processing of the sample and completion of the drug trial or at some time prior to the deletion of the key/code linking clinical identifiers and genotypic data.[1]

Contact information

Information to enable subject contact with the researcher should be clearly indicated on the IC form. This will enable a study subject to obtain further information about the pharmacogenetic research objectives, ask questions regarding his/her rights and responsibilities as a participant, communicate about possible injury due to study activities, communicate about genetic results when available and if appropriate, and/or withdraw from the study. In all situations, the researcher or a designee, or in some circumstances the IRB/IEC should remain the primary contact(s) for the subject.

Options for communication and sharing of genetic results with subjects

Any expectations or plans for contact between the subject and the researcher or research sponsor to discuss genetic results or the implications of these results should be clearly described during the process of IC. These must be considered in the context of the specific circumstances of individual studies and the results of genetic assessments including inadvertent genetic discoveries with health implications. Research by pharmaceutical companies involving pharmacogenetic analysis is fundamentally different from genetic testing utilized by patients in the clinical setting, which is performed by accredited clinical laboratories. Typically, genetic testing involves pre- and post-testing discussions of results and their clinical implications by trained genetic counselors. Many factors may influence decisions to share results of pharmacogenetic studies with study subjects, including the standard operating procedures of the research sponsor, the robustness and clinical usefulness of the pharmacogenetic results, the ability of the researchers/sponsors to provide the appropriate counseling, and regional regulations and policy statements from bioethics bodies.

It is important to describe the intended types of pharmacogenetic results to be derived from a study and to inform the subject about the realistic expectations and health implications, if any, of these results. In many types of pharmacogenetic studies, overall results are derived from analysis of aggregate genetic data (ie, population analysis); interpretations of data may be generally applicable to populations but are not specifically applicable to individual subjects. In selected protocols, such as drug trials in which pharmacogenetic data are used as inclusion criteria, it may be possible or even a requirement to discuss individual results of direct interest and benefit to study subjects. However, results of hypothesis-testing pharmacogenetic studies generally should not be shared by sponsors/researchers when they are preliminary in nature, are of no direct medical relevance to the subject, or cannot be used to guide clinical management. Such clinical guidance would not be possible until identified pharmacogenetic markers of drug response were formally validated in confirmatory studies. Moreover, such exploratory pharmacogenetic studies are generally conducted in research laboratories that are less regulated and not in accredited laboratories as for registered genetic diagnostic tests.

The coding category of a genetic sample selected for a pharmacogenetic study dictates the options for future contact to discuss genetic results.[1] For example, contact is not possible for *anonymized* samples where the key linking clinical and genetic data has been destroyed or in situations where DNA samples are pooled, thus precluding analysis of individual genotypes. *Anonymous* sampling also prevents any future contacts concerning individual research results. In these situations, aggregate results from population studies may be shared with study subjects in the context of study summaries, published manuscripts or a website posted by the research sponsor summarizing major conclusions or implications of the study. The subject's physician may be in the best position thoughtfully to communicate these results as part of follow-up healthcare contacts. If this is true for a given study and circumstance, this responsibility of the subject's physician should be indicated in the IC form.

Sharing of unintended genetic results

Sensitive genetic information may be inadvertently revealed as a result of pharmacogenetic research. For example, it may be determined that a study subject is genetically at risk for a serious disorder or is unrelated to someone previously assumed to be a family member, even though such results were not intended outcomes of the study for which IC was sought. Comparable issues are present with respect to unintended results in non-genetic studies as with the pharmacogenetic results described above, ie, the quality and veracity of individual research results and need for appropriate clinical context for result sharing *vs* the need for and benefit of disclosure of information to the subject. It should be noted that publically available commercial testing exists for questions concerning monogenic traits; these can be freely accessed by most subjects in an appropriate clinical context outside of the clinical trial. This therefore is the optimal source of genetic testing for individuals seeking such information. Some regional guidelines/laws in fact protect against such disclosures of genetic results,[16] whereas others encourage/require the sharing of genetic results in situations where such information will (or may) favorably impact the quality of life or allow preventative or therapeutic health care.[2,17] The circumstances requiring disclosure of unintended genetic results including respect for a subject's 'right not to know' must be carefully considered by weighing possible health benefits to the study subject and/or family members against possible informational risks (see the next subsection) implicit in such disclosures.

Risks and Benefits

In conventional trials of investigational drug candidates, the risks and benefits to study subjects are primarily related to the adverse or therapeutic effects of drug exposure. The perception of additional and unique potential risks and benefits associated with conduct of pharmacogenetic studies deserves consideration at the time of IC. Foremost among the potential risks is that of genetic discrimination based solely on public perceptions and societal sensitivities. At the same time, pharmacogenetic studies may offer important and unique benefits, primarily opportunities to define the molecular-genetic basis of variable drug responses. In turn, such information may lead to the development of safer and more efficacious drug regimens and predictive diagnostic tests for medical care. The IC process must convey the relative risks and benefits within the context of these considerations as well as the scientific design and expectations of a pharmacogenetic study.

