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Genetic Association Studies in Nursing Practice and Scholarship

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Abstract

Purpose: To explore the role of genetic association studies in risk assessment for common complex diseases.

Organizing Framework: An introduction to the types of genetic association studies is followed by a discussion of their potential use in risk assessment for age-related macular degeneration and type 2 diabetes mellitus. The benefits and limitations of this burgeoning technology are explored and related to nursing practice and scholarship.

Conclusions: Nurses in practice must be prepared to assist clients with decisions about seeking and interpreting results from genetic association studies and nurse researchers must apply current guidelines for conducting robust studies and applying the results of such studies in clinical practice.

Clinical Relevance: Data collected from genetic association studies will increasingly be used to identify novel prevention and treatment strategies for many complex diseases. An understanding of the principles that underlie this new science is essential for nurses in all areas of clinical practice as they design, test, and implement appropriate intervention and prevention strategies based on genetic association studies.

Keywords

genetic association studies; genomics; nursing; genetic markers; risk assessment

The genomic era in health care arrived in 2001 with the completion and publication of the Human Genome Project. This catalog of the 3 billion nucleotide bases that comprise human DNA and their organization into genes has been called both the book of life and a map to nowhere, because the power of the data is a challenge to harness (Read, 2001). Researchers and clinicians are struggling to understand the mechanisms by which sequences of nucleotides become activated to code for the proteins that regulate growth, direct metabolic processes, and cause or contribute to the development of disease.

The genetic basis of most diseases and the external factors that influence the expression of disease-related genes are complex and poorly understood. If the relationships between DNA variants and specific disease phenotypes were known, preventive and treatment strategies for complex, multifactorial disorders could be developed. Epidemiologic methods allow for analysis of these relationships through genetic association studies (GAS). The purposes of this paper are to (a) define the types of GAS, (b) use the examples of age-related macular degeneration and type 2 diabetes mellitus to show the role of GAS in understanding the complex

nature of common illnesses, (c) discuss the limitations of GAS, and (d) illustrate potential uses of GAS in general and advanced practice nursing and in clinical research.

Background

The fact that diseases run in families was commonly accepted long before science could explain the phenomenon. For example, the Mendelian patterns of inheritance that characterize single gene disorders were understood for decades before the structure of DNA and its mechanism of replication were described. Similarly, the heritability of complex disorders such as schizophrenia and diabetes mellitus can be calculated through studies of twins, but the actual genes responsible for their transmission have yet to be fully elucidated. Even when a specific mutation in a single gene is known to cause a disease, as in cystic fibrosis and sickle cell anemia, genetic information is not easily translated into therapies or cures, and numerous external factors mitigate disease severity.

Despite the challenges, the ultimate goal of genomic medicine is personalized health care that integrates information about one's genotype, phenotype, and environmental factors in order to formulate prevention and treatment options for complex disorders (Conley & Tinkle, 2007). The information gleaned from GAS shows promise in moving toward that goal.

The public availability of the human genome sequence and data from the International HapMap Project (www.hapmap.org) have already had a significant effect on conducting research, and this growth will continue with the ongoing Cancer Genome Atlas project (<http://cancergenome.nih.gov>) and the National Institutes of Health Gene Environment Initiative (<http://www.nih.gov/news/pr/sep2007/nhgri-04.htm>).

Most often, the DNA variant evaluated in GAS is a single nucleotide polymorphism (SNP), which is defined as a single base change occurring in the population at a frequency greater than or equal to 1% (Dupuis & O'Donnell, 2007). The HapMap project (Altshuler et al., 2005) cataloged SNPs that are associated with specific DNA variants in African, Chinese, European, and Japanese populations. This high-resolution map of common genetic variations can now be compared to genome sequences from people with disease-related clinical characteristics. Using sophisticated statistical techniques, GAS indicate genes that are correlated with those clinical characteristics. Despite considerable debate about the validity of the method, more than 25,000 GAS were collected in the Human Genome Epidemiology Network (HuGENet) between 2001 and 2006 (Khoury, Little, Higgins, Ioannidis, & Gwinn, 2007). Results from well-designed GAS that are validated and applicable to the population of interest might provide clinicians with useful information, including an improved understanding of the underlying pathophysiology of a complex disease or of a patient's relative genetic risk (in combination with other environmental factors) for developing a particular condition or illness. Clearly, nurses in practice and research need to become familiar with the terms and concepts related to GAS and understand appropriate applications of these important new studies.

