An Overview of Dentistry Genetics

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Importance of Genetics
• Hereditary conditions affect millions of families throughout the world.
• About 5% of all pregnancies result in the birth of a child with a significant genetic disorder, congenital malformation or disability.
• An estimated 43% of cases of severe mental retardation (IQ <50) are caused by single genes or chromosomal abnormalities (Institute of Medicine, 1994).
• In developed nations, totally or partially hereditary conditions account for about 36% to 53% of paediatric hospital admissions (Institute of Medicine, 1994).
• In developing nations hereditary conditions account for about 15% to 25% of perinatal and infant mortality (Verma and Singh, 1989; Penchaszadeh, 1993).
• Most non-infectious diseases, which are the major causes of death in developed nations, may have a genetic component (Holtzman, 1989).

Abnormalities of Tooth Development
Numerous genetic and environmental factors may cause abnormalities in tooth development. These may include:
• Defects of structure (e.g. abnormal enamel, amelogenesis imperfecta, or abnormal dentin, dentinogenesis imperfecta or dentin dysplasia)
• Abnormal position of tooth
• Reduced size and abnormal shape of teeth (e.g. "peg-shaped" incisors, taurodontism, or short root anomaly)
• Missing of one or more teeth (hypodontia, oligodontia, tooth agenesis).

Congenitally Missing teeth
Missing of one or more teeth is perhaps our most common congenital malformation.
• More than 20% of us lack one or more wisdom teeth (third molars).
• More than five percent of us lack one or more second premolars or upper second (lateral) incisors.
• Lack of a large amount of teeth, though, is much more rare.

Congenitally Missing teeth
Hypodontia refers to congenital lack of a few teeth. The population frequency is over 5% (missing of wisdom teeth not included).

Oligodontia refers to congenital lack of more than six teeth (wisdom teeth not included). The population frequency is low, especially for cases when absence of teeth is the only malformation ("isolated" cases).
• Most often oligodontia appears as part of some congenital syndrome that affects several organ systems. These include:
  • Ectodermal dysplasias, i.e. defects of skin, hair, nails, teeth and ectodermal glands
  • Oral clefting (cleft lip, cleft palate, or cleft lip and palate)
  • Rieger syndrome, Char syndrome, etc.
**Congenitally Missing teeth**

Anodontia refers to complete lack of teeth, which is very rare. Tooth agenesis, also used as partial or selective tooth agenesis, may refer to all of the above.

Most commonly missing teeth are the third molars (wisdom teeth), second premolars and permanent upper second (lateral) incisors.

Most rarely missing teeth are the upper first (central) incisors. Missing of lower second (lateral) incisors, all canines, first premolars and first molars or any of the deciduous teeth is also rare. Shapes and positions of the existing teeth may also be abnormal in association with missing teeth. The features often seen include "peg-shaped" upper second incisors, taurodontism and malpositions.

**Causes of Congenitally Missing teeth**

Several environmental factors like virus infections, toxins and radio- or chemotherapy may cause missing of permanent teeth. However, most of the cases are caused by genetic factors. The heritability of congenitally missing teeth has been shown in many studies. The genetic factors may be dominant or recessive and it is obvious that in many cases multiple genetic (and environmental) factors are acting together. The importance of genetic factors is shown by appearance of multiple cases among relatives (familial clustering) and higher concordance in identical than in non-identical twins.

**Dominant inheritance of congenitally missing teeth has been shown both in hypodontia and oligodontia.** However in both cases the amount and identity of missing teeth may vary between relatives. In hypodontia, the variability may extend to no teeth actually missing ("reduced penetrance"). The variability is probably caused by other genetic and environmental factors, and in some cases the etiology is analogous to multifactorial traits.

**Genes for Congenitally Missing teeth**

We already know several genes which, when defective, cause congenitally missing teeth. The known gene defects include mostly those that cause a multi-organ syndrome (genes EDA, EDAR, EDARADD, IKKgamma, p63, IRF6, PITX2, TFAPB2, SHH, OFD1).

Only two genes are known so far where defects cause isolated tooth agenesis. Dominant loss-of-function mutations in **MSX1** and **PAX9** cause oligodontia.

Identification of gene defects that cause isolated hypodontia, the most common type of congenitally missing teeth, has been much more difficult.
We already know several genes which, when defective, cause congenitally missing teeth. The known gene defects include mostly those that cause a multi-organ syndrome (genes EDA, EDAR, EDARADD, IKKgamma, p63, IRF6, PITX2, TFAP2B, SHH, OFD1).

