Parental Effects

A parental effect refers to a situation where, conditional on the individual’s own genotype, the phenotype of an individual depends upon the mother’s or father’s phenotype or genotype. For example, a factor complicating gene discovery in asthma is the possibility, based on epidemiologic studies, that maternal phenotype influences the inheritance of asthma and atopy [10, 12]. The presence of asthma and associated phenotypes such as atopy in children has been consistently associated with an increased prevalence of asthma or atopy in mothers [10]. The differential risk of transmission between parents may be fourfold. The mechanism, or mechanisms, for these parental effects are unknown, but possibilities include genomic imprinting (see below) or maternal modification of the developing infant’s immune system by transmission of immune factors across the placenta or through breast milk. The latter is likely to be affected by a complex interaction between maternal and fetal genetic and environmental factors. Similar parental effects have been noted in other immunologic disorders, most notably type I diabetes [21], rheumatoid arthritis [9], inflammatory bowel disease [7], and selective IgA deficiency [20], suggesting that parental effects on the developing infant’s immune system may be an important common process modifying genetic diseases that are immunologic in origin. The remainder of this article describes the phenomena of genomic imprinting and maternal effects and their implications for genetic analysis. While there are clear theoretic differences between these two mechanisms, in practice they may be difficult to distinguish in complex diseases.

Genomic Imprinting

Imprinting refers to the situation where the relationship between a genotype and a phenotype (or disease-status) in an offspring depends upon which parent passed on the disease susceptibility or phenotype-modifying gene. When imprinting exists, the penetrance of the disease susceptibility allele will be different for maternally derived vs. paternally derived alleles. The observation that certain genes are expressed differently depending on whether they are inherited from the father or mother implies that genetic alteration of a gene or its expression has taken place. For example, a chromosomal deletion of a certain part of human chromosome 15 in a father results in an offspring with Prader–Willi syndrome. However, when the same part of chromosome 15 is missing in a mother, the offspring has Angelman syndrome [2] (see Genetic Counseling).

Concrete examples of genomic imprinting derive largely from studies of transgenic mice [16, 17]. However, imprinting has been suggested to play a role in several complex human diseases in addition to asthma, including bipolar affective disorder [4] and type 2 diabetes mellitus [8]. The mechanisms causing imprinting are poorly understood, but are thought to involve DNA methylation. The effect of imprinting can range from total inactivation of a gene and its expression (see Gene Expression Analysis) to the reduced expression in specific tissues. Interestingly, the imprinting effect can appear to be heritable only in a single generation. That is, the effect is unmasked if it passes through the nonimprinting sex. For instance, a gene inactivated by maternal imprinting that is inherited by a son will be reactivated in the next generation, i.e. the offspring of the son inheriting the gene. (Note, however, that should the son then have a daughter, her children will not express the phenotype.) Conversely, the same gene inherited by a daughter will remain inactivated in the next generation.

For a quantitative phenotype assessed in a nuclear family, the possible existence of imprinting upon offspring phenotype may be crudely assessed by estimating a basic variance component model (see Variance Component Analysis, Equation (2)) or its extensions. The basic variance component model is

$$Y_i = \mu_i + G_i + C_i + E_i,$$

where \(Y_i\) is a continuous trait measured on individual \(i\), \(\mu\) is the conditional trait mean, and \(G_i, C_i\) and \(E_i\) are independent random variables with zero means and represent genetic factors, factors common to relatives (i.e. familial environmental factors), and factors specific to an individual (including measurement error, assumed to arise from nongenetic environmental factors), respectively (see Familial Correlations). The result of imprinting at a locus on the expression of a quantitative phenotype will be to reduce the expected phenotypic covariance between parents and offspring relative to that between sibs (see Genetic Correlations and Covariances). Genetic imprinting
would be suggested if the difference between the parent–offspring covariance and twice the covariance between paternal half sibs derived from (1) were significantly less than zero. Imprinting can be explicitly assessed by extending (1):

\[ Y_i = \mu_i + G_{it} + G_{tm} + C_i + E_i, \]

where the subscript t denotes components of genetic variance derived from the father, and the subscript m denotes components of genetic variance derived from the mother. Note that in an imprinting model, covariances between pairs of relatives are also estimated separately for male–male, female–female, and male–female relationships [3].