Genetic Association Studies: The Basics

GAS have case-control designs to determine the association between one or multiple DNA variants and the phenotype of interest (Dupuis & O'Donnell, 2007). In these statistical designs, the DNA of "cases" (people with a particular phenotype, such as a disease) is compared with the DNA of "controls" (people without the disease) to determine whether those with the phenotype are more likely to be carriers of a DNA variant(s). The two main approaches to the study of genetic association are "direct" and "indirect."

In direct association studies, also known as candidate gene studies, investigators assess the association of SNPs of a particular gene with a well-defined disease phenotype. The purpose

of these studies is to test a proposed hypothesis that a gene is associated with a particular phenotype. Identification of a significant association supports future genetic studies to determine disease pathophysiology, appropriate drug treatments, and eventually, disease prevention strategies. Well defined, replicable studies are important for validating these associations and are necessary for applicability to clinical practice. Three methods are used to ensure precise study design: hypothesis driven (*a priori*) gene selection, examination of well-defined intermediate phenotypes, and the tagging of SNPs.

The first method, *a priori* gene selection, is critical to the success of the candidate gene approach. Before the start of the investigation, scientists select genes based on a hypothesis indicated by data from previous research. Studies in biology, pharmacology, animal models, and previous gene association studies provide support for a hypothesis that one or more genes are involved with a particular disease (Hattersley & McCarthy, 2005). *A priori* gene selection saves valuable time and money because it allows choosing a few genes to study from a pool of more than 20,000. This targeted approach increases the likelihood that the chosen gene will truly be associated with the disease of interest.

To further increase the likelihood of finding gene associations with a particular disease, intermediate phenotypes are examined. Intermediate phenotypes are well-defined subsets of a complex, heterogeneous phenotype. For example, essential hypertension is a complex condition with multiple etiologies. Identification of a gene that is associated with such a broad phenotype is impractical (if not impossible) because of the complicated interplay of physiologic and environmental contributory factors and the thousands of potentially responsible genes. However, the study of people with well-defined subsets of essential hypertension that represent separate physiologic aspects of the broader phenotype simplifies the physiologic mechanism of the disease of interest and increases the likelihood of finding a genuine gene association (Williams, 1994; Williams & Fisher, 1997).

Currently, intermediate phenotypes are characterized via physiologic phenotype studies. In these studies, participants with a broad phenotype (e.g., essential hypertension or diabetes mellitus) are subjected to a variety of stimuli (e.g., insulin or angiotensin II infusions) and the response to stimuli defines their intermediate phenotype. For example, participants with nonmodulating hypertension (an intermediate phenotype of essential hypertension) are identified by their reduced renal blood flow and blunted aldosterone response after an angiotensin II infusion (Williams et al., 1992). This response differs from those of other types of hypertension, and helps characterize the intermediate phenotype of nonmodulation from other intermediate phenotypes of hypertension. These phenotype studies can be complex, but are useful in finding replicable gene associations (Williams, 1994). Future work to define additional intermediate phenotypes in complex heterogeneous disorders may contribute to more successful candidate gene studies that foster individualized health care through improved prevention and treatment strategies.

Finally, studies that involve tagging SNPs have additional rigor and are required for well designed candidate gene studies. Tagging SNPs are specific nucleotides that have been mapped across populations and are inherited together within a chromosome segment in blocks termed haplotypes (Schaid, 2004). Tagging SNPs identify genes that are linked to or inherited with the candidate genes (also known as genes that are in linkage disequilibrium with the candidate genes) and may contribute to the underlying disease pathophysiology. One caveat of gene association studies is that it is difficult to identify the gene causing an association when genes are inherited together in linkage disequilibrium. Tagging SNPs helps differentiate between genes inherited in an entire haplotype, enabling an analysis of multiple genes with one study. Together, these three methods allow well defined studies that increase the likelihood of

identifying an association between gene and disease that will result in the development of therapies.