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Mutations in different genes may cause different types of oligodontia (i.e. different sets of teeth are missing). For example, all individuals with a mutation in MSX1 lack all second premolars and third molars (and a variable number of other permanent teeth). Typically, mutations in PAX9 cause agenesis of most permanent molars (and again, a variable number of other permanent teeth). These differences presumably reflect different functions of these genes during development.

It is remarkable that all genes mentioned above participate in signaling between cells or regulation of cell activity. Mutations that cause tooth agenesis have not been found in genes that code structural proteins.

Genotype-Phenotype Relationship

In Simple (a) and Complex (b) Traits

a) One Gene \(\rightarrow\) One Trait

b) Multiple Genes + Environment \(\leftrightarrow\) One Trait
Estimating heritability from twin studies

Heritability (h²): \[ \frac{\text{variance in DZ pairs} - \text{variance in MZ pairs}}{\text{variance in DZ pairs}} \]

If the variability of the trait is determined mainly by environment, the variance within pairs of DZ twins will be very similar to that seen within pairs of MZ twins, and the numerator, and therefore h² itself, will approach 0; If the variability is determined exclusively by genetic makeup, variance of MZ pairs is zero, and h² is 1.

Assumptions:
1. Shared environment is similar for MZ Twins & DZ Twins.
2. Twins are representative of other siblings in their experience of the shared environment.

Polygenic and Multifactorial Inheritance

Polygenic Inheritance = Traits / diseases caused by the impact of many different genes each having a small individual effect on phenotype.

Multifactorial Inheritance = The occurrence of the condition is dependent on the combined effect of:
1. Several genes each exerting a small individual influence on phenotype.
2. Interplay of several environmental factors (each exerting a small influence) with multiple genes.

Genetic heterogeneity

Different genes can produce identical phenotypes.

Individuals with identical phenotypes may reflect different genetic causes.
- Deafness
- Albinism
- Cleft palate
- Poor blood clotting

Heterogeneous trait

A mutation at anyone of a number of genes can give rise to the same phenotype
- Many different genes generate a developmental or biochemical pathway (50 genes for hearing)
- It takes a dominant wild-type allele at each of these genes to produce a normal development or product

A recessive mutation at any one of a number of genes can give rise to the same phenotype (deafness)

The same genotype does not always result in the same phenotype

Degree of expression of particular trait being studied is quantified by looking at penetrance

Penetrance – How many members of a population with a particular genotype show the expected phenotype

Expressivity – refers to the degree or intensity with which a particular genotype is expressed in a phenotype within a population
Incomplete penetrance and phenocopies

- Some individuals with the mutated gene do not manifest the disease.
- Some individuals without the mutated allele have the disease.
- The genotype only determines the probability of disease:

<table>
<thead>
<tr>
<th>Age</th>
<th>BRCA1 +</th>
<th>BRCA1 -</th>
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<tr>
<td>40</td>
<td>37%</td>
<td>0.4%</td>
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<tr>
<td>55</td>
<td>66%</td>
<td>3%</td>
</tr>
<tr>
<td>80</td>
<td>85%</td>
<td>8%</td>
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Familial aggregation of disease

Relatives share a greater proportion of their genes with each other than unrelated individuals in the population, a primary characteristics of multifactorial disease is that affected individuals tend to cluster in families (familial aggregation).

The familial aggregation of a disease can be measured by comparing the frequency of the disease in the relatives of an affected proband with its frequency (prevalence) in the general population.

Relative risk $\lambda_r$:

$\lambda_r = \frac{\text{prevalence of the disease in a relative } r \text{ of an affected person}}{\text{population prevalence of the disease}}$

Epistasis

A gene interaction in which one gene interferes or masks the phenotypic expression of an allele of another gene.

The phenotype is governed by the epistatic gene.

Pleiotropy

The appearance of several apparently unrelated phenotypic effects caused by a single gene.

- Refers to a Mendelian disorder with several symptoms.
- Different subset of symptoms in different individuals.
- Usually means that a gene is involved in multiple processes.
- Examples: Marfan Syndrome, Porphyria.

Phenocopy

A trait caused by the environment that appears inherited.

- Exposure to teratogens
  - Thalidomide causes limb defects akin to rare inherited phocomelia.
- Infection
  - Rubella in pregnant mothers causes deafness mimicking inherited forms of deafness.

Some problems finding genes in complex diseases

- For most of these diseases multiple genes are probably involved as well as the environment.
- Genetic analysis is complicated by incomplete penetrance, genetic heterogeneity, polygenicity and phenocopies which all reduce the correlation between phenotype and genotype.
- It can sometimes be hard to define the phenotype.
- Different genes might be important in different ethnic groups.
**Why Identify Genetic Factors for Complex Diseases?**

- Some genetic factors may permit modulation
- Identifying and conditioning on genetic factors may assist in identifying environmental triggers