Risks

As a point of reference, for clinical research that is subject to federal regulation, the United States Code of Federal Regulations dictates that those risks of any magnitude (ie, greater than the risks of everyday life) require warning about the potential for harm.[14] Physical risks associated with the collection of pharmacogenetic samples (sampling of blood, buccal mucosa, or other tissue samples) are not unlike those for other types of clinical research and include adverse events associated with study procedures. The medical risks associated with pharmacogenetic sample donation are generally considered to be low, since donation most often requires phlebotomy or buccal swabbing. In contrast, an issue generally perceived to be of major relevance for clinical genetic research is the possibility of informational risks associated with intentional or inadvertent disclosure of genetic data to third parties (or to study subjects themselves). These perceived risks may pertain not only to the study subject, but also to the close relatives and, in some cases, to the community or ethnic group to which the subject belongs. The IC process should address these risks or concerns and describe the means by which study subjects are protected against such risks, even if these are minimal.

Current societal concerns of informational risk are based in large part on early experience and knowledge of the pathologic significance of genetic tests predicting monogenic traits.[18] These risks may include psychological injury, psychosocial stigma, adverse impact on family relationships, and the potential for insurance or employment discrimination. Some writers have suggested that there is a need for expanded standards of disclosure in IC for human genetic studies beyond the minimal requirements embodied in the US Federal Code of Regulations for the past 20 years.[10,19] Among the most influential documents signalling a new standard for disclosure in genetic research over the past decade was the OPRR publication in 1993 of Protecting Human Research Subjects: Institutional Review Board Guidebook.[20] Its widespread distribution to IRBs throughout the United States has raised awareness about genetic discrimination that may negatively impact the approval and conduct of pharmacogenetic research sponsored by pharmaceutical companies.

In contrast to the research and diagnostic testing associated with known serious genetic disorders, pharmacogenetic research is not generally associated with high informational risk, as the information generated is limited to the genetic basis of a response to a drug. While the overall risks may be low, these are not negligible in all cases. For example, a defined genetic marker for drug response may be of clinical significance (with health implications) if also shown to be linked to risk for a disease, especially if effective therapies for the disorder do not currently exist. Moreover, it is conceivable that knowledge about differential likelihood to respond, or to react adversely to treatment could be used by insurers in the assessment of overall underwriting risks. As is true for other (non-genetic) clinical investigations, pharmacogenetic studies may involve laboratory or clinical information of high or low sensitivity depending on the specific study. In individual protocols and IC forms, it is desirable to include specific statements, as the risks/implications vary substantially depending on the actual study objectives.

In some instances, procedures dictated by protocol design may lessen or attempt to eliminate the informational risks. Among these are the pooling of samples or data before analysis, eliminating the link between subject identity and genotype results, as with *anonymized* samples, or instituting protocol-specific procedures that may protect subject confidentiality. A further strategy may be to avoid recording both patient participation and research data in permanent medical notes, thereby protecting against access by those outside the research team. Where applicable, these safeguards should be outlined in the IC form or explained to the subject.

Benefits

A wide range of potential benefits to the biomedical research community and to future patient populations is possible through pharmacogenetic research. However, most pharmacogenetic trials are exploratory in nature and are designed to generate or test specific hypotheses about possible genotype–phenotype relationships. As such, they are not likely to provide direct benefits to study subjects such as benefits expected from use of a highly predictive and marketed genetic diagnostic tests (potentially developed in the future). This reality should be clearly stated during IC.[18] Nonetheless, subjects volunteering for such studies should be informed that their specific genetic results may eventually be beneficial to the research and medical community, and may lead to the discovery and development of new drugs or better outcomes for existing drugs. Any anticipated clinical benefits conveyed during the IC process should make reference to the actual status of genetic research and knowledge, and should convey a realistic expectation of the time interval after which new pharmacogenetic data may

meaningfully alter clinical practice. The full potential to derive pharmacogenetic benefits from specific trials and sample sets may be possible only if IC is given that allows broad pharmacogenetic analyses based on studies employing markers representing the full breadth of the human genome, or based on new knowledge or hypotheses generated in the future. This is not possible when analyses are limited to specified genes (see the section 'Purpose(s) and Intent of Pharmacogenetic Studies'). Proposals for reconsent prior to each analysis are logistically difficult, and in some cases impossible, particularly if consent is to be sought years afterwards when both subjects and physicians are no longer accessible.

A clinically relevant genetic marker defined in exploratory studies, validated in independent studies (for example, using validated CLIA or GLP specifications), and then used in subsequent pharmacogenetic trials may be of direct benefit to subjects. For example, it may be possible to shift the risk–benefit ratio for a given subject by selecting an optimal (safer) dosing regimen based on specific genotypic markers. An approved and marketed genetic diagnostic formally derived from such studies would eventually be of direct benefit to future recipients of drugs when used in conjunction with genetic diagnostic information. The potential benefits of applying a predictive genetic marker will depend on the correctness of the pharmacogenetic hypothesis, the nature and strength of associations defined, the genetic profile of the subject, and the relative unmet medical needs being addressed. Numerous beneficial applications are possible including opportunities to use knowledge of metabolism gene variants to optimize dosing regimens for diverse classes of drugs, thereby enhancing therapeutic efficacy or diminishing adverse events associated with exposure in defined subpopulations.