The phenomenon of imprinting has potentially important implications for genetic analysis. The reduction of the expected phenotypic covariance between parents and offspring relative to that between sibs caused by imprinting can lead to greatly reduced power to detect linkage for both quantitative and qualitative traits when such imprinting effects are not considered in the analysis. Similarly, association analyses are compromised when the differential risk for outcome among individuals with the same genotype (but alleles derived from different parent genders) is not considered. In an imprinting situation, genotypes of high risk are considered in the same “exposure” category as genotypes conferring no increased risk due to imprinting, biasing the association towards the null. For these reasons, inclusion of terms reflecting imprinting effects in models of quantitative and qualitative traits is important for segregation analysis, linkage analysis (see Linkage Analysis, Model-Free: Software for Genetic Epidemiology) and association analysis (see Disease–Marker Association; Family-Based Case–Control Studies).

Maternal Effects

Maternal effects arise when, for reasons that may be environmental (e.g. in utero environmental effects or the effects of breast feeding), genetic, or a combination of the two, the phenotype of an offspring depends more upon maternal phenotype than on paternal phenotype. Such an observed effect may arise due to maternal genotype (any genetic effects on the mother’s in utero environment or other nontransmitted maternal genotype effect) or maternal phenotype (any characteristic in the mother – possibly nongenetic – that influences the child’s phenotype). For example, children of mothers with the genetic disorder phenylketonuria may develop mental retardation and small head size regardless of the child’s genotype unless dietary intervention during pregnancy is pursued [5]. This disorder in the child is due to the maternal genotype rather than transmitted genes carried by the child.

The basic variance component model given in (1) (see Genetic Correlations and Covariances; Variance Component Analysis) can be extended to allow for maternal effects [25] by splitting each of the original components of variance into two components, representing the direct expression of each individual’s genotype and environmental components as well as indirect maternal components of variance:

\[ Y_i = \mu_i + (G_o + C_o + E_o) + (G_m + C_m + E_m), \]

where the subscript o denotes components of variance reflecting a direct effect of an individual’s genotype and environmental exposures, and the subscript m denotes components of variance reflecting an indirect effect of the maternal phenotype. Note that this formulation explicitly ignores epistatic sources of maternal genetic variation.

As with imprinting effects, inclusion of terms reflecting maternal effects in variance components models of quantitative traits can be readily extended to segregation analysis, linkage-component-based linkage analysis (see Linkage Analysis, Model-Free: Software for Genetic Epidemiology), and association analysis (see Disease–Marker Association; Family-Based Case–Control Studies).

Failure to account for maternal effects (when present) in variance components and segregation analysis can result in misleading inferences regarding mode of phenotypic inheritance. This is also true for linkage and association analysis of qualitative traits, where failure to account for potential maternal or paternal effects can bias tests of the null hypothesis regarding linkage or association to a particular genetic variant possessed by affected individuals [22]. For example, in the transmission-disequilibrium test (TDT) setting, maternal effects that increase risk for a disease among children (regardless of the child’s genotype) will result in an excess of affected child–mother pairs, compared with affected child–father pairs. This may lead to a false
conclusion of a maternal imprinting genetic effect, when no such genetic effect (in the children) exists.

Paternal effects, while far less common than maternal effects, can be dealt with analytically in the same way as maternal effects.

