Pharmacogenetics: potential for individualized drug therapy through genetics

Julie A. Johnson

Department of Pharmacy Practice, Department of Pharmaceutics and Department of Medicine, University of Florida, Box 100486, Gainesville, FL 32610-0486, USA

Pharmacogenetics blends important components of the disciplines of genetics and pharmacology, and aims to describe the influence of inheritance on variable drug response. This review provides an overview of the history and current status of pharmacogenetics. The role of genetics in variable drug response is now firmly established. To apply this information to the clinical setting, more sophisticated methods, such as a multiple candidate gene approach, or genomic approaches, are likely to be needed. Most drugs will require additional research if their use is be guided by a patient’s genetic make-up. However, it seems that the potential for pharmacogenetics to improve the clinical outcomes of numerous drug therapies will be realized, and will represent an important biomedical advance in the post-genomics era.

The results of drug therapy can vary within a population. Although some individuals obtain the desired effects, others can have minimal or no therapeutic response. Furthermore, certain patients might experience adverse effects that can range from bothersome to life threatening. Several factors can contribute to variable drug response, including age, race, gender, interactions with other drugs, concomitant diseases, and renal and hepatic function. However, there is increasing evidence that genetic differences can be an important (and in some cases predominant) factor influencing drug response variability.

Although pharmacogenetics is an established field, it has seen rapid growth in recent years in part owing to technological advances in the molecular sciences. In this review, I will discuss briefly the history of pharmacogenetics, highlight examples from the current literature and discuss the future of this field and its potential impact on clinical medicine. The clinical vision for pharmacogenetics is that genetic information might be used to identify the drug(s) and dosages with the highest likelihood for benefit and the lowest risk for harm in an individual patient.

History of pharmacogenetics
Pharmacogenetics is occasionally viewed as a new discipline, but the field was firmly established in the 1950s. There were several discoveries during this early period that led to the merger of the fields of pharmacology and genetics. These included the recognition that prolonged paralysis following the use of succinylcholine was the result of a variant of the butyryl-cholinesterase enzyme, that hemolytic anemia from the antimalarial drug primaquine resulted from a variant form of the enzyme glucose-6-phosphate dehydrogenase, and that peripheral neuropathies resulting from the antituberculosis drug isoniazid were as a consequence of genetic differences in the enzyme N-acetyltransferase [1,2].

For these early examples, a genetic component was identified through studies of families or ethnic populations, and careful testing of the phenotype. In common with many fields in the biomedical sciences, advances in molecular biology transformed pharmacogenetics. Therefore, the focus is now on the specific gene and the sequence variability that is contributing to the variable drug response.

The early pharmacogenetic examples were those for which a distinct phenotype could be easily characterized; understanding of the molecular genetic basis for the phenotype came later. Currently, pharmacogenetic investigations, particularly those focused on proteins other than the drug metabolizing enzymes, usually begin with an understanding of the sequence variability in a relevant gene, and then focus on how this genetic variability influences the drug response phenotype.

The evolution of pharmacogenetics is far from complete. Although much of the work to date has focused on single genes, it is clear that there are numerous genes and proteins that contribute to drug response variability. Thus, pharmacogenetics is transforming into a genomics-based field, leading to a new term, pharmacogenomics. The differences in definitions of pharmacogenetics and pharmacogenomics are often debated, but they are increasingly used synonymously, and it is likely that the term pharmacogenomics will eventually replace pharmacogenetics. However, to avoid any confusion, only the term pharmacogenetics will be used herein.

Variable drug response and pharmacogenetics
Within the discipline of pharmacology, drugs are often discussed from two perspectives: pharmacodynamics (PD) and pharmacokinetics (PK). PD describes the pharmacological effects of a drug on the body (either desired or...
The treatment for a given disease is essentially the same, management of disease is a per protocol approach, where months to accomplish. The other approach to drug patient is often through trial and error, and can often take several drugs that are reasonable first line therapy.

