Medical Genomics

Primer on Medical Genomics
Part VI: Genomics and Molecular Genetics in Clinical Practice

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An important milestone in medical science is the recent completion of a "working draft" of the human genome sequence. The identification of all human genes and their regulatory regions provides the framework to expedite our understanding of the molecular basis of disease. This advance has also formed the foundation for a broad range of genomic tools that can be applied to medical science. These developments in global gene and gene product analysis as well as targeted molecular genetic testing are destined to change the practice of modern medicine. Despite these exciting advances, many practicing clinicians perceive that the role of molecular genetics, especially that of genomics, is confined primarily to the research arena with little current clinical applicability. The aim of this article is to highlight advances in DNA/RNA-based methods of susceptibility screening, disease diagnosis and prognostication, and prediction of treatment outcome in regard to both drug toxicity and response as they apply to various areas of clinical medicine.

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ACE = angiotensin-converting enzyme; APL = acute promyelocytic leukemia; ATRA = all-*trans* retinoic acid; bp = base pair; CF = cystic fibrosis; CFTR = CF transmembrane regulator; CML = chronic myeloid leukemia; CYP = cytochrome P-450; DLBCL = diffuse large B-cell lymphoma; FAP = familial adenomatous polyposis; GERD = gastroesophageal reflux disease; HNPCC = hereditary nonpolyposis colorectal cancer; LQTS = long QT syndrome; NAT2 = *N*-acetyltransferase; RAR = retinoic acid receptor; SNP = single nucleotide polymorphism; TNF = tumor necrosis factor; TPMT = thiopurine methyltransferase

The term *medical genomics* underscores the downstream effect on both clinical practice and translational research of the recent, near-complete mapping and sequencing of the human genome as well as the unprecedented series of advances in molecular biology and bioinformatics. The practical utility of molecular genetics has been shown in a spectrum of diseases across several medical disciplines. Genomic profiling will complement targeted genetic testing in facilitating presymptomatic identification of individuals who are at risk for a specific disease and therefore allow early preventive and therapeutic intervention. Genomic studies will also contribute to the molecular characterization of diseases, which in turn will refine current disease diagnosis and classification as well as the development of targeted therapies. Treatment strategies rely heavily on the specific prognosis of a given disease in an individual, and molecular prognostication may provide more robust information in that regard. Other clinical opportunities that may result from the post-genome research include the potential for prediction of both adverse effects from and response to drug therapy. The hope is that such personalized medicine, derived from an individual's genomic profile, will replace the traditional trial-and-error practice of medical treatment.

This article focuses on a few medical disciplines—cardiology, hematology-oncology, gastroenterology, psychiatry, and psychology—to show the potential clinical value of both targeted and global genetic studies. In the future, we expect that clinicians will witness a growing armamentarium of molecular diagnostics ranging from routine mutational analyses for primary disease-causing pathogenic mutations to assays for genomic biomarkers that prognosticate risk or predict response to therapy. Molecular diagnostics will allow identification of (1) presymptomatic, preclinical at-risk individuals harboring a genetic substrate for a heritable disease, (2) genetic determinants of the molecular basis of disease (functional polymorphisms or modifier genes), and (3) genetic determinants influencing response to drug therapy (pharmacogenomics). The intent of this article is to provide a "snapshot" of the potential effect of genomics on the practice of medicine by highlighting select examples from the clinical disciplines of

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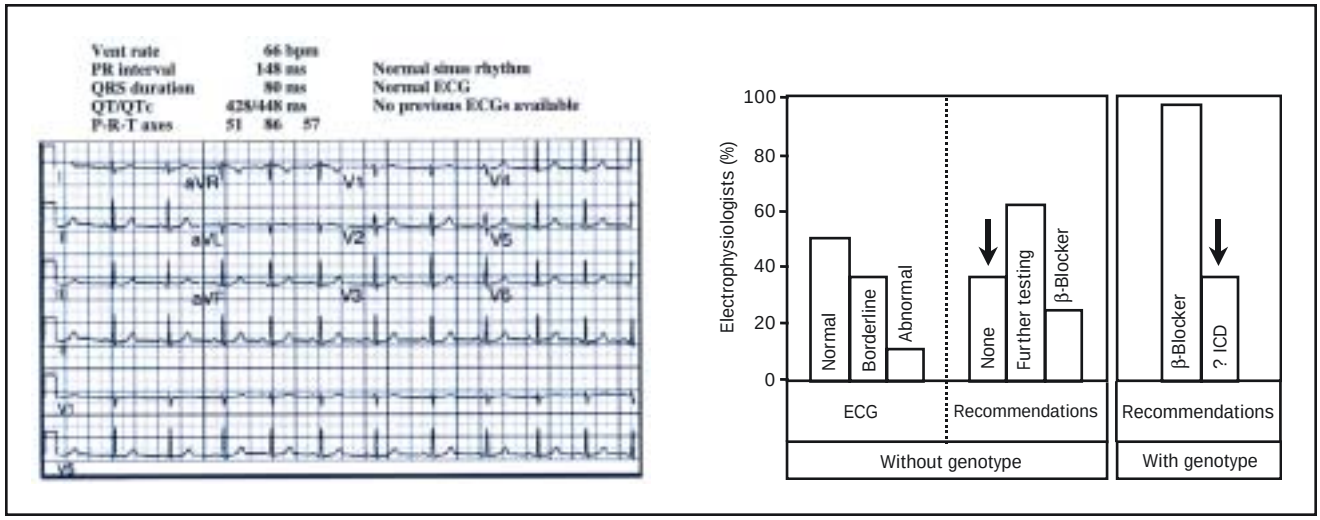