**Linkage Analysis**

Methods to test and account for imprinting when evaluating linkage have been proposed for model-based linkage analysis, model-free allele-sharing methods and variance component methods. Model-based linkage analysis can be performed by specifying male and female recombination fractions separately [15], or by fixing the recombination fraction of the assumed imprinting gender at 0.5 and then estimating the recombination fraction of the other gender [7]. Alternatively, a four-penetrance model can be created in which the disease locus heterozygotes have different penetrances depending on the parental origin of the particular alleles [18]. Because imprinting can occur for dominant and recessive modes of inheritance, maximized lod score (mod score) analysis can also be pursued under this four-penetrance model [14, 18]. Tests of linkage can be carried out via likelihood ratio testing of the four-penetrance model under linkage vs. the same model under no linkage. Explicit tests of imprinting can be carried out by comparing the four-penetrance model under linkage with a standard three-penetrance model, which assumes the two types of heterozygotes have equal penetrance. The GENEHUNTER-IMPRINTING software can perform parametric lod score linkage analysis under the four-penetrance model (see Software for Genetic Epidemiology).

Imprinting can be detected in model-free linkage as differential results when stratifying family sets according to paternal and maternal meioses [13]. For quantitative traits, marker allele sharing can be estimated for maternally derived and paternally derived alleles separately, and variance components or Haseman–Elston regression (see Linkage Analysis, Model-Free) used to assess linkage as departure from the expected 25% sharing of a particular parental allele [6]. A similar method for qualitative traits has also been described [11]. Under the variance component framework, linkage in the presence of imprinting can be assessed by comparing the likelihood of the data using the maximum likelihood estimators (MLEs) of the parent-specific major-gene variance components with the likelihood obtained when constraining these to 0. Imprinting can be tested in a manner similar to that described for the model-based methods described above by comparing a likelihood where both parent-specific major gene variance components are estimated with a model where they are constrained to be equal (but not necessarily 0). A similar strategy can be employed for Haseman–Elston regression by estimating regression coefficients for paternal allele sharing and maternal allele sharing separately, and testing whether they are equal to 0 (test of linkage) or whether they are equal to each other (test of imprinting). These analyses can be carried out using available identity-by-descent (see Identity Coefficients) estimation software and standard statistical packages for variance components and linear regression. Testing for maternal or paternal effects not due to imprinting can be allowed for in linkage analyses by the inclusion of parental phenotype through conditioning, covariate adjustment or, in the case of a quantitative phenotype, inclusion of random effects representing the indirect parental components of individual phenotypic variance (as in (2) above).

**Association Analysis**

Association analyses that incorporate parental effects must include parental information. For parental genotype effects and imprinting effects, family-based association methods are needed. The most commonly used method of family-based association, the TDT, has been extended to allow for parent-of-origin effects [19, 22–24]. As mentioned above, failure to account for imprinting or parental effects can bias TDT results because decreased expression of phenotypes among children of the imprinting gender may dilute transmission effects. Simple comparisons of transmission estimates for father–child pairs vs. mother–child pairs can also lead to erroneous conclusions about imprinting and genetic effects, when nontransmitted parental effects influence the phenotype [22]. For these reasons, recent methods have proposed the use of conditional logistic [22] or log-linear models [23], expressed in terms of direct genetic effects, imprinting effects, and additional (nontransmitted) parental effects. For both approaches, trios can be characterized by the joint mother, father, and child genotypes, resulting
in 15 distinct trio-types whose expected frequencies can be calculated theoretically according to the (child) genotype [genetic association], imprinting, and parental genotype (or environment) effect sizes. **Logistic regression** conditional on trio-type or log-linear regression of expected trio-type cell counts can be used to estimate these effect parameters and test for association using likelihood ratio methods. Such methods can be carried out in standard statistical software packages for conditional logistic regression and Poisson regression.

**Conclusion**

While the theory is well developed for parental effects, little empirical work in human genetics has focused on these issues. The identification of imprinted genes, methodologic development to assess and incorporate parental effects into genetic analysis, and further understanding of the imprinting mechanism all represent important challenges for genetic epidemiology.

**References**


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