes merge to form the philtrum of the upper lip, as well as the columna and apex of the nose.



f0010 **Figure 2** (a) Human embryonic palate at ~54 days (×12); UL = upper lip, P = palatal process (shelf). (b) Human embryonic palate at ~57 days; 1° = primary palate. (c) Human embryonic palate at ~17 weeks; arrows delineate the median palatal raphe, the site of palatal shelf (process) fusion. (a, b) The secondary palate derives from bilateral shelf-like outgrowths (P) from the internal surfaces of the paired maxillary processes. Beginning in the 9th week, the shelves fuse in an anterior/posterior direction. (c) This fusion is complete by the 12th week, and the palate is fully modeled by week 17.

which develops as a downgrowth from the merged medial processes. During fusion of all structures, the apposed epithelia form an epithelial seam which is soon lost and allows complete fusion and mesenchymal continuity.

p0055 The human lip and palate thus form as a result of the cell proliferation (growth), apposition, and fusion of embryonic facial processes between the 5th and 12th weeks of gestation. This requires that the processes appear in the correct place at the



f0015 **Figure 3** Abnormal prenatal lip and palate development and postnatal phenotypes. (a, b) First trimester failure of the left maxillary process to merge with the left medial nasal process results in left-sided cleft of the lip and alveolus. (c, d) Failure at ~44 days of the right maxillary process to merge with the right medial nasal process results in a right-sided cleft lip and a secondary cleft of the palate. (e, f) Bilateral failure prior to ~52 days of the maxillary processes and the medial nasal processes to merge results in bilateral cleft lip and palate seen here in a stillborn infant. (g, h) Failure of embryonic palatal process (shelf) growth results in cleft of the palate alone.

correct time, achieve the correct shape and size, and have no obstruction to fusion. Given the complex nature of this oral development, one can readily imagine a long list of potential mishaps (Figure 3). Most prominent among these is the abnormal growth of facial processes. Indeed, while the phenotype cleft or no cleft may seem to be a dichotomous trait, it is in reality a quantitative trait, that is, process or shelf growth.

s0010 Inheritance of Oral Clefts

p0060 The growth phenotypes of facial processes are quantitative in nature and continuous in distribution. With respect to the genetic transmission of these phenotypes, there is no patent segregation into readily recognizable classes showing typical Mendelian ratios. Thus, the inheritance patterns of CL ± P and CP are not classically Mendelian, but appear to be characterized by the interaction of numerous genes, the influence of diverse environmental factors (teratogens), and genetic heterogeneity within and between families and populations. This etiologic fact is broadly designated as the 'Fraser–Juriloff paradigm'.

p0065 Complex genetic diseases such as oral clefting are generally far more common than Mendelian disorders because selection against the disease alleles is considerably weaker. Compared to Mendelian (simple) diseases, it has been highly problematic to identify genes related to complex disease susceptibility. The power of gene-mapping studies for complex traits like CL ± P and CP depends upon the number of causative loci. For CL ± P and CP, this number is entirely a black box, not least because if there are large numbers of low-frequency alleles at most relevant loci, these will be difficult to detect. Still, after decades of heroic efforts, human genetic studies, mouse models, and expression analyses point to nearly 40 genes and candidate genes for clefting of the lip and palate.

p0070 Clear identification of CL ± P and CP susceptibility loci, and their function and interactions, continue to be a formidable challenge. Even if successful, it would only scratch the surface for these complex genetic traits. The recent identification of other genetic and epigenetic variations, as well as subtle environmental factors, has upped the ante on ever being able to truly identify etiology and pathogenesis as a prelude to prevention. In other words, the text (DNA sequence) has a context and we know little real detail about either.