In contrast to direct association studies, which begin with a specific genetic location and association with clearly defined phenotypes, in genome-wide association studies (GWAS) or “indirect” association studies investigators scan the entire genome to generate hypotheses about gene regions that are associated with various phenotypes. GWAS represent a major shift in how genomic research is conceptualized and conducted. Recent advances in technology, including rapid advances in high-throughput techniques, cost-effective methods for genotyping, increased availability of large collections of DNA coupled with clinical data, and the high-resolution SNP database from the HapMap project fostered the success of GWAS (Christensen & Murray, 2007; Dupuis & O'Donnell, 2007). The National Institutes of Health currently funds many GWAS, which they define as “Any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition” (U.S. Department of Health and Human Services, 2007, p. 1).

A recent example of GWAS uses data from the Framingham Heart Study (Cupples et al., 2007). Investigators compared DNA samples from study participants to 100,000 common SNPs on a commercially available gene chip to generate hypotheses about associations between genetic loci and various disease-related characteristics of the participants. Results of the first 17 GWAS from the Framingham Heart Study data were published in the September 19, 2007 edition of *BioMed Central Medical Genetics* (<http://www.biomedcentral.com/bmcmedgenet/8?issue=S1>), available as open access with unrestricted distribution. Among the phenotypes studied were cardiovascular risk factors (such as diabetes mellitus, blood pressure, lipid levels, and inflammatory biomarkers), breast and prostate cancer, heart rate variability, hemostatic factors, longevity, bone mass, and body mass index. The authors are candid about the limitations of these studies, but are optimistic that they lay the groundwork for replication and evaluation that will deepen our understanding of the role of genetic variation in common diseases.

Examples of GAS That Show Genes Implicated in Common Diseases

Although discussions about genetic disease conjure images of single gene disorders, these actually account for only a small proportion of genetic diseases. The major causes of mortality in the United States, cardiovascular disease, cancer, and cerebrovascular disease (Minino, Heron, Murphy, & Kochanek, 2007), are heterogeneous and caused by a combination of environmental and genomic factors.

Despite the difficulty of identifying the genetic basis for complex disorders, the advent of GAS enabled a lot of progress in this area in a relatively short amount of time. This is evident when reviewing research before GAS. Earlier gene studies showed strong associations between a common variant in the major histocompatibility complex on chromosome 6 and autoimmune disease. Those painstaking studies used extended family data to search for areas in the genome shared by affected family members. Recent studies have uncovered genetic variants common in complex illnesses in a few years rather than over decades of study.

GAS of type 2 diabetes and diabetes mellitus indicated significant results without the labor intensive techniques and large data sets required of family studies. These results were analyzed relatively quickly and provide extremely useful clinical information, highlighting the importance of GAS.

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in adults over the age of 50. Known risk factors include age, hypertension, obesity, smoking, and

lack of exercise, but genetic factors influence the development of the disorder. The pathophysiology involves inflammatory changes that lead to the accumulation of small yellow deposits (called drusen) or abnormal growth and breakage of blood vessels in the retinal pigment epithelium. It has been estimated that 7 million people in the United States are at risk for complications of AMD, and 3 million will have those complications by the year 2020 (Friedman et al., 2004).

In the April 15, 2005 issue of *Science*, three separate labs reported the results of their search for genes associated with AMD (Edwards et al.; Haines et al.; Klein et al.). Using GAS of separate cohorts of AMD patients, the three groups found a common variant in the complement factor H gene (*CFH*) on chromosome 1q31 that contributes a substantial fraction of the difference between affected and unaffected people. The complement system is activated by certain triggers (e.g., microorganisms) and participates in the inflammatory process. When a tissue activates the complement cascade, chronic inflammation and tissue destruction occur in the area. The fact that drusen contain complement proteins supports the theory that variants in the *CFH* gene contribute to the pathogenesis of AMD (Daiger, 2005), but the disease is too complex to be explained by any one process.