Figure 1. Potential effect of preclinical molecular diagnostic testing in patients with long QT syndrome (LQTS). Electrophysiologists were asked to review screening electrocardiograms (ECGs) (current standard of care) obtained from family members of an identified LQTS proband whose sentinel event was death after near-drowning. A molecular autopsy revealed a *KVLQT1* potassium channel mutation in the decedent. Only 25% of the electrophysiologists recommended prophylactic β-blocker therapy for the younger (18-year-old) asymptomatic sibling based on her ECG. However, after learning that she harbored the LQTS pathogenic mutation, there was universal agreement for drug therapy, and about 40% of electrophysiologists would consider a recommendation for implantable cardioverter-defibrillator (ICD) therapy as primary prevention. bpm = beats/min; QTc = corrected QT interval.

cardiology, hematology-oncology, gastroenterology, psychiatry, and psychology.

PRESYMPTOMATIC IDENTIFICATION OF HIGH-RISK PATIENTS

Cardiovascular Medicine

During the previous decade, scientists elucidated the molecular-genetic underpinnings of several cardiovascular diseases including the heritable arrhythmia syndromes (channelopathies) like congenital long QT syndrome (LQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia as well as the heritable cardiomyopathic syndromes like hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic right ventricular dysplasia-cardiomyopathy.[1-3] Uniformly, these various disease processes have underscored a complicating theme in cardiovascular pathogenomics—profound genetic heterogeneity.

To illustrate this, compare the molecular underpinnings of a monogenic (single gene) disease like cystic fibrosis (CF) with LQTS.[4] An autosomal recessive condition, CF affects approximately 1 in 3000 white newborns and is due to mutations of the CF gene that encodes for a protein product termed the *CF transmembrane regulator* (CFTR). Besides forming epithelial cell chloride ion channels, the CFTR regulates sodium ion transport across the same membrane. Although more than 900 mutations are scattered throughout the *CFTR* gene, a single mutation, F508del, accounts for approximately 70% of CF. In contrast, approximately two thirds of LQTS is identifiable genetically with hundreds of mutations scattered among 5 genes encoding critical ion channels in the heart. Moreover, there are no genetic "hot spots" for LQTS, with most families possessing their own unique mutation. This poses a tremendous challenge to routine molecular diagnostic testing for such pathogenic mutations.

Ultimately, these technological challenges will be overcome, and presymptomatic, preclinical individuals at risk for these potentially lethal heritable syndromes will be identified. The potential effect of such preclinical molecular diagnostic testing is shown in Figure 1. In this case, electrophysiologists were asked to review screening electrocardiograms (current standard of care) obtained from family members of an identified LQTS proband whose sentinel event was death after near-drowning.[5] A molecular autopsy revealed a *KVLQT1* potassium channel mutation in the decedent. Only 25% of the electrophysiologists recommended prophylactic β-blocker therapy for the younger (18-year-old) asymptomatic sibling on the basis of her electrocardiogram (Figure 1). However, after learning that she harbored the LQTS pathogenic mutation, there was universal agreement for drug therapy (Figure 1). Without the genetic test result, nearly 40% of electrophysiologists had dismissed her as a healthy person. With the molecular

diagnostic test result, nearly 40% would consider a recommendation for an implantable cardioverter-defibrillator. Thus, the molecular diagnostic information singularly caused a dramatic change in the proposed clinical management of this patient.

Although presymptomatic detection of a potentially lethal arrhythmia syndrome is preferred, these molecular diagnostic tools will certainly transform the forensic evaluation of unexplained sudden death through a "molecular autopsy." By conducting a state-wide, population-based molecular autopsy on cases of sudden infant death syndrome, Ackerman et al[6] showed that 2 of 58 white infants had pathogenic mutations in the gene (*SCN5A*) encoding the cardiac sodium channel.

It is anticipated that these advances will soon affect more common cardiovascular diseases. As further genetic features are determined that identify individuals at high risk for cardiac failure, coronary artery disease, and hypertension, targeted therapies and interventions will be developed to improve the long-term outcome of these patients.