Confidentiality of Subject Information

Concern for informational risks were drivers of the *Standards for Privacy of Individually Identifiable Health Information*,[21] the EU Data Protection Directive,[22] and other regional or international policy statements or guidelines for safeguarding the privacy of healthcare data.[17] The provisions of these regulations, policy statements, and guidelines differ, but IRBs/IECs are generally now charged with determining whether researchers and research sponsors have taken adequate steps to safeguard genetic information and with evaluating plans for data security. These methods include various coding mechanisms and other procedures designed to insure that genetic information from pharmacogenetic trials is appropriately protected, disclosed and utilized.[17] Those selected for each study should be described (in understandable language) during the IC process.

To enable IRBs/IECs as well as study subjects to understand the level of confidentiality provided, the nature and scope of pharmacogenetic research to be carried out must be clearly defined. The intended uses of samples for analyses of drug-specific genetic associations and/or disease-specific genetic analysis should be described. IRBs/IECs may favor more selective genetic objectives focused on the collection of data concerning a single or limited number of genes, in contrast to broad objectives such as unspecified analyses of all genes (for example, genome-wide scan approach) which may be associated with generation of more data points and hence greater risks including opportunities for inadvertent genetic discoveries. Defined short-term objectives together with timelines for destruction of genetic materials are often considered to provide more certainty of adequate protection.

However, it seems clear that the most important component of subject's privacy protection is rigorous attention by the researcher and research sponsor to data protection SOPs. These procedures should provide well thought-out plans for the handling of subject's withdrawal of specimen, the use of database firewalls, internal stringent data access control, consent for secondary use of samples in additional genetic studies, plans for archiving or destruction of pharmacogenetic samples, and possible options, if any, for future contact with study subjects to discuss genetic results or participation in future studies. Disclosure of these plans should allow both subjects and IRBs/IECs to adequately assess the overall level of confidentiality provided.

The research sponsor/researcher has a responsibility to limit access to genetic data, equally important as their responsibility to limit access to clinical data. The IC process should define those who will have access to genetic data and the conditions under which data access is possible during and after completion of the study. Supplemental materials describing how the current data security systems limit access to subjects' data may be helpful when provided to IRBs/IECs to assist in their ascertainment of the level of data protection. The subject should understand that no disclosures of genetic information are authorized outside of those stipulated during IC or in the research sponsor/researcher's standard operating procedures. For circumstances in which data access by health or regulatory authorities may be required (for example, during study audits), the possibility of government record audits and the procedures by which confidentiality will be maintained should be described. Audit trails may be employed within the research sponsor/researcher's organization as a further safeguard of healthcare data by identifying those who actually have had access to the database.

Coding mechanisms are widely employed to protect subject confidentiality in the conduct of clinical genetic research.[17] Research sponsors/researchers must be able to demonstrate to IRBs/IECs that they possess sufficient expertise and have procedures in place adequately to protect data. Recently defined categories of genetic sample collection afford various levels of security in pharmacogenetic studies based on a spectrum of coding procedures.[1] *Identified* samples carry the highest potential for inappropriate disclosure because there are no additional safeguards ensuring data confidentiality beyond those generally

applied to the remainder of a subject's medical records. Data generated from *coded* samples are processed in a manner analogous to that of other medical or laboratory data collected in clinical trials. The widespread use of *coded* clinical and laboratory data in clinical trial conduct has demonstrated an excellent track record in protecting subject confidentiality.

The risk that genetic data may become part of the study subject's permanent medical record is substantially reduced by the use of *de-identified/double-coded* samples.[1] *De-identification* requires rigorous procedures dictating the handling of coded genotypic and clinical information; greater confidentiality is achieved by limiting access to the coding keys of databases to a trusted/secure third party, either within or outside the sponsoring entity, thereby significantly reducing the likelihood of inadvertent or unintended disclosure of data to any party including study subjects and researchers. Even these safeguards can be overcome under certain conditions, such as when directed by a subpoena from a court of law or government authority. In the United States, laws/policies have been established to protect against such disclosures for certain types of research[16] and to protect against genetic discrimination based on disability status.[23] Use of *coded* or *de-identified/double-coded* samples is necessary in those trials in which pharmacogenetic analyses and data represent a pivotal part of the drug's registration and label information. These categories allow for the possibility of regulatory audits, which may request decoding of datasets for analysis of an individual's genetic data. *Anonymized* or *anonymous* sample categories offer an alternative approach for genetic data security, but these sample categories cannot be selected for registration trials or for studies requiring recontact with subjects.[1]

COMMERCIALIZATION

Clinical research sponsored by pharmaceutical companies or other private entities and some academic institutions, has commercial as well as scientific objectives. In the IC process associated with pharmacogenetic studies, the prospective subject should be informed that the contribution of his/her pharmacogenetic sample might result in commercial gains or intellectual property for the sponsoring pharmaceutical company (who should be named) or other designated parties. This may eventually result in the development of a pharmacogenetic diagnostic test, the approval of a new drug, the acquisition of intellectual property based on genetic discoveries, and/or the transfer of genetic materials to third parties.[24] Subjects should be informed if other parties may derive direct economic benefit from the study, and importantly, whether they will or will not share in financial gain as individuals. A disclosure of the researcher's financial interest or affiliation with a research sponsor should be provided, regardless of how clinical samples are obtained or the level of confidentiality that is assigned to them.

