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Editorial

Gene-Gene Interaction in Maternal and Perinatal Research

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Recent genomic research increases our understanding of the causes of complex diseases and strengthens the evidence that many complex diseases, even those with late age of onset, are caused in part by genetically induced, adverse prenatal environments. This special issue of the Journal of Biomedicine and Biotechnology specifically examines the evidence that gene-gene interactions during early development influence human traits and diseases.

Mothers largely determine the fetal environment; therefore the maternal genotypes are expected to influence fetal development. Two types of gene-gene interactions are possible during pregnancy, intragenerational interaction, and intergenerational interaction. Intragenerational effects concern gene-gene interactions within an individual's genome to affect their own disease outcome. Intergenerational effects lead to conflicts between a mother and her fetus in some cases and, in other cases, they lead to beneficial environments that protect against disease. Intergenerational interactions can occur between genes in a child's genome affecting the mother's phenotype or between genes in a mother's genome affecting the child's phenotype. There can also be interactions between the maternal genes and fetal genes, such as maternal-fetal genotype incompatibility, that cause changes in the mother's or the child's phenotype.

Maternal-fetal genotype (MFG) incompatibility is not just a theoretical possibility. The most well-known example of this form of gene-gene interaction is Rhesus factor D-induced hemolytic disease of the newborn [1], in which a Rhesus-negative mother develops antibodies to her Rhesus-positive fetus, leading to destruction of fetal red blood cells. Gene-gene interactions have also been studied as causes of pregnancy complications such as gestational hypertension and diabetes [2], but they have rarely been studied as risk factors beyond pregnancy complications. MFG incompatibility, in particular, has been reported to play an important role in the development of a number of disorders, including preeclampsia, preterm delivery, small-for-gestational-age neonates, and schizophrenia. Although genetic conflict has been postulated as playing a role in these disorders, rigorous modeling and quantitative analysis of these gene-gene interactions have only begun recently, as a result of biotechnological developments that have made it possible to conduct these investigations.

Researchers conducting genome-wide association studies (GWAS) occasionally test for intragenerational gene-gene interactions, but they seldom test for maternal genetic influences on the phenotypes—and almost never test for intergenerational gene-gene interactions. There are several reasons for these omissions. First, testing for maternal genetic influences requires that both mothers and children be genotyped. Very often, the father's genotype is also required by numerous analytical methods. This requirement increases the number of individuals who must be genotyped and also increases the number of tests conducted, which makes the study expensive. Second, it may even be impossible to obtain maternal genotypes if the disease has an adult onset.

It is our contention that limiting gene discovery to single-gene analysis using unrelated individuals is a mistake. With much of the genetic architecture of complex traits left unexplained, more investment into intergenerational gene-gene interactions is warranted. The evidence for multiple genetic influences during early development takes on a variety of forms and the eight articles chosen for the special issue reflect this variety.

Lupo et al. [3] examine gene-gene interactions in folate metabolic genes as risk factors for relatively common birth defects such as conotruncal heart defects (CTHDs), following up on their earlier work showing that some polymorphisms in folate metabolic genes are associated with CTHDs when these polymorphisms are analyzed separately [4]. In the current paper, they not only test for child gene-gene interactions, but also for maternal gene-gene interactions. Interestingly, their most significant results are observed for a maternal gene-gene interaction between CBS844ins68 and rs1801133. Neither locus is significantly associated in the marginal analysis of maternal effects. Given that they also observe child allelic effects, it would be interesting to know whether there are any maternal-fetal genotype incompatibilities.

It is natural to wonder just how widespread intergenerational gene-gene interactions are. Is it reasonable to suggest that maternally expressed genes or interactions between mother's and child's genes represent a substantial portion of the attributable risk of complex disease? Priest and Wade [5] use evolutionary population genetic theory to tackle this question. Their simulations of two unlinked loci, one expressed maternally and the other expressed in the child, demonstrate that maternally expressed alleles that increase disease susceptibility in the child can have higher frequencies and persist longer than child expressed alleles that increase disease susceptibility. Gene-gene interactions between maternal and fetal genes can lead to even greater frequency and persistence of these fitness-reducing alleles. They provide some intuition for these results by pointing out that deleterious genes that are expressed maternally hide out unexpressed in fathers, and are thus partially shielded from purifying selection. Their results also show that maternally expressed genes and maternal-fetal gene interactions will be difficult to detect in typical linkage disequilibrium mapping study designs like GWAS.

Many of the analytical methods designed to test for maternal allelic effects or MFG incompatibility rely on an assumption of mating symmetry in the population. Mating asymmetry and maternal allelic effects can be confounded in these methods [6], so it is important to have an analysis method that is robust to mating symmetry violation when mating asymmetry is suspected in the population. By comparing methods through simulation, Healy et al. [7] find that the case-triad/case-control hybrid test performs well under mating asymmetry. They then apply the test to examine the association of SNPs in the promoter of cell-cycle genes with childhood pre-B acute lymphoblastic leukemia to find both maternal allelic and child allelic effects.