Hematology and Oncology

In the management of malignant disease, certain individuals are more susceptible than others to specific cancers or to cancer in general. Two people exposed to the same agent may have extremely different risks of cancer on a biologic basis and therefore may react differently both to carcinogen exposure and to risk-reduction methods. For example, the enzyme *N*-acetyltransferase (NAT2) is involved in detoxifying aromatic amines, which are known carcinogens found in tobacco smoke and certain dyes. Individuals who carry the normal enzyme are termed *rapid acetylators*. Those who carry a mutation in *NAT2* have weakened enzymatic activity and are termed *slow acetylators*. Carcinogenicity of aromatic amines depends on the balance of metabolic activation and elimination, and slow acetylators are inefficient in eliminating the active form of a chemical carcinogen. In Western populations, there is an approximate 50-50 split between slow acetylators (homozygous for the deficient acetylation allele) and rapid acetylators. Meta-analyses of NAT2 slow acetylators and bladder cancer[7] consistently show an increased risk for slow acetylators.[8] That is, cigarette smokers who have increased exposure to aromatic amines exhibit an increased risk of developing bladder cancer if they possess the slow acetylation genotype-phenotype.

Genetic susceptibility is responsible for a substantial portion of colorectal cancer. At least 20% of colorectal cancer occurs within familial aggregates. Roughly one third of these familial aggregates, ie, 8% of the total colorectal cancer burden, are related to hereditary nonpolyposis colorectal cancer (HNPCC) or familial adenomatous polyposis (FAP). Currently, genetic testing for these 2 autosomal dominant conditions can be used to recognize individuals with either HNPCC or FAP and to guide screening and performance of predictive genetic testing in at-risk family members. For HNPCC kindreds, immunohistochemistry of the DNA mismatch repair enzymes (hMLH1, hMLH2, and MSH6) in combination with DNA microsatellite instability testing can be performed on tumor tissue, and then germline DNA sequencing can be used to identify the precise mutation. In FAP, causative germline activated protein C mutations are identified in an affected individual through a combination of a protein truncation test and conformation sensitive gel electrophoresis.[9]

Other molecular markers of cancer susceptibility involve the *BRCA1* and *BRCA2* tumor suppressor genes. Mutations of these genes confer a lifetime risk of breast and ovarian cancer of 50% to 85% and 15% to 45%, respectively. However, only 5% to 10% of all breast cancers are related to *BRCA1* or *BRCA2* mutations, and such cases are often hereditary. Therefore, screening for *BRCA1* or *BRCA2* mutations in family members of patients with breast cancer may be appropriate in certain (hereditary cases) but not all (sporadic cases) circumstances. In general, the appropriateness of genetic-genomic screening for cancer in asymptomatic patients depends on test sensitivity, specificity, and feasibility based on both cost and access.

Gastroenterology and Hepatology

Gastroesophageal reflux disease (GERD) is a spectrum ranging from symptoms (usually heartburn and acid regurgitation) without damage of the esophageal lining, so-called nonerosive reflux disease; to erosive reflux esophagitis in which the normal squamous lining of the esophagus is damaged by refluxed gastric contents; to Barrett esophagus, an acquired condition in which the normal lining is replaced by preneoplastic columnar epithelium; to esophageal adenocarcinoma. In research aimed at determining whether GERD symptoms, reflux esophagitis, and Barrett esophagus aggregate in families and have a heritable component, Mayo investigators have prospectively studied GERD symptoms in families of patients with reflux esophagitis, Barrett esophagus, and/or esophageal adenocarcinoma and showed that the parents and siblings of index patients with Barrett esophagus and esophageal adenocarcinoma meet criteria for GERD symptoms twice as often as do the parents and siblings of their spouses.[10,11]

In a recent landmark study of more than 6000 monozygotic and dizygotic twins performed in Sweden in collaboration with researchers at the Mayo Clinic, Cameron et al[12] showed that the heritability of GERD symptoms is 31%. Furthermore, recent results show that after adjustment for age, male sex, and GERD symptom duration, there is a

greater than 2-fold increase in risk of Barrett esophagus in family members compared with controls. Therefore, a family history of Barrett esophagus appears to be a risk factor for both Barrett esophagus and reflux esophagitis[13] and suggests the presence of an underlying GERD susceptibility gene. Thus, it may be important for physicians to inquire about family history of GERD, Barrett esophagus, or esophageal adenocarcinoma and consider screening members in high-risk families.

Kindreds with a high penetrance of Barrett esophagus may be analogous to families with a high penetrance of colon cancer, and studies in these families may provide an invaluable resource for identifying the genetic aberrations important for neoplastic progression to esophageal adenocarcinoma. Since 1998, the Barrett's Esophagus Genomic Study group has identified 59 well-defined multigenerational families in which 3 or more members have long-segment Barrett esophagus, with or without esophageal adenocarcinoma, for linkage analysis.[14] The Mayo Clinic Esophageal Adenocarcinoma and Barrett's Esophagus Registry is a unique resource that combines phenotype (endoscopy, pathology, quality-of-life and symptom instruments) with genotype (blood and tissue) and environmental risk factor information. The goal of the registry is to enroll all persons with long-segment Barrett esophagus or esophageal adenocarcinoma seen at the Mayo Clinic. This registry will be used to identify candidate genomic loci for the full spectrum of GERD phenotypes and to determine the sequence of genomic changes required for the transformation from Barrett esophagus to adenocarcinoma.