An explanation of these issues may be beneficial as part of the IC process. For example, it could be explained that any genetic discoveries or commercial products derived from a study would require the collective contributions of many genetic samples as well as the long-term resource commitments of the sponsor. The subject may disagree with any rationale obviating his/her opportunities for financial gain and choose not to participate in the study, but is nonetheless able to make this decision based upon clear disclosures in the IC process. It can be emphasized to the subject that while individual economic benefits may not be possible, a sharing of benefits with the community may be possible (and is intended) through the development of novel drugs or tests eventually to be derived from new genetic knowledge.

Disclosing commercial objectives in the IC process for pharmacogenetic research is a transparent and honest approach and allows study subjects to make an informed choice as to whether to contribute genetic materials. Although this has sometimes been regarded as exculpatory,[25] this wrongly assumes that subjects have a 'right' to remuneration. This issue is not one of 'rights' but of providing a clear and unequivocal basis for subjects to make a knowing and informed choice. This is consistent with the United Kingdom Medical Research Council guidance document stating that the subject needs to understand that he/she is making a donation of the sample for use in research and be informed as to who will be responsible for the custodianship of the sample.[4] Each sponsor of pharmacogenetic research may need to develop internal standards or policies to address commercial issues after consultation with legal representatives. However, a harmonized approach used by researchers, research sponsors, and IRBs/IECs is desirable to facilitate the approval of this research.

Compensation

The process of informed consent for pharmacogenetic research should distinguish the issues of compensation associated with the reimbursement of expenses incurred by subjects who participate in a study from those issues of financial compensation that would be an inducement for subjects to participate in pharmacogenetic research. In general, guidance at the international and national level permits payment for the reimbursement of reasonable expenses or costs (ie, parking, transportation, childcare, and missed work hours) involved in clinical research including genetic research (MRC Guidelines, HUGO). The remuneration of these expenses should be fair and reasonable. Likewise, it is important to indicate the type and amount (where possible) of reimbursement or to indicate if there will be no reimbursement of expenses.

As for investigational drug trials, it is generally considered unacceptable to provide financial compensation to induce research subjects to participate in pharmacogenetic studies. Guidance policies of many international, regional or national ethical–legal bodies prohibit payment for human genetic samples (reviewed by Knoppers *et al* co-workers[17,24]). Selected policy positions maintain that the human genome is 'common heritage of humanity' and not 'personal property'

and that human genetic materials are part of the 'person' (*vs* 'property'), which may only be shared as a 'gift' for research purposes. 'This principle of non-commercialization traces back to the concept of the inherent dignity of the human person and the human body as sacred and distinct from things that can be bought and sold in the marketplace'.[24]

The Ethics Committee of The Human Genome Organization in its *Statement on the Principled Conduct of Genetic Research* contends, 'inducement through compensation for individual participants, families or populations should be prohibited'.[26] The 1997 version of the UNESCO Declaration mandates that 'the human genome in its natural state shall not give rise to financial gain'.[27] Other ethical–legal policies share the opinion that (individual) financial benefit represents 'an inducement which compromises free consent'.[23,28,29]

The process of IC for pharmacogenetic research should take into consideration these fundamental issues and policy positions. In the context of multinational drug trials with pharmacogenetic objectives, it is probable that no common approach/language will permit the approval and implementation of all studies in all regions or countries. In defining appropriate IC language for individual studies, research sponsors must work together with IRBs/IECs to ensure study approvals while at the same time complying with regional attitudes or laws. For example, in the United States, financial reimbursement of subjects involved in pharmacogenetic as well as other types of clinical research is an accepted practice. This is typically for 'out of pocket' expenses such as travel and/or to remunerate subjects for their personal time and inconvenience of participation in the research trial; these remunerations typically vary depending on the amount of time and nature of procedures involved. If subject compensation is allowed by IRB/IEC approval, the amount and form of compensation should be recorded in the IC form. If prohibited by regional policies, laws or attitudes, the IC language should clearly indicate that study subjects will not be financially or otherwise compensated for their participation.

CONCLUSIONS

Creating an understandable IC form and an effective process for communication of disclosures for pharmacogenetic research that includes the necessary and often complex information and accurately addresses the potential benefits, risks, and procedures is challenging. Study subjects are generally concerned about how their confidentiality will be maintained and how their samples will be used. Some important or unique considerations for pharmacogenetic trials include: unfamiliar terminology; study purpose that may be difficult for subjects to understand; perceived informational risks that may result in discrimination or psychological distress; potential societal benefits such as a better understanding of the underlying causes of variable drug response and discoveries of safer and more effective drugs; possible extended durations of genetic studies that far exceed the subject's participation (and that genetic research can continue indefinitely); potential commercial benefit that the sponsor may derive; and the issue of compensating study subjects. Only by assuring an appropriate IC process and document can subjects fully understand the implications of a decision to participate in pharmacogenetic research.