For drug treatment of diseases such as hypertension, diabetes, depression, schizophrenia, arrhythmias, esophageal reflux and others. For these diseases, there are genetic reflux and others. For these diseases, there are for drug treatment of diseases such as hypertension, diabetes, depression, schizophrenia, arrhythmias, esophageal reflux and others. For these diseases, there are for drug treatment of diseases such as hypertension, diabetes, depression, schizophrenia, arrhythmias, esophageal reflux and others. For these diseases, there are for drug treatment of diseases such as hypertension, diabetes, depression, schizophrenia, arrhythmias, esophageal reflux and others. For these diseases, there are for disease. The first is a trial and error approach, employed for drug treatment of diseases such as hypertension, diabetes, depression, schizophrenia, arrhythmias, esophageal reflux and others. For these diseases, there are several drugs that are reasonable first line therapy. Finding the drug(s) that is most effective in a given patient is often through trial and error, and can often take months to accomplish. The other approach to drug management of disease is a per protocol approach, where the treatment for a given disease is essentially the same.

Clinical application of pharmacogenetics

Figure 1. Key components in pharmacogenetics. There are two broad areas of research in pharmacogenetics, specifically, pharmacokinetics (PK) and pharmacodynamics (PD). Drug metabolizing enzymes and drug transporters frequently contribute to variable PK. Proteins involved in mediating drug effects are broadly defined as drug targets, and include not just the direct protein targets of a drug but any proteins involved in a drug action (e.g. signal transduction proteins, proteins mediating adverse effects). Any of these types of proteins could contribute to inter-patient variability in drug efficacy or toxicity and thus could be candidate genes in pharmacogenetic studies. The broken line indicates that drug transporters are also occasionally the drug target, in addition to contributing to drug PK.

Evidence that genetic variability contributes to observed differences in drug response in different individuals has been mounting in recent years. Some examples are highlighted in Table 1, (for more examples see Refs [3–5]). Most of the genetic polymorphisms relevant to pharmacogenetics are common in the population, and exhibit racial differences in their distribution. There is clear evidence from the pharmacogenetic literature that gene sequence variability can contribute to variable drug response.

Figure 2. Clinical potential of pharmacogenetics. Patients with the same empirical diagnosis (e.g. hypertension, leukemia, etc.) are typically treated in the same manner, although their responses to drug therapy will not be the same. Pharmacogenetics has the potential to provide a tool for predicting those patients who are likely to have the desired response to the drug, those who are likely to have little or no benefit and those at risk for toxicity. This would allow tailored therapy that should reduce adverse reactions to drugs and increase efficacy rates.

Clinical application of pharmacogenetics

Figure 2 highlights the current drug treatment paradigm, along with the potential clinical benefits of pharmacogenetics. Currently one of two general treatment approaches is typically employed in the pharmacological management of disease. The first is a trial and error approach, employed for drug treatment of diseases such as hypertension, diabetes, depression, schizophrenia, arrhythmias, esophageal reflux and others. For these diseases, there are several drugs that are reasonable first line therapy. Finding the drug(s) that is most effective in a given patient is often through trial and error, and can often take months to accomplish. The other approach to drug management of disease is a per protocol approach, where the treatment for a given disease is essentially the same for everyone with that diagnosis. Examples of diseases treated in this way include most cancers, heart failure, myocardial infarction and post-transplantation patients. In both scenarios, a certain percentage of patients will obtain no benefit from a given drug, or will experience serious adverse effects. Thus, there are two general goals for the clinical application of pharmacogenetics; the ability to predict those patients at high risk of toxicity (and in whom a lower dose or a different drug would be administered) and the ability to predict those patients who are most likely to obtain the desired therapeutic effect from the drug.

Prediction of toxicity risk or beneficial effects could be helpful in numerous ways. Much of the drug metabolism pharmacogenetics literature focuses on reducing toxicity through identification of those patients at risk of toxicity owing to excessively high plasma or tissue drug concentrations. In this situation, toxicity can often be avoided through a reduction in drug dose.

Although reducing pharmacokinetic-related toxicities through pharmacogenetics is currently possible in some situations, reducing toxicities that are not predictably related to drug concentration might be more challenging. These so-called idiosyncratic toxicities are rare but often serious. Examples include drug-induced Torsades de Pointes (TdP), hepatotoxicity, rhabdomyolysis and agranulocytosis. Efforts are currently underway to identify the genetic basis of several of these types of toxicity, yet this might ultimately prove to be the most challenging area in which to use pharmacogenetic information. This is because the drugs causing these types of toxicities with any frequency are not approved for use (or are withdrawn from the market). Because, these toxicities are rare, it is a daunting challenge to
Research in this area is complicated by the low numbers of patients who have experienced TdP. Investigators have therefore established an international registry to which physicians can submit information relating to those patients who have experienced drug-induced TdP or QT prolongation (http://www.arizonacert.org/medical-pros/qt-registry/index.html). It is hoped that sufficient numbers of patients might be accrued to enable identification of genetic and other risk factors. Many researchers, particularly in the pharmaceutical industry, have great hope that pharmacogenetics will provide a way to help avoid rare but serious drug toxicities such as TdP [11,12]. However, the reality of using pharmacogenetic information in this area seems very far in the future.