Hereditary hemochromatosis is the most frequent single gene disorder in the white population, with a frequency of heterozygotes of 1 in 20 and of homozygotes, 1 in 250 individuals. Although there is variable penetrance of the disorder, affected individuals are at risk of developing cirrhosis with portal hypertension and hepatocellular carcinoma. The cloning of the human hemochromatosis gene (*HFE*), which is responsible for most cases of hereditary hemochromatosis, was a landmark event for applying genomics to hepatology. Subsequently, clinical tests have been developed for the major mutations responsible for the disease and are used to confirm the diagnosis and to screen potentially affected relatives.

Psychiatry and Psychology

In psychiatry, linkage studies have been performed on the psychiatric illnesses that aggregate within families. Altmüller et al[15] examined the features of more than 100 genome wide screens and noted that 2 of the 4 most studied conditions were schizophrenia and bipolar disorder. However, results from these studies have been limited. For schizophrenia, only 2 of 10 studies achieved the level of "significant linkage," with a logarithm of odds score of 3.6 to 5.3, for bipolar disorder, only 1 of 7 studies achieved the level of significant linkage. None have been confirmed in an independent sample. Reasons that linkage studies fail confirmation include technical issues such as sample size, variability in the marker set used for a given study, variable ethnicity of the groups being studied, problems with diagnostic nosology, and the fact that psychiatric illnesses are believed to be complex diseases (eg, polygenetic with environmental influences). In complex diseases, the effect of the size of individual genes is likely to be small; very large sample sizes are needed to yield reproducible results.

Despite these limitations, a recent study by Meyer et al[16] of familial periodic catatonic schizophrenia yielded interesting results. Linkage analysis of a large pedigree revealed linkage to 22q13. Analysis of genes around the linkage site disclosed a novel gene, *WKL1*, that appears to be a cation channel. An L309M mutation of *WKL1* was reported to cosegregate with familial periodic catatonic schizophrenia in the pedigree. This finding is particularly interesting because several "periodic" or episodic illnesses, including seizure disorders and cardiac arrhythmias, are associated with channelopathies. Thus, this finding involving a cation channel reflects that seen in other illnesses with an episodic course. If this work is replicated and the pathophysiologic mechanism for this illness is fully understood, pharmacological approaches to treat the illness can be designed.

INCREASED UNDERSTANDING OF THE MOLECULAR BASIS OF DISEASE

Cardiovascular Medicine

Factor V Leiden (R506Q) mutation testing represents one of the best examples of a functional polymorphism that influences or "modifies" a disease process and is currently a standard, routine molecular diagnostic test in clinical practice.[17] The R506Q missense mutation in factor V (named factor V Leiden for its identification in Leiden, the Netherlands) was discovered in 1994 as the cause of activated protein C resistance. Factor V Leiden is a member of the heritable thrombophilias (hypercoagulable states) and is the most common genetic risk factor for venous thrombosis and pulmonary embolus. Factor V Leiden is believed to have arisen de novo in northern Europe, and all individuals with factor V Leiden share this common ancestor. The mutation is present in 5% of white North Americans, 20% of patients with idiopathic deep venous thrombosis, and 60% of venous thrombosis cases in pregnant women. Individuals heterozygous (5% in white persons) for factor V Leiden have a 7-fold increase in the relative risk of venous thrombosis, whereas the risk is about 80-fold for the 1 in 400 white persons homozygous for factor V Leiden. Currently, neither random screening of

the general population nor prenatal-newborn screening is recommended. However, there is a growing consensus that factor V Leiden mutational testing is the standard of care in evaluating any venous thrombosis that occurs in persons younger than 50 years, venous thrombosis in unusual sites, recurrent venous thrombosis, venous thrombosis in persons with a family history of thrombotic disease, venous thrombosis in pregnant women or women taking oral contraceptives, relatives of individuals younger than 50 years with venous thrombosis, and myocardial infarction in female smokers younger than 50 years.[17]

Research is ongoing to determine the extent to which functional polymorphisms in the renin-angiotensin-aldosterone cascade influence outcome in cardiovascular disease. For example, there is a common deletion-insertion polymorphism (designated DD, DI, and II) in the gene encoding the angiotensin-converting enzyme (ACE). The deletion (D) allele is associated with increased enzymatic activity compared with the insertion (I) allele. Early studies implicated the D allele in myocardial infarction and coronary artery disease, but subsequent studies did not show this association.[18] The DD-ACE genotype has been associated with many end points, including increased left ventricular wall thickness, submaximal exercise hemodynamics in postmenopausal women, diabetic nephropathy, leukoaraiosis (abnormalities of periventricular and subcortical white matter) in lacunar syndromes, genetic susceptibility to asthma, and elite short-distance Russian athletes. In contrast to factor V Leiden genotyping, ACE genotyping has not yet become standard clinical practice.