The 'points to consider' discussed in this communication are intended to highlight elements of pharmacogenetic research encountered by pharmaceutical companies that are of key relevance to the IC process and a subject's participation. It is important to re-emphasize that no rules are uniformly appropriate for all situations. Researchers and sponsors must independently consider in each case what is appropriate to ensure both valuable research and adequately informed subjects. IRBs/IECs and regulatory authorities should, among other factors, take into account the critical need for innovative healthcare research that extends across national and regional boundaries.

DUALITY OF INTEREST

None declared.

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Case Study

MR. HELIX is 45 years of age, and has high blood pressure and hardening of the arteries, or atherosclerosis. His physician has just read about a study involving a medicine that treats atherosclerosis. Results from the study show that patients who have a certain variation in their genetic code are helped by the medicine, while those with a different variation are not.

His physician suggested that a medicine response test be used to determine which variation of the gene he has and whether he is one of the individuals who can be helped by the medicine. If he is, then his physician can prescribe the right medicine for the right patient.

gsk GlaxoSmithKline

GSKCS-17493 4/01

STUDYING THE

genetics

OF MEDICINE RESPONSE

AT GLAXOSMITHKLINE

PHARMACOGENETICS

What WE DO ... AND *Why* WE DO IT

Incorporate pharmacogenetic research into GlaxoSmithKline clinical trials to help healthcare providers prescribe the right medicine for the right patient.

Researchers are beginning to understand how our genes affect the way our bodies respond to medicines. GlaxoSmithKline is incorporating pharmacogenetic research into clinical trials with the hope that this research will enable healthcare providers to more accurately prescribe the right medicine for the right patient.

Follow recommendations for conducting genetic research ethically.

Patient privacy and confidentiality are important to GlaxoSmithKline in all its clinical studies, including genetic research. The measures we have adopted incorporate the recommendations from the United Nations' "Universal Declaration on the Human Genome and Human Rights" and the Human Genome Organization's "Principled Conduct of Genetic Research" and were put in place after consultation with independent ethics experts.

Provide information on pharmacogenetic research and require informed consent.

We want patients to be aware of the risks and benefits of participating in pharmacogenetic research. To help the doctors who are conducting the clinical trials explain pharmacogenetic research to patients, we give them information to share with their patients. Patients must give written informed consent before participating in clinical trials and pharmacogenetic research.

Do not know patient names or identities.

The doctors conducting pharmacogenetic research collect blood samples and family histories from patients. The samples and medical information are labeled with a number (no names are used). The samples and patient information are valuable research tools for scientists. GlaxoSmithKline scientists do not not know – and do not want to know – patients' identities.

Extract DNA from blood samples.

Once scientists obtain DNA from the blood sample, it can be stored and studied.

Study DNA by using modern technologies.

Researchers may be able to classify patients' responses to medicines according to the differences they see in the DNA from many individuals from different populations.

Enter the DNA data and clinical study information into a computer.

DNA consists of 3 billion base pairs. Because GlaxoSmithKline is studying many thousands of these base pairs, scientists need computers to help them keep track of such a large amount of information.

Apply statistical analyses to the results.

Statistical analysis may tell us if different responses to medicines are the result of genetic variations in patients.