Healy et al. [7] do not directly test for maternal-fetal genotype incompatibility. This test requires modifying the underlying model of the case-triad/case-control hybrid test to allow for maternal-fetal genotype interaction. In their analysis of the association of TNF-α G308A polymorphisms with preterm delivery (PTD), Liang et al. [8] make the necessary modifications to a hybrid case-parent trio and control-parent model to allow for MFG incompatibility. Rather than limiting the analysis to a specific form of MFG incompatibility such as HLA matching [6] or noninherited maternal antibody effects [9], they model joint maternal and child allelic effects, which requires 6 parameters for a diallelic locus. The maternal and fetal main effect model requires only 4 parameters, so the null hypothesis of no MFG incompatibility can be tested with a likelihood ratio test that compares these two models without specifying the MFG mechanism. The disadvantage of their approach is a loss of power when the MFG incompatibility mechanism is known and requires fewer parameters (such as the case for RHD incompatibility).

The effects of maternal-fetal genotype incompatibility are not limited to neonatal, or even childhood, disorders. In her review article, Palmer [10] summarizes the evidence that MFG incompatibilities are risk factors for schizophrenia. She also provides compelling biological arguments to support the viewpoint that RHD and HLA-B incompatibilities are consistent with the neurodevelopmental hypothesis of schizophrenia. Interestingly, the two MFG incompatibilities, which have different mechanisms of action but ultimately may be risk factors because they both can lead to hypoxia, show different sex effects. RHD incompatibility has a stronger effect in males than females and HLA-B incompatibility has a stronger effect in females than males. Palmer [10] points out that olfactory deficits in the parents of schizophrenics may play a role in HLA-B incompatibility, and this could certainly be true. Olfactory deficits produce mating-type frequencies for the parents of cases that are different from the mating-type frequencies for the parents of controls. The MFG test is independent of the mating-type frequencies of controls [6] and so cannot be used to test this hypothesis. The significant results in [11], however, cannot be explained by this gene-environment covariation alone [12] because they are the consequence of mating asymmetry to a lesser extent and of transmission distortion to a greater extent [6, 9, 11]. Olfactory deficits in the parents should not lead to transmission distortion.

Developmental effects on adult onset, complex disease are often far from simple in their mechanism. Perinatal environmental effects can be highly variable depending on the child's genetic makeup. The correlation of birth weight to adult blood pressure has been much studied, but the reasons for the association are unclear. Using data from the Bogalusa Heart Study, a longitudinal prospective study documenting cardiovascular risk factors, Chen et al. [13] determine that the degree of association between birth weight and age-related trends in diastolic and systolic blood pressure is dependent on polymorphisms in beta-adrenergic receptor genes by finding significant three-way interactions of β_2-AR ARG16GLY, β_3-AR TRP64ARG, and birth weight. Interestingly, the main effects of these genes and their two-way interactions are not significant.

The effects of maternal fetal genotype incompatibilities must be modulated by prenatal environment. As an example, maternal infections during pregnancy have been implicated as risk factors for disorders in children as diverse as congenital abnormalities [14], hearing loss [15], and schizophrenia [16, 17]. Indeed there may be gene-by-maternal urinary tract infection effects in schizophrenia [18]. Thus it is

important to understand the genetic risk factors underlying recurrent urinary tract infection (UTI). Zaffanello et al. [19] summarize the research into the genetic determinants of UTI and find that, of the candidate genes studied, only HSPA1B, CXCR1, CXCR2, TLR2, TLR4, and TGF-β1 are significantly associated with recurrent UTI. Of these genes, CXCR1 is the most extensively studied and supported. CXCR1 encodes the receptor for the IL-8 chemokine [20], and chemokines are an important part of the inflammatory process. The research into the genetic basis of recurrent UTIs has only just begun, so more work is needed to determine whether any of these 6 genes interact intra- or inter-generationally.

Nowhere is the complex interplay of maternal and fetal genetics more intriguing than for phenotypes originating with the placenta. Hoegh et al. [21] profile gene expression of placenta tissue from women affected with preeclampsia and compare this gene expression profile to the gene expression profile of placenta tissue from women whose pregnancies were normal. Due to the relatively small sample size, their study may be limited to those genes that show large differences in expression; however, they still find 21 differentially expressed genes that can be classified into a number of roles, including placentation, oxidative stress, inflammatory response, and blood pressure regulation. Their results and earlier work implicating joint maternal and fetal risk factors [22] suggest that a complex network of concerted maternal-fetal gene actions is responsible for preeclampsia.

Research into methods to detect maternal and perinatal gene-gene interactions and to understand the mechanisms of these interactions is just beginning. The articles in this special issue represent a broad range of approaches and each one provides additional evidence that these gene-gene interactions play a significant role in human disease. More research is needed, however, to determine just how great an impact maternal and perinatal gene-gene interactions have in determining human phenotypes. It is hoped that a thorough understanding of maternal and perinatal gene-gene interaction will lead to major breakthroughs in prevention, treatment, and therapeutics.

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