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Genetic Susceptibility to Birth Defects in Humans: From Gene Discovery to Public Health Action

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ADVANCES IN HUMAN GENETIC RESEARCH

With the relentless progress of the Human Genome Project, by the year 2001, most--if not all--of the estimated 100,000 human genes will have been found (Collins, '98). Close to 10,000 genes have already been cataloged (Online Mendelian Inheritance in Man, '98), and tests for more than 700 genes are already available in medical practice (Pagon, '98). The genes identified thus far range from those associated with rare metabolic disorders to those associated with common diseases including cancer and adult-onset conditions. Genetic variants confer increased susceptibility to a variety of environmental factors (including chemical, infectious, physical, social, psychological, behavioral, and nutritional factors), thus increasing the risk of carriers for many diseases including birth defects.

Although birth defects remain the leading cause of infant mortality in the United States (CDC, '98), the causes of most birth defects remain elusive. Nevertheless, an increasing number of clinical and epidemiologic studies are beginning to identify risk factors for birth defects (Khoury, '95). Over the last two decades, numerous investigators have identified malformations associated with rare single-gene disorders. Table 1 shows the results of a quick search of the Online Mendelian Inheritance in Man Catalog on the Internet. As can be seen, dozens of genes (mostly in a few families) have been reported to be associated with a variety birth defects leading to malformation syndromes. Increasingly, more common gene variants have been associated with the risk for common birth defects. For example, the methylene tetrahydrofolate reductase (MTHFR) polymorphism has been associated with the risk for neural tube defects (Posey, '96). The interaction between gene variants at multiple loci with environmental exposures is likely to explain most common defects such as neural tube defects, oral clefts, and congenital cardiovascular malformations.

As a result of genetic research, information on differential genetic susceptibility to birth defects will be accumulating. Ideally, information on genetic susceptibility to birth defects will be used to target beneficial interventions that reduce the risk for birth defects (e.g., nutritional interventions such as folic acid), or to avoid certain pregnancy exposures for individuals at greatest risk (e.g., avoiding certain anti-epileptic drugs on the basis of a person's genetic metabolic profile). However, complex ethical, legal, and social issues are already being raised about the pitfalls of genetic testing in general (Lewontin, '96). The effective use of genetic knowledge and technology is becoming a crucial challenge to the public health community. The manner with which genetic information can be used to promote health and prevent disease and disability, especially birth defects, has scarcely been explored. Informa-

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tion is lacking about the population distribution of genotypes associated with birth defects, the benefits and risks of genetic testing, and the efficacy of interventions. The complex and controversial issues that have emerged--about quality assurance for laboratory testing, rapid commercialization of genetic tests, lack of availability and access to effective and acceptable interventions, and potential discrimination against and stigmatization of individuals and groups--call for public health leadership (CDC, '97).

A FRAMEWORK FOR THE IMPACT OF GENE DISCOVERIES ON PUBLIC HEALTH ACTION

In 1997, the Centers for Disease Control and Prevention created the Office of Genetics and Disease Prevention to highlight the emerging role of genetics in the practice of public health in the United States, and to provide internal coordination and promote external partnerships in activities related to genetics and disease prevention and health promotion. This action was recommended in an agency-wide strategic plan that outlines a conceptual framework for a public health program in genetics (CDC, '97). The strategic plan is based on the assumption that, broadly defined, virtually all human diseases of important public health impact are the result of the interaction between human genetic variation and the environment. It is also based on the assumption that the use of genetic information in public health is appropriate in diagnosing, treating, and preventing disease, disability, and death among people who inherit specific genotypes. Prevention includes the use of medical, behavioral, and environmental interventions to reduce the risk for disease among people susceptible because of their genetic makeup. The plan supports the responsible use of genetic tests and services, including adequate family history assessment and genetic counseling, for promoting health and preventing disease in different communities. The plan assumes that much of the delivery of genetic tests and services will be done within the context of the evolving health care system, including by managed care organizations, rather than by public health agencies. Public health agencies, however, will have an increasing role in assessing the health needs of populations, ensuring the quality of genetic tests and services, and evaluating the impact of interventions.