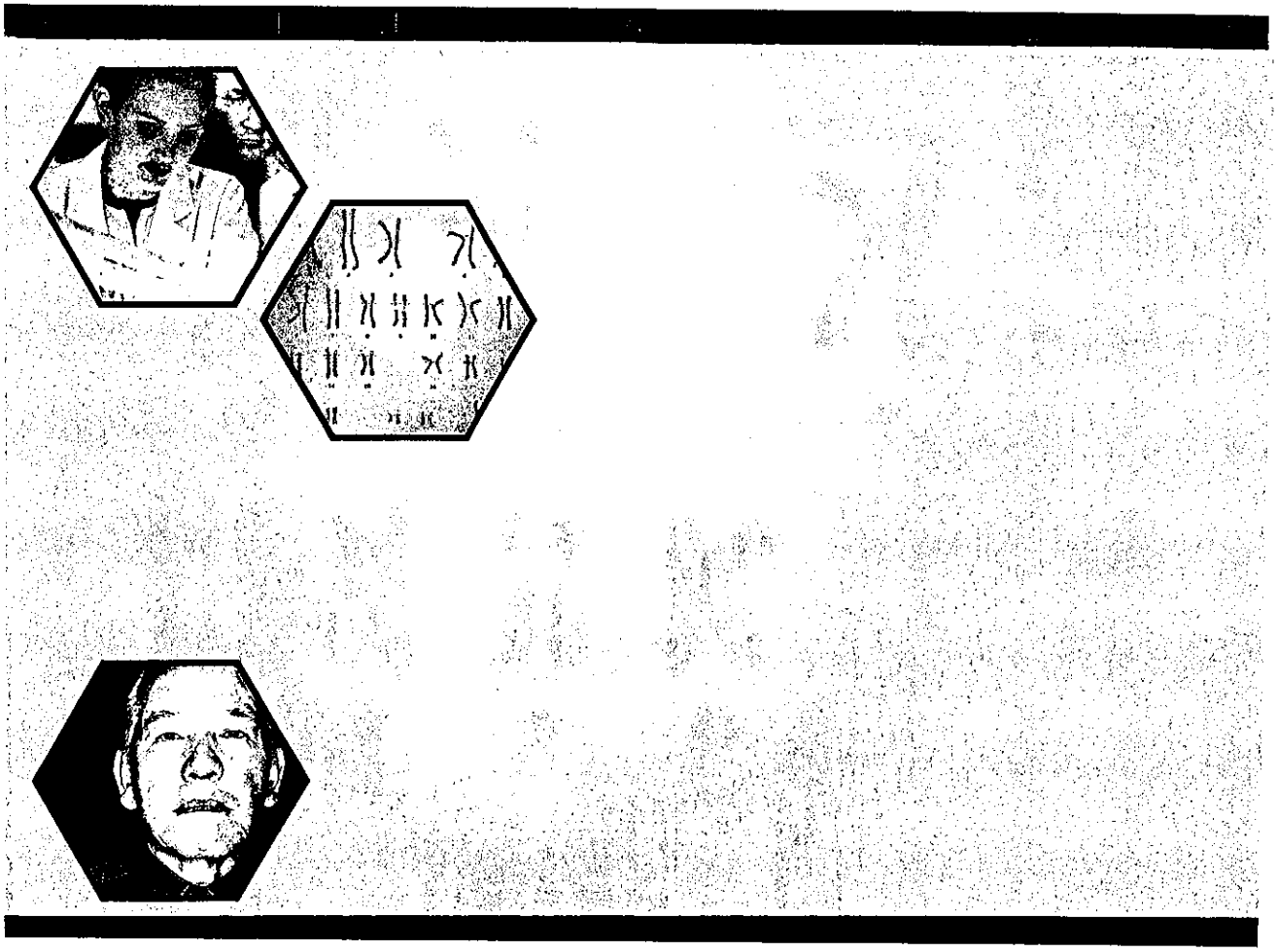
In the future, apply the findings of pharmacogenetic research to help develop new medicines and deliver them to those patients likely to benefit.

Our goal is to match the safety and effectiveness of our medicines with particular genetic variations so we can help doctors determine the right medicine for the right patient.

FINDING CLUES TO THE RIGHT MEDICINE FOR THE RIGHT PATIENT

The Genetic Connection

GlaxoSmithKline



Have you ever wondered why one medicine works for you with no side effects, but causes problems for other people? Researchers are trying to answer that question, and we hope you will be interested in helping. This brochure tells how you can participate in *pharmacogenetic* research, that is, research to help discover why people respond differently to the same medicines.

This research is sponsored by GlaxoSmithKline ("GSK"), a research-based pharmaceutical company that discovers new medicines. GSK is conducting an international program that will look for clues in people's genetic makeup to see if it is possible to predict who will benefit from a certain medicine and who will not. People who are already enrolled in one of our clinical studies (designed to test the effects of a particular drug) may also participate in this pharmacogenetic research.

We believe it is possible to learn why some people respond well to medicines, while others don't respond or have side effects. This information may then be used to help doctors choose the right medicine for the right patient. It will also be helpful in making new medicines for people who don't respond to current treatments.

THE GENETIC CONNECTION

WHAT WILL I HAVE TO DO?

If you decide to participate, here are the things you will be asked to do:

- Sign a consent form that explains the pharmacogenetic research being conducted in greater detail.
- Give a blood sample.

Depending on the study, you may also be asked to:

- Answer questions about your medical condition and history.
- Answer questions about your family's medical history.

WHY DO I NEED TO GIVE A BLOOD SAMPLE?

Your blood contains your DNA (deoxyribonucleic acid), the blueprint for your genetic makeup. The DNA in your genes determines your physical characteristics, everything from the colour of your eyes and hair, to your risk factors for disease, to how your body responds to different medicines.

We know that 99.9% of humans' genetic makeup is exactly the same from one person to another—that's why we all have basic features in common, such as two eyes, a nose, a mouth.

It's the other 0.1% of our genetic makeup—one tenth of one percent—that makes us different from each other. These differences come from the genes we inherited from our parents, and the way those genes interact with our environment, such as the diet, chemicals and air we are exposed to during our lifetime.

By studying the similarities, differences, and patterns in the DNA of many people, pharmacogenetic researchers hope to discover genetic factors that affect how people respond to medicines.

HOW WILL MY DECISION AFFECT MY PARTICIPATION IN THE CLINICAL STUDY?

Your participation in the clinical study is not affected by your decision about the pharmacogenetic research. You can still take part in the clinical study, even if you choose not to participate in the pharmacogenetic research.

WILL I NEED TO TAKE ANY EXTRA MEDICATION?