The other area in which pharmacogenetics might be of benefit is in predicting those patients most likely to experience the desired therapeutic effect from the drug under consideration. For patients with diseases treated by a trial and error method, this would have several potential benefits, including a shorter time period in which their disease state is poorly controlled or uncontrolled, a decreased risk of negative outcomes that might occur if accrue sufficient numbers of patients who have experienced the toxicity.

Drug-induced TdP is one example of a serious toxicity for which predictive pharmacogenetic testing could be highly beneficial. Drug-induced TdP is a life-threatening ventricular arrhythmia that results from drug-induced changes in ventricular repolarization, evidenced by prolongation of the QT interval on the electrocardiogram. This serious, life-threatening adverse effect has been the serious drug toxicities such as TdP [11,12]. However, the potential for identifying predictive polymorphisms for use in screening (for the purposes of withholding drug therapy in the identified high-risk patients) is difficult to envision. Research in this area is complicated by the low numbers of patients who ever experience TdP. Investigators have therefore established an international registry to which physicians can submit information relating to those patients who have experienced drug-induced TdP or QT prolongation (http://www.arizonacert.org/medical-pros/qt-registry/index.html). It is hoped that sufficient numbers of patients might be accrued to enable identification of genetic and other risk factors. Many researchers, particularly in the pharmaceutical industry, have great hope that pharmacogenetics will provide a way to help avoid rare but serious drug toxicities such as TdP [11,12]. However, the reality of using pharmacogenetic information in this area seems very far in the future.

The other area in which pharmacogenetics might be of benefit is in predicting those patients most likely to experience the desired therapeutic effect from the drug under consideration. For patients with diseases treated by a trial and error method, this would have several potential benefits, including a shorter time period in which their disease state is poorly controlled or uncontrolled, a decreased risk of negative outcomes that might occur if

Table 1. Representative examples of genetic associations with drug response, drug toxicity or drug PK