In 2006, two other labs reported the association of a different gene region with AMD (DeWan et al., 2006; Yang et al., 2006). A SNP in the promoter region of the *HTRA1* gene on chromosome 10q26 (rs11200638) was identified as a major genetic risk factor for a particularly severe type of AMD in both Chinese and Caucasian populations. This SNP is associated with elevated levels of the *HTRA1* mRNA and a serine protease and is purported to be involved with the development of light-detecting cells in the retina (Marx, 2006). The *CFH* and *HTRA1* studies show the contribution GAS can make toward our understanding of the pathophysiology of common diseases; nevertheless, AMD, like other common adult-onset diseases, results from multiple interacting genetic and environmental factors.

Tremendous progress toward identifying genetic risk factors for type 2 diabetes mellitus (T2DM) has also occurred. T2DM has been referred to as a “geneticist's nightmare” for over 30 years (Neel, 1976) because of its complex, multifactorial etiology. Environmental factors such as physical inactivity and poor food selection have certainly contributed to a recent increase in prevalence, but the heritability of T2DM is well-established. People with a first-degree relative with T2DM have a 3.5-fold increased risk compared to the general middle-aged population (Rich, 1990). Frayling (2008) summarized some of the recent GAS that confirmed a strong link among the *CDKAL1*, *TCF7L2*, and *FTO* genes and T2DM.

Investigators in these studies used rigorous methods to avoid bias and error, but the results will only be meaningful after the studies have been replicated. Sladek and colleagues (2007) published a study involving a comparison of hundreds of thousands of SNPs from patients with and without T2DM. They identified four additional genetic loci and confirmed the *TCF7L2* association. Two of the genomic regions identified are involved in the development or function of insulin-secreting beta cells, and one plays a role in the transport of zinc, an important mineral required for the production of insulin. Widespread detection of specific gene markers for T2DM risk assessment or personalized treatment will not be feasible until these studies have been replicated and their results published as meta-analyses, but given the pace of gene-finding expeditions for T2DM in numerous research labs across the world, optimists believe that this might not be far off. Studying gene association in well-defined intermediate phenotypes of diabetes can also increase the likelihood of finding a true gene association with this complex illness. Investigators are currently conducting these studies.

Identifying and Addressing the Limitations of GAS

Despite high expectations that GAS will one day lead to therapies tailored to the genome of the individual, there are numerous challenges to study designs and data interpretation. As Dupuis and O'Donnell (2007) explain, clinicians are increasingly bombarded with GAS reports, and the trend toward GAS necessitates the separation of “fool's gold from gold.” Most studies published in the past 10 years showed gene associations that could not be replicated, owing primarily to the fact that only a few of the common SNPs are likely to be associated with a particular disease (Frayling, 2008).

The rigor of GAS is complicated by phenotypic variation in common diseases, the tendency for disease-related genes to exist in multiple forms (“allelic heterogeneity”) or with a variable number of repeats, and the elusive influence of environmental factors. Other problems can occur when the population being studied is from varying ethnic backgrounds, if errors exist in genotyping, or if the effect of the particular gene is weak (Hattersley & McCarthy, 2005).

Several authors have suggested strategies for decreasing the pitfalls of GAS (Cupples et al., 2007; Hattersley & McCarthy, 2005; Ionannidis et al., 2008). The consensus is that strong statistical evidence from GAS requires thousands of cases and controls and the use of extremely low statistical significance values ($p < 1 \times 10^{-7}$). A conventional $p < 0.05$ for statistical significance would result in many false-positive results.

In addition to strong statistical analyses, there should be evidence of replication, inclusion of data in meta-analyses, and protection from biases in GAS. Prospective studies of the development of disease in people with gene variants would validate findings of GAS, and quantification of the differences in phenotypes among homozygous and heterozygous carriers could also provide useful information (Daiger, 2005).