Epigenetic Modification of Gene Expression s0015

p0075 It is certain now that one major complication in the genetics of susceptibility to complex diseases is the modification of the disease phenotype by epigenetic factors. Prominent among these is DNA methylation, a potent mechanism for gene silencing. Although typically there is biallelic expression of individual autosomal genes in each diploid cell, in a subset of these autosomal genes one of the alleles is inactivated, often in genes whose protein products play an essential role during embryonic development.

p0080 Monoallelically expressed autosomal genes fall into two distinct classes. The first class includes autosomal imprinted genes whose monoallelic expression is regulated in a parent-of-origin-specific manner. Two genes in this class, *Igf* and *Igf2r*, are suggested by mouse models to be important to abnormal palate formation, not because of DNA sequence differences but because of methylation differences. Imprinted genes are found in clusters, and these clusters are conserved between mouse and humans. There are likely to be others in this class that contribute to the etiology of CL ± P and/or CP. The second class includes autosomal genes subject to random monoallelic expression regardless of parental origin. It appears that a majority of the genes in this class are developmental genes. However, it is presently unknown which ones, if any, contribute to CL ± P and CP etiology. Nevertheless, assuming this to be operative, Melnick and Shields, nearly 35 years ago, demonstrated that this phenomenon was consistent with the population genetics.

Environmental Factors s0020

p0085 Numerous studies over many decades suggest that environmental risk factors (teratogens) for oral clefting are likely to

include maternal exposure to tobacco smoke, alcohol, inadequate nutrition (particularly deficiencies of folate and/or vitamin B6), and prescribed drugs (phenytoin, phenobarbital, and diazepam). There are almost certainly many others that are found at home, at the workplace, among approved medications, and in countless other venues. The ubiquitous presence of most will make them difficult to document with any statistical certainty.

p0090 One lesson we can learn from those we are reasonably certain of concerns their interesting interaction with the genome. For example, a new mouse model indicates that one of the consequences of gestational alcohol exposure is aberrant DNA methylation and excessive transcriptional silencing. Similarly, since folate is a methyl-group donor, another recent murine model has shown that folate deficiency also results in aberrant DNA methylation, contrastingly too little transcriptional silencing. Finally, bisphenol A (BPA), an emerging mega-teratogen, has also been shown in mouse models to downregulate DNA methylation and transcriptional silencing in ways detrimental to embryogenesis.

s0025 Recurrence Risk

p0095 Because the etiologies of CL ± P and CP are largely undefined, the counseling of affected families relies almost entirely on empirical studies of recurrence risk. For Caucasians, it has been found that if the cleft proband has other affected first- and/or second-degree relatives, the risk to subsequent siblings or offspring is about 15%. If the proband has no other affected first- and/or second-degree relatives, the risk to subsequent siblings or offspring drops to about 5%. Less rigorous empirical risk determinations for other racial groups suggest that the above estimates are reasonable for non-Caucasians as well.

s0030 Prenatal Diagnosis of Cleft Lip and Palate

p0100 Because of near universal utilization of ultrasound in quality prenatal care, and the dramatic improvements in imaging technology, cleft lip and palate is more commonly identified prenatally than ever before. Nevertheless, while the specificity of prenatal ultrasound cleft diagnosis is high, the sensitivity lags behind. Though a majority of parents may favor prenatal diagnosis and the opportunity to prepare for the birth and subsequent treatment of a cleft child, such prenatal diagnosis of oral clefts can be problematic. To wit, ultrasound cleft diagnosis may present parents with a choice regarding continuation or termination of the pregnancy, and the moral and ethical dilemmas attendant to that choice. Afterall, nonsyndromic cleft persons are most often normal in all other ways, lead a productive life, provide for their children, and some are even leading men on stage and screen.

See also: Complex Traits (00308); Epigenetics (00480); Prenatal Diagnosis (01206).

Further Reading

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Biographical Sketch

Dr. Melnick is a professor of genetics and developmental biology at the University of Southern California in Los Angeles. He has earned degrees at New York University (BA, DDS) and Indiana University (PhD). He established the Laboratory for Developmental Genetics in 1981. Over the past three decades, with support from the National Institutes of Health, Dr. Melnick has investigated the genetic complexities of normal and abnormal embryonic development. Dr. Melnick has published more than 120 peer-reviewed scientific papers and five books. He has been elected a Fellow of the American Association for the Advancement of Science (AAAS). Currently, Dr. Melnick is investigating the cellular genetic response to cytomegalovirus infection as it relates to birth defects and adult tumor formation.