<table>
<thead>
<tr>
<th>Gene*</th>
<th>Polymorphism</th>
<th>Minor allele frequency**</th>
<th>Drug(s)</th>
<th>Genetic association</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug metabolizing enzymes</strong>&lt;br/&gt;TPMT</td>
<td>Multiple</td>
<td>0.3% of Caucasian population carry two nonfunctional alleles</td>
<td>Thiopurines</td>
<td>Hematological toxicities</td>
<td>[19–22]</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Multiple</td>
<td>1–2% of Asians and African descent and 6–8% of Caucasians carry two nonfunctional alleles</td>
<td>Numerous cardiovascular drugs, antidepressants, antipsychotics</td>
<td>Enhanced drug effect and increased toxicity</td>
<td>[19,23–25]</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*2 (Arg144Cys) and *3 (Ile359Leu)</td>
<td>0.02–0.10 and 0.02–0.08</td>
<td>Warfarin</td>
<td>Decreased drug efficacy</td>
<td>[26,27]</td>
</tr>
<tr>
<td>Drug Transporter&lt;br/&gt;ABCBI</td>
<td>3435C→T (Ile1145Ile)</td>
<td>0.10–0.50</td>
<td>Numerous, including anticonvulsants, protease inhibitors, digoxin and others</td>
<td>Differences in plasma drug concentration and efficacy</td>
<td>[3,31–34]</td>
</tr>
<tr>
<td><strong>Drug-targets or pharmacological response proteins</strong>&lt;br/&gt;ADRB1</td>
<td>Ser49Gly</td>
<td>0.15–0.30</td>
<td>β-blockers</td>
<td>Blood pressure lowering by β-blockers</td>
<td>[35,36]</td>
</tr>
<tr>
<td></td>
<td>Arg389Gly</td>
<td>0.25–0.47</td>
<td>β-agonists</td>
<td>Bronchodilation and cardiovascular responses to β-agonists</td>
<td>[37,38]</td>
</tr>
<tr>
<td>ADRB2</td>
<td>Arg16Gly</td>
<td>0.41–0.54</td>
<td>β-agonists</td>
<td>Bronchodilation and cardiovascular responses to β-agonists</td>
<td>[39–41]</td>
</tr>
<tr>
<td>DRD3</td>
<td>Ser9Gly</td>
<td>0.30–0.70</td>
<td>Antipsychotics</td>
<td>Differential antipsychotic efficacy, antipsychotic-induced tardive dyskinesia and acute akathisia</td>
<td>[39–41]</td>
</tr>
<tr>
<td>ADD1</td>
<td>Gly460Trp</td>
<td>0.06–0.60</td>
<td>Diuretics</td>
<td>Differential antihypertensive response and differences in degree of reduction in risk for myocardial infarction and stroke in hypertensives</td>
<td>[42–44]</td>
</tr>
<tr>
<td>GNB3</td>
<td>C825T (creates splice variant)</td>
<td>0.32–0.76</td>
<td>Diuretics, antidepressants</td>
<td>Differential drug efficacy</td>
<td>[45,46]</td>
</tr>
<tr>
<td>APOE</td>
<td>c2 Cys130 and Cys176</td>
<td>0.04–0.16</td>
<td>Tacrine, statins</td>
<td>Differential drug efficacy</td>
<td>[47–49]</td>
</tr>
<tr>
<td></td>
<td>c3 Cys130 and Arg176</td>
<td>0.60–0.85</td>
<td>Diuretics</td>
<td>Differential drug efficacy</td>
<td>[47–49]</td>
</tr>
<tr>
<td></td>
<td>c4 Arg130 and Arg176</td>
<td>0.09–0.25</td>
<td>Differential drug efficacy</td>
<td>[47–49]</td>
<td></td>
</tr>
<tr>
<td>F5</td>
<td>Arg506Gln (Factor V Leiden)</td>
<td>Absent to 0.04</td>
<td>Estrogen, oral contraceptives</td>
<td>Increased venous thromboembolism risk</td>
<td>[50,51]</td>
</tr>
</tbody>
</table>

*The genes and the proteins they encode are listed: ABCB1, P-glycoprotein; ADD1, α-adducin; ADRB1, β₁-adrenoceptor; ADRB2, β₂-adrenoceptor; APOE, apolipoprotein E; CYP2D6, cytochrome P450 2D6; CYP2C9, cytochrome P450 2C9; DRD3, dopamine receptor D3; F5, Factor V; GNB3, G-protein α3; TPMT, thiopurine S-methyltransferase.

**Minor allele frequency differs by race for each example in the table.
the disease is not controlled (e.g. suicide in depressed patients), fewer visits to a doctor because an effective therapy would be identified earlier, and a reduction in healthcare costs resulting from all of these factors.

For those treated by the per protocol approach, pharmacogenetic testing to identify patients likely to be nonresponders would help avoid the use of ineffective drug therapies. This would circumvent the attendant toxicities and reduce the healthcare costs resulting from these, as well as, reduce the costs associated with administering the drug.

The pharmaceutical industry is also using pharmacogenetic information with increasing frequency to streamline efforts and reduce costs during both drug discovery and drug development [5,13]. However, a discussion of the use of pharmacogenetics within the pharmaceutical industry is beyond the scope of this article.

Current status of pharmacogenetic testing in the clinical setting

Figure 2 and the previous discussion highlights the potential clinical benefits associated with the use of genetic information in drug therapy decision-making. How close this paradigm is to reality depends on the example one considers. In the case of thiopurine S-methyltransferase (TPMT), there is a Clinical Laboratory Improvement Act-certified test available (http://www.prometheuslabs.com) and clinical use of this test is increasing as physicians become more aware of the benefits of genotyping before treating patients with thiopurines. Additionally, the FDA-approved product labeling for azathioprine (Imuran®, http://www.prometheuslabs.com) indicates that prospective TPMT genotyping might help identify those patients at risk of hematological toxicities. This is an example where there is enough evidence to warrant genotyping in the clinical setting, and mechanisms for doing so are in place.