The rapid proliferation of GAS and the heightened awareness of the inherent challenges prompted establishment of collaborative networks to design and complete large scale, well designed, improved GAS. Two such networks are the Wellcome Trust Case Control Consortium (WTCCC; 2007) and the Genetic Association Information Network (GAIN; 2007). These groups are striving to “develop robust, common approaches to study selection, genotyping, quality control, data analysis and data sharing, as well as cross-study analyses of common phenotypes, common controls, and genotyping artifacts” (GAIN, 2007, p. 1045). Just as researchers have identified the need to participate in collaborative efforts to relate genetic variants to disease phenotypes, clinicians must be aware of what can and cannot be inferred from GAS in order to make meaningful decisions about client care.

Genetic Association Data in Nursing Practice and Scholarship

Recent progress in genomics has permanently redefined our understanding of health and disease. For most health problems, multiple genes interact with environmental and lifestyle factors to cause the symptom complex. As the largest group of healthcare practitioners in the United States, nurses are deeply involved in the care of patients with complex disorders that are often the subject of GAS. Nurses must apply genetic information in the practice setting and participate in scholarly activities that contribute new knowledge to the science of genomics and the discipline of nursing. The recent publication of the Essential Nursing Competencies for Genetics and Genomics (Jenkins & Calzone, 2007) provides guidance for nursing education and practice in the genomic era.

Among essential competencies are the incorporation of genetic and genomic technologies into practice and the interpretation of genetic information for clients. In the future, nurses working with an interdisciplinary team will use information obtained from GAS to provide risk

assessment for adult onset disorders, formulate individualized treatments for complex illnesses, educate patients about the implications of GAS, explain research protocols, and predict individual differences in drug toxicity and response.

The speed with which the lay public becomes aware of scientific advances such as GAS is accelerating. Subsequently, misconceptions and false hope about the implications of GAS will require education and support. For example, consumers are now able to directly obtain genetic testing for the TCF7L2 single nucleotide polymorphism. This test, called DECODET2™, allows estimating a person's susceptibility to type 2 diabetes and can be ordered for \$300 through DNA Direct (www.dnadirect.com).

Little is known about the effect of genetic testing that confers a probability estimate with a weak association for an adult-onset disease with a significant environmental component. What information would a nurse give to a client who inquires about this test? Is there a danger that test results could negatively influence the adoption of proven prevention strategies like healthy diet and exercise?

Despite controversy, companies that market genetic susceptibility tests based on GAS data directly to consumers are not waiting for unequivocal sensitivity and specificity information or proven genetic counseling strategies before they make the product available (Zeggini & McCarthy, 2007). At this time, clinicians must know what questions to ask about GAS data, be willing to search for up-to-date information, and be comfortable with the fact that definitive answers are still unknown.

Research opportunities for nurses related to the techniques of GAS include bench science, clinical studies, and policy development. Nurse scientists interested in GAS should seek the resources of the National Institutes of Health (NIH), such as the National Institute of Nursing Research (NINR) Summer Genetics Institute (NINR, 2008). This intensive training program provides a foundation in molecular genetics for use in research and clinical practice. Graduates of the SGI possess the knowledge and skills required to perform GAS as part of a multidisciplinary research team.

Participants at SGI also receive education on policy issues that pertain to GAS, including the privacy and confidentiality issues of participants, the necessary elements of informed consent and potential risks and benefits of participating in GAS, and the practicalities of developing a centralized data repository (National Institutes of Health, 2006). These are important issues that must be addressed when conducting scientific research with genomic information. Nurse scientists must be cognizant of the implications of using genetic information in research and take steps to protect study participants from potential harm, including psychological harm related to learning of their or their families' genomic risk for disease (Derenzo & Moss, 2006). Further information related to these issues can be found at the NIH website on GAS (National Institutes of Health, 2006).

Nurse scientists are well-positioned to facilitate the translation of genomic research from the lab to the bedside as well as advance the science of GAS (Conley & Tinkle, 2007). Nurse investigators can use GAS to answer research questions related to disease causation and disease pathophysiology. Further, through the study of associations among SNPs, protein markers, and disease phenotype, scientists can understand the multiple biologic systems involved in complex disease onset and use this information to prevent and treat disease (Wang & Moulton, 2001).