Hematology and Oncology

Advances in genomics have allowed the medical research community to identify a large number of genetic and phenotypic changes as markers of prognosis in various types of solid and hematologic cancers. For example, the *HER-2/neu* oncogene, which normally encodes for the receptor for epidermal growth factor, is amplified in approximately 20% to 30% of breast and ovarian tumors, and this oncogene's amplification and/or overexpression indicates a poor prognosis.[19,20] The *HER-2* assays have been useful for distinguishing patients at higher risk of breast cancer recurrence and for identifying a subset of patients who are more likely to have a poor response to adjuvant hormonal therapy or chemotherapy.[21-23] This observation has led to clinical trials investigating the HER-2/neu monoclonal antibody trastuzumab combined with chemotherapy to target specifically the cancer cells overexpressing HER-2/neu.

In a study on breast cancer, van't Veer et al[24] used global gene expression profiling, with the use of DNA microarrays, to identify a gene expression signature for patients with node-negative breast cancer who are carriers of the *BRCA1* mutation and for those who were likely to develop distant metastasis. These findings suggest the potential of global genomic studies to improve the diagnosis of hereditary breast cancer and provide a powerful tool to identify patients who will benefit from adjuvant therapy for breast cancer. The same study also identified a set of genes that were differentially overexpressed in tumor tissue and were associated with a poor prognosis. The products of such genes may be considered potential targets for the rational development of new cancer drugs.

Another example of the potential value of global gene expression assays involves patients with a subtype of non-Hodgkin lymphoma classified as diffuse large B-cell lymphoma (DLBCL). According to recent reports, it is possible to subclassify DLBCL into 2 molecularly distinct groups based on DNA microarray analysis of gene expression. The 2 molecular groups displayed a gene expression profile that was analogous to that of either a germinal-center B cell or an activated peripheral B cell.[25] Individuals with germinal-center B-cell–like DLBCLs had a prolonged overall survival compared with those with activated peripheral B-cell–like DLBCLs. Patients with the former disease type responded well to conventional anthracycline-based lymphoma treatment regimens, whereas those in the latter group did not. In a related global gene expression study, Shipp et al[26] applied a supervised learning prediction method to identify cured vs fatal or refractory DLBCL. The algorithm classified 2 categories of patients with extremely different 5-year overall survival rates (70% vs 12%) and identified 13 genes that separated patients into those whose disease was likely to be cured and those whose disease would be refractory and relapsing. Rosenwald et al[27] also recently used 17 genes to construct a gene-based predictor of overall survival after chemotherapy for DLBCL. This information is being used to select previously untreated DLBCL patients for whom up-front investigational therapy represents a more appropriate treatment approach.

Knowing the genomic constitution of patients with malignancy substantially affects clinical practice. Patients with mutations in cancer susceptibility genes have unusually high risks of developing more than one primary malignancy, and this fact commonly changes the management approach in these patients. For example, choosing the appropriate treatment strategy for a patient with hereditary breast cancer (mastectomy vs lumpectomy plus irradiation) may be influenced by the information that a particular patient has a 60% chance of developing a second breast cancer or by recalling that some patients may have a genetic sensitivity to the carcinogenic effects of ionizing radiation. Similarly, in colon cancer treatment, bowel-conserving surgery for the diagnosis of a carcinoma or dysplastic adenomatous polyp may not be the best choice in

persons with FAP or HNPCC in whom the likelihood of subsequent colon malignancies is high. Therefore, the treatment strategy selected for such a person may differ from that recommended for an individual without a genetic predisposition.

Gastroenterology and Hepatology

Genomic approaches are being used to improve treatment, detection, and prevention of Barrett esophagus. Krishnadath et al[28] showed that current clinical markers of cancer progression based on histological analysis are insufficient to determine cancer risk, and they are now assessing possible genetic markers for cancer progression in Barrett esophagus. Because spectral analysis with techniques such as Raman spectroscopy has the potential to detect abnormal proteins in cells that contain genetic mutations, these investigators are using novel optical biopsy techniques to correlate abnormalities in mucosal fluorescence with areas of genetic instability. Finally, they are developing a chemoprevention program using animal models of esophageal adenocarcinoma to identify genetic markers that predict the ability of specific interventions to interrupt the process of carcinogenesis.

The development of high-density oligonucleotide microarray platforms[29] has generated enormous anticipation in the field of hepatology. Although often criticized as being non-hypothesis driven, sequential or differential gene expression profiling studies provide a time course or comparison, at a messenger RNA level, of the events associated with changes in hepatobiliary physiology and disease. This type of analysis is currently limited by high costs and the labor-intensive nature of the methods. Short-term goals are to identify novel therapeutic and diagnostic targets of prevalent hepatobiliary diseases.

