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The Integration of Genomics into Obstetrics and Gynecology: A HuGE challenge

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The completion of the Human Genome Project continues to fuel expectations for near term applications of human genome discoveries in personalized health care and disease prevention in all fields of medicine, including obstetrics and gynecology (1–4). Many conditions are associated with Mendelian (single gene) transmission, (5) such as hereditary breast and ovarian cancers (6), but the vast majority of disorders seen by obstetricians and gynecologists are etiologically and pathogenetically complex, involving multiple genetic and environmental factors. There are now numerous reports of associations of genetic variants with these common complex obstetric and gynecologic disorders, such as preterm delivery (7,8) and the factor V Leiden mutations with a range of maternal health and pregnancy outcomes (9). In addition, we are witnessing the emergence of molecular markers in diagnosis and prognosis of gynecologic cancers, such as early detection of cervical cancer (10). News stories of scientific discoveries of human genetic variants that may affect the risks for one or more of the major common diseases are increasing (11). Yet, the immediate clinical and public health significance of most of these discoveries remains elusive. In spite of the scientific excitement and the predictions for personalized prevention and drug treatment, the promise for health promotion and disease prevention has yet to be fulfilled.

To interpret and apply the relationship between DNA variants in health and disease in obstetrics and gynecology, population-based clinical and epidemiologic studies are urgently needed to assess the impact of the thousands of genetic variants (and their interactions with modifiable risk factors) on the burden of these diseases (incidence, prevalence, as well as morbidity, disability and mortality). A sound epidemiologic approach to genomics is now needed for common complex disorders attributed to gene-environment interactions as a scientific basis for using genetic information in health care and disease prevention (12).

Although gene discoveries for various diseases continues on a fast and furious pace using mostly family-based studies (13), there is also an increasing number of epidemiologic association studies, especially case-control designs using genome-wide association

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approaches that assess simultaneously hundreds of thousands of genetic variants (14). Many of these studies go beyond gene discovery to evaluate the relationship between specific genetic variants at one or more loci and the risk of various diseases. Since 2001, the CDC has maintained and continuously updated an online searchable published literature database (15). The number of relevant epidemiologic articles on gene-disease association published each year is rapidly growing (16). As of October 1, 2006, more than 23,400 articles were indexed in the database. Most of these articles describe gene-disease or gene-environment associations (86%); fewer studies evaluated gene-gene or gene-environment interactions (17%), prevalence of DNA variants (10%), or genetic tests (3%). However, the clinical implications of findings from many such studies remain unclear. Often, the potential clinical importance of a reported association is impossible to evaluate because many such associations are not replicated in subsequent studies (17) and/or contain methodological biases (18).

Because of the complexities emerging 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, launched in 1998 an open international collaborative initiative, the Human Genome Epidemiology Network (19). HuGENet 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 HuGENet 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 resource 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 (20).

The term “human genome epidemiology” (HuGE) denotes an evolving field of inquiry that uses systematic applications of epidemiologic methods and approaches in studies of the impact of human genetic variation on health and disease in populations (12). The spectrum of topics addressed in human genome epidemiology range from basic to applied population-based research on discovered human genes. Human genome epidemiology can be used to assess: 1) the prevalence of gene variants in different populations; 2) the magnitude of disease risk associated with gene variants; 3) the magnitude of disease risk associated with gene-gene and gene-environment interactions; 4) the validity and impact of genetic tests for screening and prevention.

HuGE collaborations in obstetrics and gynecology

We would like to point out to the readership several avenues of involvement with human genome epidemiology, including systematic reviews and meta analyses, publication of well-designed epidemiologic studies with “null” results, and involvement in the network of investigator networks.

Conducting human genome epidemiology reviews (HuGE reviews)

Several journals have partnered with the Human Genome Epidemiology Network to publish systematic, peer-reviewed synopses of epidemiologic aspects of human genetic variants in relation to the risk of various diseases (HuGE reviews, 20–21). These reviews are essential to accelerate the global knowledge base of genes and health outcomes and uncover areas for further research. As of October 1, 2006, 48 HuGE reviews have been published in various journals and posted on the HuGE Net website. In addition, more than 480 additional systematic reviews with quantitative synthesis (meta-analysis or pooled analysis) have been done outside of the HuGE Net movement (see a listing of these on the HuGE Net website (20)).

We would like to invite investigators in obstetrics and gynecology to contribute HuGE reviews in their field. Guidelines are posted on the HuGE Net website (see reference 20 for the URL link). These reviews will be important in the synthesis and dissemination of the rapidly evolving understanding on genes and human health.

Encouraging publication of methodologically sound gene-disease association “null” results

The communication of research findings in human genome epidemiology is important. Publication bias is a well-known phenomenon that affects clinical and basic sciences fields (22). Many “null” studies may not be published, and there is a 2-fold likelihood that statistically nonsignificant studies will not be published. As the area of genomics grows, the risk of publication bias grows as well. We need to work together with researchers to avoid the pitfalls of publication bias and encourage research communication of all well-conducted epidemiologic studies of human genes and health outcomes regardless of the nature of the findings. Some journals, notably *Cancer Epidemiology, Biomarkers and Prevention*, have begun accepting papers under the category of “Null Results in Brief” (22).

For this journal, we encourage researchers and prospective authors to submit null results based on well-designed and analyzed epidemiologic studies, including important *a priori* hypotheses tested with sufficient statistical power. These manuscripts clearly should add to the current knowledge of genetic factors in obstetrics and gynecology and be useful to investigators making decisions regarding replication and/or inclusion in HuGE reviews. A greater priority for acceptance will be given to studies with prior publication on the topic with a positive association and for which there is a biological rationale for such an association. More generally, the ability to synthesize knowledge on gene-disease associations will benefit from open and inclusive reporting of all findings, positive, negative or null.

Developing collaborative investigator networks

In order to accelerate the knowledge base on human genes and health outcomes, HuGENet launched in 2005 networks of investigators collecting data for human genome epidemiology research in different fields (23,24). This initiative currently is comprised of 23 networks of

investigators addressing specific diseases or research topics, representing several hundreds of investigators. The collaboration brings together several teams from obstetrics and gynecology, including preterm delivery, assisted reproduction and craniofacial anomalies (23). We invite researchers in obstetrics and gynecology to join the registries and existing networks and to create additional networks as needed. The network of networks aims to register these teams and investigators; be a resource for information about or connections to the many networks, promote sound design and standardization of analytical practices, generate systematic reviews, and facilitate confirmation of findings. For further information on the network of networks, please consult the HuGENet website (20).

Concluding remarks

In this editorial, we have challenged researchers in obstetrics and gynecology to help improve the understanding of the thousands of genetic variants and their relevance to the health and disease of our patients. The *Journal* is committed to accelerate the process of knowledge base development in this area. We encourage researchers and potential authors to select one or more avenues of collaboration and publication in the field of human genome epidemiology, such as systematic reviews, publication of “null” results, and participation in collaborative networks. We believe these endeavors are important in the translation of gene discoveries into opportunities for improving health outcomes and preventing disease in our population.

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