### Glossary

**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.

**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).

**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.

**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.

**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.

**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.

**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).

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**Cleft Lip and Cleft Palate**

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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 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 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.

**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 median 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)).

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,
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.

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
Inheritance of Oral Clefts

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 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’.

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.

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.

Environmental Factors

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.

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.

Recurrence Risk

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.

Prenatal Diagnosis of Cleft Lip and Palate

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


Relevant Websites

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.