Roche Diagnostics (http://www.roche-diagnostics.com/) also recently announced the availability of a cytochrome P450 microarray-based kit that tests for numerous polymorphisms in the genes encoding the cytochrome P450 isoforms CYP2D6 and CYP2C19. Although these enzymes contribute to the metabolism of a large number of drugs, the situations where prospective genotyping of CYP2D6 or CYP2C19 would be clearly beneficial are limited, and additional research is required to identify circumstances where prospective genotyping is most warranted. Interestingly, the value of CYP2D6 genotyping is likely to decrease over time, as many pharmaceutical manufacturers will no longer pursue a compound whose primary metabolism is via CYP2D6. These three examples are the only pharmacogenetic tests that are commercially available.

In order for a pharmacogenetic test to be useful clinically, there must be enough evidence that the genetic information has sufficient predictive value to provide meaningful information to clinicians. In most cases, this is not yet the case. There seems to be two major reasons why genotyping of certain drug metabolism polymorphisms has reached the point of clinical utility, whereas the genotyping other pharmacogenetic markers has not, namely:

(i) the type of mutation; and (ii) the relative contribution of the protein in question to the PK or action of the drug.

TPMT, CYP2D6 and CYP2C19 are all highly polymorphic genes, for which certain polymorphisms represent inactivating mutations. Therefore, those who are homozygous for these mutations have little to no drug metabolizing capability through that enzyme, and are typically called poor metabolizers. PK are markedly different on the basis of genotype (e.g. concentrations of the drug that are five to tenfold higher for poor metabolizers) for those drugs whose metabolism is predominantly (i.e. >50–70% of overall elimination) through one of these enzymes. Although elevated drug concentrations in this setting are highly predictable, they do not always translate into problems in the clinical setting. It is where the pharmacokinetic differences lead to clinical problems (e.g. prodrugs and narrow therapeutic index drugs) that there is current clinical utility for pharmacogenetic testing. In these situations these drug metabolism examples are comparable to monogenic diseases, where single gene mutation can have a serious effect. By contrast, most of the PK and drug action pharmacogenetic examples have polymorphisms with less dramatic functional consequences for the protein, [e.g. nonsynonymous or promoter single nucleotide polymorphisms (SNPs)] and/or the protein in question is one of many that influence the PK or action of the drug. Individuals who are poor metabolizers will have only slight elevations in drug concentration if the enzyme in question accounts for a small percentage (e.g. 20% as opposed to 70%) of the metabolism of the drug. Thus, the profound effect on enzyme function imparted by an inactivating mutation has minimal consequences on drug PK because there are other enzymes that contribute importantly to the metabolism of the drug.

Similarly, the pharmacological effects of drugs are almost universally mediated through multiple proteins and signaling cascades. This is highlighted in Figure 3, which shows a simplified schematic of the signal transduction cascade for G-protein-coupled receptors that couple to $\alpha_4$ [e.g. $\beta$-adrenoceptors, ($\beta$-ARs)]. Although the drug might only bind to the receptor, there are numerous proteins involved in transducing the effect of the drug, with signal transduction cascades for many drugs being even more complex than that shown in Figure 3. Sequence variability in the genes for any of the downstream proteins might contribute to variable drug response. In addition, proteins involved in the physiology or pathophysiology of the system, but not directly in the signal transduction cascade, might also have genetic variability that contributes to variable drug response. Therefore, it seems likely that for most drugs, pharmacogenetics has the greatest potential to be clinically useful if information on multiple genes is used to predict efficacy or risk of toxicity. In this context, the pharmacogenetics of most drugs is likely to be comparable to the genetics of common complex diseases. In both cases there are numerous proteins involved, and the genetic variability in each might contribute to the overall variability observed clinically.
Future directions in pharmacogenetics

The past ten years have provided substantial evidence that genetic polymorphisms in drug metabolizing enzymes, drug transporters and drug targets contribute to interpatient variability in drug efficacy and toxicity risk. An important goal for the next decade is to advance the field to the point that significantly more drugs might be individualized for patients based on their genetic information.

Figure 4 shows a pyramid of the steps required to help move from knowledge of sequence variability to providing data that would support use of pharmacogenetic information in the clinical setting. One challenge for the future lies in documenting enough of the drug response variability to make the genetic information clinically predictive. In some cases this might only require information on a few polymorphisms or genes, in others it might require very complex studies that involve relatively large numbers of genes or a genomic-based approach.