Gene expression profiling has already begun to yield dividends in these areas. Histologically, progressive hepatitis C virus infection was recently shown to be associated with overexpression of a distinct set of immunomodulatory and proapoptotic genes, including secreted apoptosis-related proteins CD147 and CD167.[30] Similarly, increased expression of genes of the Wnt and notch pathways, including c-jun, c-myc, and c-fos, was noted in patients with primary biliary cirrhosis.[31] Gene expression profiling studies of viral carcinogenesis and progression of hepatocellular carcinoma have identified an array of differentially expressed genes and expressed sequence tags associated with the development of hepatocellular carcinoma.[32] Similar work is under way in other hepatobiliary diseases, including cholangiocarcinoma, primary sclerosing cholangitis, and fatty liver disease.

Observations made in genomic studies will likely facilitate the development of novel therapeutic targets and diagnostic markers. Similarly, gene expression profiling is likely to increase substantially our ability to distinguish responders from nonresponders (eg, treatment of hepatitis C virus with pegylated interferon and ribavirin) and to identify patients with susceptibility to drug toxicity. When coupled with existing methods and applied with scientific rigor, the methods of genomics (eg, high-density microarray analysis) and proteomics (high throughput tandem mass spectrometry) have the potential to substantially affect our understanding of the underlying mechanisms of hepatobiliary disease and contribute to the diagnosis and treatment of these disorders.

The technique of fluorescent in situ hybridization was recently applied to the diagnosis of malignant biliary strictures in brush specimens obtained on endoscopic retrograde cholangiopancreatography. This technique uses hybridization of genomic probes from different regions of the genome as a sensitive test for cellular aneuploidy. Fluorescent in situ hybridization shows a significantly higher sensitivity for the diagnosis of malignant strictures than does routine cytology and may substantially improve the early diagnosis of cholangiocarcinoma in patients with primary sclerosing cholangitis.

Psychiatry and Psychology

In the study of mental illness, investigators frequently evaluate single nucleotide polymorphisms (SNPs) and other variations in candidate genes selected after linkage studies or after findings in nongenomic research. Specifically, researchers have studied several members of the serotoninergic neurotransmission system after low cerebrospinal fluid 5-hydroxyindoleacetic acid levels were associated with both suicidal behaviors and impulsivity. The serotoninergic genes that have been studied include the tryptophan hydroxylase gene (*TPH*), the serotonin transporter gene (*SLC6A4*), and the serotonin receptor genes 1B (*HTR1B*) and 2A (*HTR2A*). The *TPH* gene catalyzes the oxygenation of tryptophan to 5-hydroxytryptophan, which is then decarboxylated to serotonin by another enzyme. Several polymorphisms of this gene have been studied in reference to suicide. For example, for the intron 7 A779C SNP, the 779C allele has been associated with suicidal behavior[33-36] as has the intron 7 A218C SNP, 218C allele.[37,38] Other studies have found no association between the intron 7 A218C and A779C SNPs and suicidal behaviors[39,40]; however, the haplotype –6526G, –5806T, 218C was associated with suicidal behaviors.[39] Finally, the $(CT)_m(CA)_n(CT)_p$ allele, termed *194*, has been associated with suicidal behaviors.[41]

SLC6A4 terminates the action of serotonin by its high affinity reuptake into presynaptic terminals. This transporter is the target of the serotonin reuptake inhibitor class

of antidepressants. The gene has a 44-base pair (bp) insert/deletion in the promoter region that has been studied in reference to suicide. The 44-bp insert has been shown to increase SLC6A4 amounts in cultured cells, possibly through increased transcription efficiency of the gene, thus leading to the hypothesis that there would be more reuptake of serotonin and less serotonin activity at the synaptic cleft resulting in illness.[42] One study found a higher frequency of the 44-bp insert among depressed suicidal individuals.[43] Other researchers have obtained contradictory results that a shorter allele was associated with suicidal behaviors.[44-46]

HTR1B has been studied because of its role in serotoninergic neurotransmission and because *HTR1B* knockout mice are aggressive and impulsive. The G816C (V287V) polymorphism was associated with suicidal behaviors in a US population sample[47] but not in a Japanese sample.[48]

Finally, *HTR2A* has been studied. In a Chinese sample,[49] the –1438G/–1438G allele was associated with suicide, and in one Japanese sample,[50] the T102C, 102C allele was associated with suicide attempt. But in another Japanese sample, neither SNP was associated with suicidal behavior.[51]

These results are interesting, but some results directly conflict with one another and must be considered in that light. The reason for these conflicting results may be due to the fact that different ethnic groups and different diagnoses were studied in association with suicidal behavior.

MORE PRECISE DRUG TREATMENT

Cardiovascular Medicine

Compared with the clinically available tests to determine genetic variation in cytochrome P-450 (CYP) or methyltransferase drug–metabolizing enzymes, no pharmacogenomic assays are performed clinically to determine whether a particular patient is likely to be a responder or a nonresponder to treatments such as cholesterol-lowering agents, chemotherapeutic agents, and antipsychotic or antihypertensive medications. However, such assays may be developed in the future.