Data from these studies can support prevention and intervention strategies to reduce the morbidity and mortality that result when complex disorders are mismanaged. For example, knowing that a patient is at increased risk for insulin resistance and diabetes mellitus can prompt a nurse to initiate education on prevention strategies at an earlier date. Further, knowledge that

a person might respond better to one drug versus another facilitates appropriate prescription selection by clinicians. Most important, nurses must realize that data from GAS should be applied in tandem with consideration of multiple factors including a client's environment, lifestyle, and personal values. For example, GAS might indicate a medication that would be of benefit to a person at risk for T2DM with a particular genotype, but decisions must be made about whom to test and how and when to educate clients about the process. Assessment of a client's ability to take the medication as prescribed, willingness to modify fitness and diet habits, and adaptation to chronic illness are all essential aspects of a client's care.

Conclusions

The significant health problems of the 21st century are common, chronic disorders with multiple etiologic factors. GAS emerged as a technology with the potential to indicate specific genes that contribute to the development of those diseases or indicate treatment options. Despite the excitement about its promise, GAS can only illuminate one aspect of an etiology that almost always includes environmental and lifestyle factors. Nursing is a profession with a long tradition of recognizing that human health is a result of genes in continuous interaction with the environment in a context of personal values and choices. As such, nurses are situated to use GAS in practice, theory, and research. They must be knowledgeable about the promise as well as the limitations of GAS in order to make decisions about the use of information in practice, assist clients with decisions about seeking and interpreting GAS results, and apply current guidelines for conducting robust studies.

Clinical Resources

- dbGAP, a database of all SNPs provided by the National Library of Medicine. <http://www.ncbi.nlm.nih.gov/sites/entrez>
- GeneClinics, a publicly funded medical genetics information resource developed for healthcare providers and scientists. <http://www.geneclinics.org/>
- The International HAPMAP Project. <http://www.hapmap.org/>
- International Society of Nurses in Genetics (ISONG). <http://www.isong.org/>
- National Human Genome Research Institute (NHGRI). <http://www.genome.gov/>
- National Information Resource on Ethics and Human Genetics (NIREHG). <http://bioethics.georgetown.edu/nirehg/>
- National Institute of Nursing Research (NINR), Summer Genetics Institute. <http://www.ninr.nih.gov/Training/TrainingOpportunitiesIntramural/SummerGeneticsInstitute/>
- Office of Genomics and Disease Prevention, Centers for Disease Control and Prevention (CDC). <http://www.cdc.gov/genomics/>
- Online Mendelian inheritance in man, a searchable database of genetic syndromes, including links to published articles and gene numbers. <http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim>
- Genome bioinformatics site, includes reference sequence numbers and working draft assemblies for many genomes. <http://genome.ucsc.edu/>

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Glossary of Terms

Case Control Study:	An epidemiologic study in which the risk factors of people with certain diseases (cases) are compared with those without those diseases (controls).
Genetic association studies (GAS):	Studies in which correlations between diseases and SNPs are assessed in a population. Research designs include direct (candidate gene analysis) and indirect (genome-wide association) methods.
Genotype:	The genetic identity of a person that does not show as outward characteristics.
Intermediate phenotypes:	Homogeneous subsets of distant, heterogeneous disorders. These subsets are often specific physiologic entities of the heterogeneous condition. For example, insulin resistance is an intermediate phenotype of Type 2 diabetes mellitus.
Linkage disequilibrium:	In a population, co-occurrence of a specific DNA marker and a disease at a higher frequency than would be predicted by random chance.
Phenotype:	Observable traits or characteristics of an organism, for example hair color, weight, or the presence or absence of a disease. The phenotype results from interactions of the environment and genotype.
Reference SNP number:	A reference number assigned to a particular SNP and used for identification in manuscripts and research such as is 11200638.
Single nucleotide polymorphisms (SNPs):	Common, but minute, variations that occur in human DNA at a frequency of one every 1,000 bases. These variations can be used to track inheritance in families. SNP is pronounced "snip."

Note. Adapted from Hartl & Jones (2004); Gene Tests (2008); National Institutes of Health (2008); Williams (1994).