The most logical multiple candidate gene approach is likely to take into consideration polymorphisms in genes for types of proteins highlighted in Figure 1. One example of a multigene pharmacogenetic approach was taken by Arranz et al. who studied the antipsychotic response to clozapine [14]. They analyzed 19 polymorphisms in ten genes and found that six of these polymorphisms provided 96% sensitivity and 76% positive predictive value for a positive response to clozapine.

Another, and perhaps ultimately more attractive approach is a genomic-based approach that does not rely on our understanding of the action of a drug. A SNP map approach is not feasible in most settings at present. However, it will become increasingly feasible as genotyping technologies become faster and cheaper, and data from the Haplotype Map (http://www.genome.gov/10001688) provide insights into the minimal number of SNPs to genotype to capture the bulk of the common sequence variability in the genome. In fact, it is believed by many...
that pharmacogenetics might be one of the first fruits of the Human Genome Project and Haplotype Map Project to reach clinical utility [15]. Microarray techniques using tissue samples are also a pharmacogenomic approach that is attractive where the relevant tissue for drug action is clear and easily accessible (e.g. cancers). However, in many situations, there are multiple tissues or organs involved in the drug response and/or the relevant tissue is not readily obtainable from subjects (e.g. brain and heart). Thus, a SNP-based genomic approach is likely to be more broadly applicable in pharmacogenetics.

Once studies have identified the constellation of genetic polymorphisms that best describe variable drug response, then studies can address whether pharmacogenetic-guided therapy is superior to more conventional approaches. Without this evidence, it will be difficult to justify the costs of pharmacogenetic testing and to convince clinicians to use pharmacogenetic testing to aid their clinical decision-making.

A number of challenges remain for clinical based pharmacogenomics to become a reality. Access to patient populations and clinical trials of adequate size will be required to provide sufficient power for pharmacogenomic studies. Addressing the adequacy of informed consent, privacy and future uses of the genetic samples are also areas where pharmacogenetic researchers must focus. There are also myriad ethical, social and legal considerations that are attendant to any type of genetic testing [16]. These fields need to keep in step with the scientific advances so that once the scientific data support wider use of pharmacogenetic information in the clinical setting, these nonscientific issues do not hinder the clinical approval process [17,18].

**Summary**

Data documenting genetic polymorphisms that contribute to variable drug response have expanded dramatically in the past decade. There is clear evidence that genetic polymorphisms in drug metabolizing enzymes contribute to variable PK, and this is most dramatic for those patients who have inactivating mutations. There is also mounting evidence that sequence variability in the genes for drug transporters and drug targets contribute importantly to variable drug response. There is sufficiently strong evidence for a few drug metabolism examples, but most pharmacogenetic cases require additional research to bring them to the point of having sufficient predictive power. Although much work remains, it seems likely that in the future the decision to use an increasing number of drugs will be made on the basis of the patient’s genetic make-up.

**Acknowledgements**

This work was supported in part by: NIH grants R01 HL64691, K24 HL68834, U01 HL69758 and R01 HL64924 and a grant from Abbott Laboratories, Inc. I thank Drs Zineh and Langeree and Ms Miller for assistance with figure preparation.

**References**

CYP2D6 on the metabolism of codeine and its derivatives, hydrocodone and oxycodone. Anesth. Prog. 45, 154–156
43 Glorioso, N. et al. (1999) The role of alpha-adducin polymorphism in blood pressure and sodium handling regulation may not be excluded by a negative association study. Hypertension 34, 649–654

Editorial policy for Genome Analysis papers

The Trends in Genetics Genome Analysis section includes original observations concerning the function, organization and evolution of the human genome. All sequences used in the analysis must be available through GenBank. Although other articles in TIG are generally invited by the Editor, authors wishing to publish a Genome Analysis paper should send a synopsis of their proposed article directly to the Advisory Editor Dr E.V. Koonin at National Center for Biotechnology, NIH, Bethesda, MD 20894, USA (email: koonin@ncbi.nlm.nih.gov).

For further information, please contact:
The Editor, Trends in Genetics, Elsevier London, 84 Theobald’s Road, London, UK WC1X 8RR.
Tel: +44 (0)20 7611 4400; Fax: +44 (0)20 7611 4470; e-mail: tig@current-trends.com

http://tigs.trends.com