For example, Turner et al[52] identified that a polymorphism (C825T) in the G protein β3 subunit mitigates responsiveness to diuretic therapy in patients with essential hypertension, and TT genotyped patients experienced the greatest blood pressure response to 4 weeks of hydrochlorothiazide monotherapy. Subsequently, in a large population-based controlled study, Psaty et al[53] showed that diuretic therapy was associated with a dramatic reduction in the risk of combined myocardial infarction or stroke compared with other antihypertensive therapies for patients harboring the functional polymorphism (G460W) in α-adducin.

In contrast to these studies that show that genetic variants confer favorable response to drug therapy, Yang et al[54] recently showed that ion channel variants were identified in 10% to 15% of patients who had experienced an "idiopathic" drug-associated proarrhythmic event. In fact, these authors speculate on a future role for "preprescription genotyping" in an attempt to identify patients potentially vulnerable to particular drugs before drug treatment is initiated.

Hematology and Oncology

An increased understanding of molecular genetics has allowed investigators to unravel the molecular basis of various malignant diseases and to develop targeted therapies based on the molecular differences between malignant and normal cells. A good example is the identification of the molecular pathogenetic lesion in chronic myeloid leukemia (CML). It was first shown that the so-called Philadelphia chromosome was the product of a reciprocal translocation between the long arms of chromosomes 9 and 22, t(9:22)(q34;q11).[55,56] Subsequently, the molecular consequence of this event was further characterized and involved the generation of a chimeric *bcr-abl* gene, formed by juxtaposition of the *c-abl* oncogene on chromosome 9 with sequences from the breakpoint cluster region (*bcr*) on chromosome 22.[57]

Additional insight into the pathogenesis of CML came from the study of the Abelson murine leukemia virus.[58] The transforming protein of this virus, v-Abl, was shown to be a tyrosine kinase with its transforming ability dependent on this activity.[59] Subsequently, the bcr-abl fusion product proved to display similar tyrosine kinase activity. The constitutive tyrosine kinase activity of bcr-abl causes activation of various intracellular signaling pathways, leading to alterations in the proliferative and survival properties of CML cells.[60] Recently, the Food and Drug Administration approved an oral drug called imatinib mesylate (STI571) for the treatment of CML. Imatinib was specifically designed as a selective inhibitor of the bcr-abl tyrosine kinase.[61] Data from phase 1 and 2 trials in patients with CML showed a 98% hematological response rate with an acceptable toxicity profile, and a subsequent phase 3 study confirmed the therapeutic superiority of imatinib over conventional drug therapy for CML.[62-65]

Similar examples of molecular-targeted therapy include the treatment of acute promyelocytic leukemia (APL) with a vitamin A derivative (all-*trans* retinoic acid [ATRA]) and the use of trastuzumab in breast and other tumors overexpressing the *HER2/neu* oncogene. The treatment of APL with ATRA targets the novel genetic lesion created by a disease-specific chromosomal translocation, which alters the retinoic acid receptor (*RAR*) gene.[66] Disruption of the *RAR* gene or blocking its response element by any one of

several possible translocations leads to a reduction in the functional amount of its product. Standard treatment now consists of replacing *RAR* with ATRA. ATRA appears to reverse the arrest in the maturation of malignant promyelocytes, created by APL's pathogenic 15;17 chromosomal translocation, allowing them to undergo normal maturation and death. ATRA plus chemotherapy is now standard treatment of APL.

As mentioned previously, trastuzumab is a monoclonal antibody that targets the protein product of the *HER2/neu* oncogene. The HER2 protein is overexpressed in 25% to 30% of primary breast cancers. Trastuzumab has been shown in both in vitro assays and in animals to inhibit the proliferation of human tumor cells that overexpress HER2.[67-69] The drug has been approved by the Food and Drug Administration as an effective single-agent treatment of metastatic breast cancer that is characterized by HER2 overexpression. The median overall survival rate of patients with metastatic breast cancer who were treated with trastuzumab was found to be superior to that reported with other second-line chemotherapy. It has also been shown that trastuzumab may potentiate the antitumor effect of paclitaxel chemotherapy for breast cancer.[70]

Gastroenterology and Hepatology

Therapeutic recombinant proteins currently used in the treatment of Crohn disease include the mouse-human chimeric antibody to tumor necrosis factor (TNF), infliximab, for induction of remission and closure of fistulas in patients with active Crohn disease,[71,72] the humanized anti-TNF antibody CDP571 for treatment of active Crohn disease and corticosteroid sparing,[73,74] and the humanized antibody to α-4 integrin, natalizumab, for induction of remission in patients with active Crohn disease.[75] Novel biotechnological therapies currently under investigation for inflammatory bowel disease include the fully human soluble p-55 receptor to TNF (onercept) for Crohn disease, a humanized antibody to α-4 β-7 integrin (LDP-02) for both ulcerative colitis and Crohn disease, a humanized antibody to interleukin 12 for Crohn disease, a humanized antibody to interferon gamma for Crohn disease, granulocyte macrophage colony-stimulating factor (sargramostim) for Crohn disease, and interferon beta for ulcerative colitis and Crohn disease.