No. Participants in the pharmacogenetic research are not given any additional medication. You will take only the medication associated with the clinical study.

HOW WILL THE CONFIDENTIALITY OF MY INFORMATION BE PROTECTED?

To protect your confidentiality, your blood sample and medical information will be labeled with your study subject number, not your name. Such items are said to be "coded." Your study doctor will hold the link or the code to your sample and information.

Study doctors have been told to keep your informed consent for the pharmacogenetic research in a special, secure file, which is not part of your medical records.

In addition, GSK has instructed your study doctor not to include any record of your participation in this pharmacogenetic research in your medical records. Your medical records will not hold your individual pharmacogenetic results from this research. Your name will not appear in any publications or reports produced from this research.

Access to the results will be restricted to GSK employees, people working with GSK, and people who work for the government drug agencies that approve certain medications. We will not return any results to patients, study doctors, insurers, or employers unless required by law.

WILL I GET TO SEE THE RESULTS OF MY PHARMACOGENETIC RESEARCH?

No. We will not give pharmacogenetic results to anyone, including you, unless required by law. The aim of the research is to examine the genetic similarities, differences, and patterns of a large group of people. None of the research findings will be specific to treating your personal medical condition.

CAN I CHANGE MY MIND ABOUT PARTICIPATING IN THE PHARMACOGENETIC RESEARCH?

Yes. You may withdraw from the clinical study, the pharmacogenetic research, or both, at any time. If you withdraw from the clinical study, you can still remain in the pharmacogenetic research. If you withdraw from the pharmacogenetic research, you can still remain in the clinical study.

If you withdraw from the pharmacogenetic research, GSK will destroy your DNA sample, but will keep all the information collected up to that point.

WHAT ARE THE RISKS TO ME IF I PARTICIPATE IN PHARMACOGENETIC RESEARCH?

If you choose to participate in this pharmacogenetic research, the only *physical* risk to you will be the usual risk associated with taking a blood sample from a vein.

There is also the possibility of a *non-physical* risk to you: the risk that your individual pharmacogenetic results or other confidential information generated by this research will be disclosed inappropriately.

GSK has put policies and procedures in place to minimize the chances of such disclosure (see "How will the confidentiality of my information be protected"); however, GSK cannot guarantee that your individual pharmacogenetic results could never be linked to you.

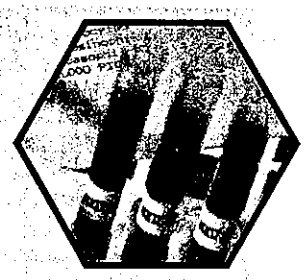
WHY WOULD I PARTICIPATE IN PHARMACOGENETIC RESEARCH?

You will not receive any direct benefits from participating in this pharmacogenetic research, but GSK may use the results to develop new and better medicines. Your decision to participate in pharmacogenetic research may help to deliver the right medicine for the right patient. Most patients who participate in clinical studies have the same interests as those of us at GSK: *We all want to help stop disease and develop better medicines.*

GSK MISSION STATEMENT

GlaxoSmithKline is committed to improving the quality of human life by enabling people to do more, feel better and live longer.

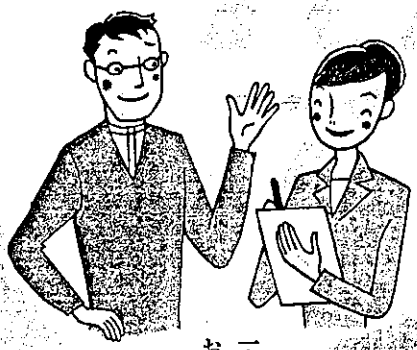
Visit us at *http://genetics.gsk.com*.



GlaxoSmithKline

遺伝子レベルで薬の手掛かりを探る

ファーマコジェネティクスについて



一人一人に最適な薬をお届けするために

gsk GlaxoSmithKline

一人一人に最適な薬を届けたい

ファーマコジェネティクスとは？

同じ薬でも、人によって、合う、合わないがあるのは何故でしょうか？その答えを遺伝子レベルで解明するため、ファーマコジェネティクス（薬理遺伝学）と呼ばれる研究が急速に進んでいます。ファーマコジェネティクス研究とは、患者さん一人一人により最適な薬をお届けしようとするものです。

研究成果は多くの人に期待されています

研究開発に基盤を置く製薬企業グラクソ・スミスクライン（GSK）では、それぞれの薬に合う人や合わない人を遺伝情報から予測するためのファーマコジェネティクス研究を国際的に進めています。その研究成果は、一人一人の患者さんに良く効き、副作用の少ない薬を処方するために利用されます。また、多くの患者さんに安心して使っていただく新薬の開発にも役立つものと期待されています。

そのためにあなたの力が必要です。

多くの方に参加いただくことを願います

臨床試験に参加いただいた方のうち、同意いただけた方にファーマコジェネティクス研究への参加をお願いしています。一人でも多くの方がこの趣旨に賛同され、参加を検討いただけることを願います。

このパンフレットでは、研究への参加を検討いただいている方々から寄せられる一般的な疑問点や質問に、主任研究員のあやがお答えしていきます。

主任研究員のあやです。よろしくお願いします。

Q1

ファーマコジェネティクス研究に参加するにはどのようにしたら良いのですか？

ファーマコジェネティクス研究へ参加いただく場合には、

- 参加する研究について詳しく説明した同意書に署名をしていただきます。
- 血液検体を採取させていただきます。

一人一人に最適な薬を届けたい。
そのためにあなたの力が必要です。

Q2

なぜ、血液検体を提供する必要があるのですか?

