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How do Gene-Environment Interactions Affect the Risks of Birth Defects?

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For decades teratologists have indicated that 65-75% of birth defects have an unknown cause; only a small percentage of causes can be attributed to infections, environmental exposures and a limited number, perhaps up to 25%, can be attributed to known genetic or cytogenetic causes. As a key teratologic concept, it is commonly posited that many, perhaps most, structural birth defects are caused by the combined effects of individual host susceptibilities (genetic factors) that interact with exogenous exposures (environmental factors). Despite this long accepted prevailing principle, research efforts to comprehensively examine the role of genetic variation and the interaction of these genetic variants with environmental exposures and lifestyle factors in the etiology of birth defects have been relatively few. This is an area of study that will likely pay big etiologic dividends in the coming years now that the costs associated with genomic interrogations are ever more economical, facilitating their incorporation into larger scale epidemiologic investigations.

Interactions or effect modifications can arise between a particular gene or set of genes and one factor or potentially multiple factors. The complexity of such interactions can quickly become challenging to tease out analytically and to test experimentally in a rigorous hypothesis driven manner. The underlying biologic relationship that is hypothesized is critical to how one approaches the analysis and the subsequent attendant inference(s). As hypothetical disease examples: does the genetic factor exacerbate the risk factor (or vice versa) to increase overall disease risk? Or, are both the genetic factor and the risk factor necessary to increase the disease risk? Additional questions can also arise as to whose genetic background (mother, father, or infant) and whose exposure (mother or father) is most pertinent.

As with other observational studies of the human condition, identification of risks between a gene and an environmental factor requires a careful assessment of whether the observed relationship has arisen by chance or bias. For example, has some selective force in the study design or methods allowed an excess of cases (or a deficiency of controls) with both the genetic and the environmental factor? In this chapter, we offer a few examples where investigations of the interplay of gene-environment factors have furthered the etiologic understanding of certain birth defect phenotypes.

Genetic variation affects food tolerances and may also influence dietary requirements. A good example is the striking finding about the critical role played by a simple vitamin, folic acid (vitamin B9), in normal embryonic development. Neural tube defects (NTDs) are common congenital malformations, occurring in approximately 1 per 2000 liveborn infants, and are known to have both an environmental and genetic component to their development. Epidemiologic and experimental

studies demonstrate the benefit of folic acid supplementation in preventing NTDs and other congenital anomalies, although just how it provides these benefits remains unknown. There are some NTDs that are not preventable by folic acid supplementation, suggesting that a “genetic subpopulation” may exist that is either less responsive to folic acid supplementation, or has a different underlying cause for these malformations. Researchers have investigated variants in genes associated with folate metabolism and transport as potential risk factors for NTDs. These genes include: folate receptor alpha (FRα); reduced folate carrier (SLC19A1); 5,10-methylenetetrahydrofolate reductase (MTHFR); cystathionine β-synthase (CBS); methionine synthase (MTR); methionine synthase reductase (MTRR); methylenetetrahydrofolate dehydrogenase (MTHFD1); betaine-homocysteine methyltransferase (BHMT); and thymidylate synthase (TYMS). Interactions between maternal folate intake and variations in folate genes (e.g., MTHFR C677T, MTRR A66G, and SLC19A1 A80G) have been suggested by these studies. For example, in a population-based case–control study conducted in California, infants with an 80GG genotype of the SLC19A1 gene born to mothers who did not take vitamin supplementation during early pregnancy had a significantly higher risk of developing spina bifida than did those with the same genotype whose mothers were receiving exogenous folates. In another study from California, investigators observed that the risk of spina bifida was only slightly elevated for infants who possessed the risk SNP, rs11627387, in another folate-related gene, MTHFD1, but for infants who also had low folate intake the risk of spina bifida increased four-fold.

Another example of gene-environment interaction involves anticonvulsant drugs, long recognized as causing birth defects in infants exposed in utero. However, only about 11 to 20% of these infants will exhibit neurodevelopment impairment with or without structural defects, while about 3% to 10% will be born with structural malformations alone. In animal studies, there are clear differences in anticonvulsant-induced NTD susceptibility between inbred mouse strains. It is likely that a comparable situation exists for humans, where an estimated 1 to 2% of infants exposed in utero to valproic acid will be born with spina bifida or other forms of NTDs. Detoxification enzymes involved in metabolizing drugs and other chemicals, as well as toxic compounds produced by the mother or fetus, may play a determining role in whether the exposed embryo expresses an abnormal phenotype. Variant forms of both Phase 1 (cytochrome P450 enzymes) and Phase 2 (e.g., epoxide hydrolase, glutathione transferases, sulfotransferases, and N-acetyl transferases) enzymes are likely to increase risk of congenital malformations, because poor metabolizers may experience a “build-up” of toxic chemicals in susceptible embryonic tissues, or because enhanced, rapid metabolism by Phase 1 enzymes may produce more toxic intermediates than the Phase 2 enzymes can handle. Phase 1-generated intermediates that are chemically reactive and bind to protein or DNA may be teratogenic, mutagenic, or carcinogenic.

Only a few clinical studies have investigated some of these enzyme variants with respect to risks of structural birth defects. Recently, the MTHFR C677T genotype, which reflects impaired one carbon metabolism was studied regarding the frequencies of major malformations following in utero exposure to antiepileptic drugs. Most of the clinically important antiepileptic drugs inhibit folic acid metabolism. Neither the “risk allele” (T) nor the antiepileptic drug-exposure alone had a significant impact on the rate of serious malformations in the offspring, but when these two factors co-existed, the risk increased, suggesting that genetic testing may help predict which infants are at the greatest risk of developing birth defects from exposure to anticonvulsant drugs.

Cigarette smoking and the risk for having an infant with an orofacial cleft is an example of a gene-environment interaction. Maternal smoking during pregnancy is associated with cleft lip and/or palate. Several animal studies have also demonstrated the adverse effects of cigarette smoking on development of cleft lip and/or cleft palate. Gene-environment interactions have been investigated between maternal smoking and more than two dozen genes, including nitric oxide synthase 3 (NOS3), aryl hydrocarbon receptor (AhR) pathway genes, several detoxification genes (CYP1A1, EPHX1), the glutathione transferase gene family (GSTs), arylamine N-acetyltransferase gene family

(NATs), hypoxia-induced factor-1 (HIF1), folate pathway genes (e.g. MTHFR), muscle segment homeobox1 (MSX1), and other developmental genes. One example in this area is transforming growth factor α (TGF). A study involving both nonsmoking and smoking pregnant women found that heavy smokers who carried the rare 'risk' variant of this gene were twice as likely to have a baby affected with cleft lip or palate than nonsmoking women with the more common gene variant. Infants who possessed the rare gene variant were six times as likely to have cleft lip or palate when the mother was a heavy smoker. Another more elaborate example, one reflecting an investigation of environment x environment x gene interaction, showed that women who smoked and did not use vitamins with folic acid and whose infants had selected variants of NOS3 were at approximately 5-fold increased risk to have cleft lip and palate.

Although medicine is still far from individualized, preventive measures for birth defects, understanding how specific environmental factors interact with an individual's genetics, or "genotype," may yield critical clues that will ultimately lead to new approaches to modify the risks of preventable birth defects.

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