The framework for the role of genetics in public health is based on an extension of the Institute of Medicine model of the future of public health (IOM, '88). This extended framework identifies four essential components of public health genetics programs:

1) Public health assessment using surveillance and population-based epidemiologic studies to assess how risk for disease and disability in different populations is influenced by the interaction of human genetic variation with modifiable risk factors.
2) Evaluation of genetic testing policies and of the quality of genetic testing to ensure the appropriateness and quality of population-based genetic testing.
3) Development, implementation, and evaluation of public health programs that ensure that genetic tests and services are integrated into population-based interventions that promote health and prevent disease and disability.
4) Communication and information dissemination to provide timely and accurate information to both the general public and professional audiences on the role of genetics in the promotion of health and the prevention of disease and disability.

In order for these activities to be done, three cross-cutting critical issues that can affect each program component need to be addressed: partnerships and coordination; ethical, legal, and social issues (e.g., using stored samples such as newborn blood spots for conducting large-scale epidemiologic studies of

birth defects etiology); and training of the public health workforce and education of the general public.

In the field of birth defects, the existing model of public health assessment involves conducting surveillance for birth defects and population-based epidemiologic studies to find the causes of those birth defects. This model can easily be extended to begin looking simultaneously at genetic risk factors along with environmental factors to explain the complex etiology of the most common malformations. In fact, this work is currently been done collaboratively by several birth defects surveillance programs and members of the National Birth Defects Prevention Network (NBDPN, '97), as well as by birth defects registries and academic institutions from around the world. In particular, case-control studies that use data from population-based birth defects registries will prove to be exceptionally useful for gathering information about the effect of gene-environment interactions on the risk for birth defects, especially for rare defects (Khoury, '94). Alternatively, large-scale collaborative prospective studies can be mounted to answer numerous questions regarding the etiology of birth defects and other reproductive outcomes with a focus on gene-environment interaction.

HUMAN GENONE EPIDEMIOLOGY NETWORK (HuGE Net)

Because of the complexities of information that will emerge from gene discoveries and the need for a systematic epidemiologic approach to the evaluation of new genes and their variants, the Centers for Disease Control and Prevention (CDC), with many partners, recently launched a new collaborative initiative, the Human Genome Epidemiology Network (HuGE Net: Khoury and Dorman, '98). HuGE Net represents the collaboration of individuals and organizations from diverse backgrounds who are committed to the development and dissemination of population-based human genome epidemiologic information. The goals of HuGE Net are to 1) establish an information-exchange network that promotes global collaboration in the development and dissemination of peer-reviewed epidemiologic information on human genes; 2) develop an updated and accessible knowledge base on the World Wide Web; and 3) promote the use of this knowledge base by health care providers, researchers, industry, government, and the public for making decisions involving the use of genetic tests and services for disease prevention and health promotion.

The term human genome epidemiology (HuGE) denotes an evolving field of inquiry that uses systematic applications of epidemiologic methods and approaches in population-based studies of the impact of human genetic variation on health and disease. The spectrum of topics addressed in human genome epidemiology range from basic to applied population-based research on discovered human genes. Human genone epidemiology can be used to:

1) Assess the prevalence of gene variants in different populations.
2) Assess the magnitude of disease risk associated with gene variants in different populations (relative and absolute risks).
3) Assess the contribution of gene variants to the occurrence of the disease in different populations (attributable risks).
4) Assess the magnitude of disease risk associated with gene-gene and gene-environment interaction in different populations.
5) Assess the validity of genetic tests in predicting disease risk in different populations (positive and negative predictive values).
6) Evaluate how frequently genetic tests and services are used in different populations and the determinants of their use.
7) Evaluate the impact of genetic tests and

services on morbidity, disability, mortality and cost in different populations.

HuGE Net will provide a coordinated global means of disseminating the epidemiologic information resulting from the Human Genome Project. It will evolve as a collaboration among epidemiologists, geneticists, basic scientists, and medical and public health practitioners from governmental, professional, academic, industrial and consumer organizations worldwide.

In the field of birth defects, there is a growing need to conduct epidemiologic studies of genetic susceptibility to birth defects as well as to disseminate the results of systematic epidemiologic reviews of the association between specific gene variants and specific defects. Such a public health assessment can be viewed as the first crucial step in translating discoveries of genes associated with birth defects into policies and interventions that reduce the risk for birth defects among susceptible populations. For further information on joining this global collaborative effort, please consult the HuGE Net web site at www.cdc.gov/genetics/huge.htm.

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