Azathioprine is metabolized via the enzyme thiopurine methyltransferase (TPMT) to an inactive metabolite, 6-methylmercaptopurine, or to the putative active metabolites, the 6-thioguanine nucleotides.[76] Approximately 1 in 300 patients are unable to metabolize azathioprine because of absence of TPMT activity, and approximately 10% of patients are hypometabolizers. Recent studies show that a portion of the leukopenia observed in patients treated with azathioprine and a related compound, 6-mercaptopurine, for inflammatory bowel disease is related to decreased or absent TPMT enzyme activity.[77,78] It is now standard practice to measure TPMT activity before initiation of treatment with azathioprine or 6-mercaptopurine for inflammatory bowel disease.

A recent report showed that resistance to therapy with corticosteroids for ulcerative colitis or Crohn disease is related to expression of an inactive form of the glucocorticoid receptor (glucocorticoid receptor b)[79] and separately to the presence of the multidrug resistance gene (*PG170*), which acts to pump corticosteroids out of cells.[80] Assays for these molecular causes of resistance to corticosteroid therapy will likely be developed in the future, allowing earlier discontinuation, or perhaps avoidance, of corticosteroids in patients unlikely to respond to therapy.

Psychiatry and Psychology

Genomic research promises to lead to the ideal of individualized psychopharmacotherapy. Responsiveness to drugs depends on at least 2 variables, assuming normal absorption. One variable is an individual's unique drug target structure, and the second is the genetically determined rates of drug metabolism. Target structure primarily depends on the sequence of the gene encoding the target. Accordingly, assays must be designed to determine the effect of drugs on variations in drug targets. The effect of genetic variation on drug metabolism is an area of intense research and is summarized subsequently.

With most psychiatric drugs, CYP enzymes are essential for metabolism. The CYP2D6 isoform is involved in the metabolism of many psychotropic drugs and nearly all serotonin reuptake inhibitors, although other isozymes, including CYP2C19, contribute to the metabolism of some psychotropics. The *CYP2D6* gene has considerable molecular diversity that affects the rate at which the enzyme metabolizes substrates. Many *CYP2D6* alleles have reduced activity, and duplications of normal alleles also occur. Once an individual's *CYP2D6* alleles are genotyped, metabolic rates for substrates can be predicted. Most individuals carry 2 copies of a normal (also called *wild-type* or *wt*) allele of the *CYP2D6* gene. These individuals extensively modify substrates for CYP2D6 and are called *extensive metabolizers*. If an individual carries one wild-type *CYP2D6* allele and one mutated allele with reduced function, this individual will have decreased CYP2D6 enzyme activity and is called an *intermediate metabolizer*. Those with 2 alleles with reduced function are known as *poor metabolizers*, and those with duplications of wild-type alleles metabolize their substrates at a very high rate and are called *ultrarapid metabolizers*. There are large ethnic differences in the frequency of these alleles. Among white

people, about 6.7% are poor metabolizers regardless of their geographic origin. In most other ethnic groups, the percentage of poor metabolizers ranges from 0.9% to 3.8%, although 18.8% of the Kung San Bushmen are reportedly poor metabolizers.[81] Conversely, 1% of Scandinavians, 3.6% of Germans, 10% of Spaniards, 20% of Saudi Arabians, and 29% of Ethiopians carry duplications of 2D6 and are ultrarapid metabolizers.[82] Kirchheiner et al[83] reviewed the literature with the aim of providing dosage recommendations for antidepressants based on *CYP2D6* and *CYP2C19* genotyping. Once verified by clinical research, the approach outlined by Kirchheiner et al may become a mainstay in the clinical management of patients taking several drugs. In fact, genotyping of individual CYP isoforms might become routine in the future for all individuals receiving drugs. Justification for this approach comes from a case report of a child with a poor metabolizer genotype who died of complications of antidepressant treatment because of extremely high blood levels of fluoxetine.[84]

CONCLUSION

Substantial advances are being made frequently in the area of genomics, and the results are beginning to play an important role in the general practice of clinical medicine. Some of the advances are now the standard of care, but some of the findings have led to conflicting results. Further studies in these areas of discrepant results are clearly needed before firm recommendations can be made regarding clinical practice. Many more questions and issues remain that are beyond the scope of this article. Issues of cost-effectiveness and reimbursement, potential misuse of genomic information, clinical and analytic validity of genetic testing, and the clinical utility of genomic information in the face of environmental factors and the polygenic basis of many diseases need to be addressed more completely.

We believe that it is imperative that physicians involved in clinical practice become more aware of emerging genomic data and participate in integrating medical genomic information into current standard clinical practice. Clearly, the practice of medicine is being influenced by genomics.

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