身体の特徴や体質、髪の色や病気のかかりやすさ、さまざまな薬に体がどのように反応するかまで、すべてDNA(デオキシリボ核酸)の塩基配列によって影響されます。私たちの遺伝情報の99.9%はすべての人間に共通していることが解っています。目が2つ、鼻が1つ、口が1つ、といった基本的な特徴が共通に備わっているのはこのためです。従って個人としての特徴は残りの0.1%、つまり1%のそのまた10分の1によって生み出されています。これは、両親から受け継いだ遺伝子と、これに食物、化学物質、空気などの環境要因が絡み合った結果なのです。
ファーマコジェネティクス研究は、多くの方々のDNAを比較した際に見られる一定の傾向を調べることで、薬の効き方に影響を与える遺伝要因を見出そうとするものです。血液にはその人のDNA、つまり遺伝情報が含まれています。そこで血液を提供していただくのです。

ファーマコジェネティクス研究は、病気へのかかりやすさや遺伝性疾患について調べるものではありません。

Q3

ファーマコジェネティクス研究に参加しないことが、臨床試験への参加に影響しますか?

影響されることはありません。
ファーマコジェネティクス研究への参加の有無に関わらず、GSKの臨床試験には参加いただけます。

Q4

ファーマコジェネティクス研究用に特別の薬を使うのですか?

ファーマコジェネティクス研究用に特別の薬を使うことはありません。すでに同意をいただいている臨床試験で予定されている薬のみです。

一人一人に最適な薬を届けたい。
そのためにあなたの力が必要です。

Q5

個人情報の保護体制はどのようになっているのですか?

血液検体や病歴などの個人情報は個人名ではなく、すべて特有の番号で管理されます。個人名を知るのは試験担当医等、医療カルテを見ることが許されている方のみです。

医療カルテに解析結果が収められることはありません。また、この研究から得られた結果を論文や出版物にする際にも、参加してくださった方の個人名が使われることは決してありません。

患者さん本人、試験担当医、保険会社、雇用先に個人の研究結果を知らせることはありません。ファーマコジェネティクス研究の個別の結果を見ることができるのは、薬の承認を行う政府当局担当者、研究に携わるGSKの社員、共同研究員に限られています。個別の研究結果は個人名でなく特有の番号で管理され、個人名への結びつけは行いません。

Q6

自分の研究結果は教えてもらえるのですか?

ファーマコジェネティクス研究の目的は、多くの方々の遺伝情報から集団としての一定の傾向などを調べることですが、残念ながら、すぐには個人の治療に役立つ情報が得られるものではありません。そこで、研究の結果は、参加してくださった本人を含め、どなたにもお知らせしません。

Q7

研究への参加を途中でやめることはできますか?

臨床試験、ファーマコジェネティクス研究のいずれも、自由に参加を取りやめることができます。臨床試験をやめて、ファーマコジェネティクス研究だけを続けることも、また、その逆もできます。

ファーマコジェネティクス研究への参加をやめた場合、参加してくださった方のDNAはGSKが責任を持って廃棄します。しかし、それまでに得られた解析結果はGSKの所有とし、その後の研究に継続して使わせていただきます。

一人一人に最適な薬を届けたい。
そのためにあなたの力が必要です。

Q8

参加にはどのようなリスクが伴うのですか?

身体に生じる可能性のあるリスクとしては、採血の際若干の痛みがあったり注射のあとが残ったりすることがあるかもしれませんが、ごく一般的な採血と何ら変わりません。もう一つのリスクは、個人情報が不正に漏洩するかもしれないという点が考えられますが、ファーマコジェネティクス研究で得られる結果には個人やそのご家族の遺伝疾患等に関する内容は含まれていませんし、GSKでは、不正な漏洩を防止するため、万全の体制を敷いています(「Q5:個人情報の保護体制はどうなっているのですか?」の項目をご覧ください)。

一人一人に最適な薬を届けたい。
そのためにあなたの力が必要です。

Q9

参加する意義は何ですか?

ファーマコジェネティクス研究は、参加してくださる方々に直ちに役に立ったり利益をもたらすものではありません。しかし、その研究成果はより良い新薬を開発し、一人一人に最適な薬をお届けする研究に役立っていくのです。

グラクソ・スミスクラインの使命

"生きる喜びを、もっと Do more, feel better, live longer"
グラクソ・スミスクラインは、より良い薬を創り病気をなくし、世界中の人々がより充実して心身ともに健康で長生きできるよう、生活の質の向上に全力を尽くすことを企業使命としています。

下記ホームページもご興味があればご覧ください(英語版)。
http://www.genetics.gsk.com

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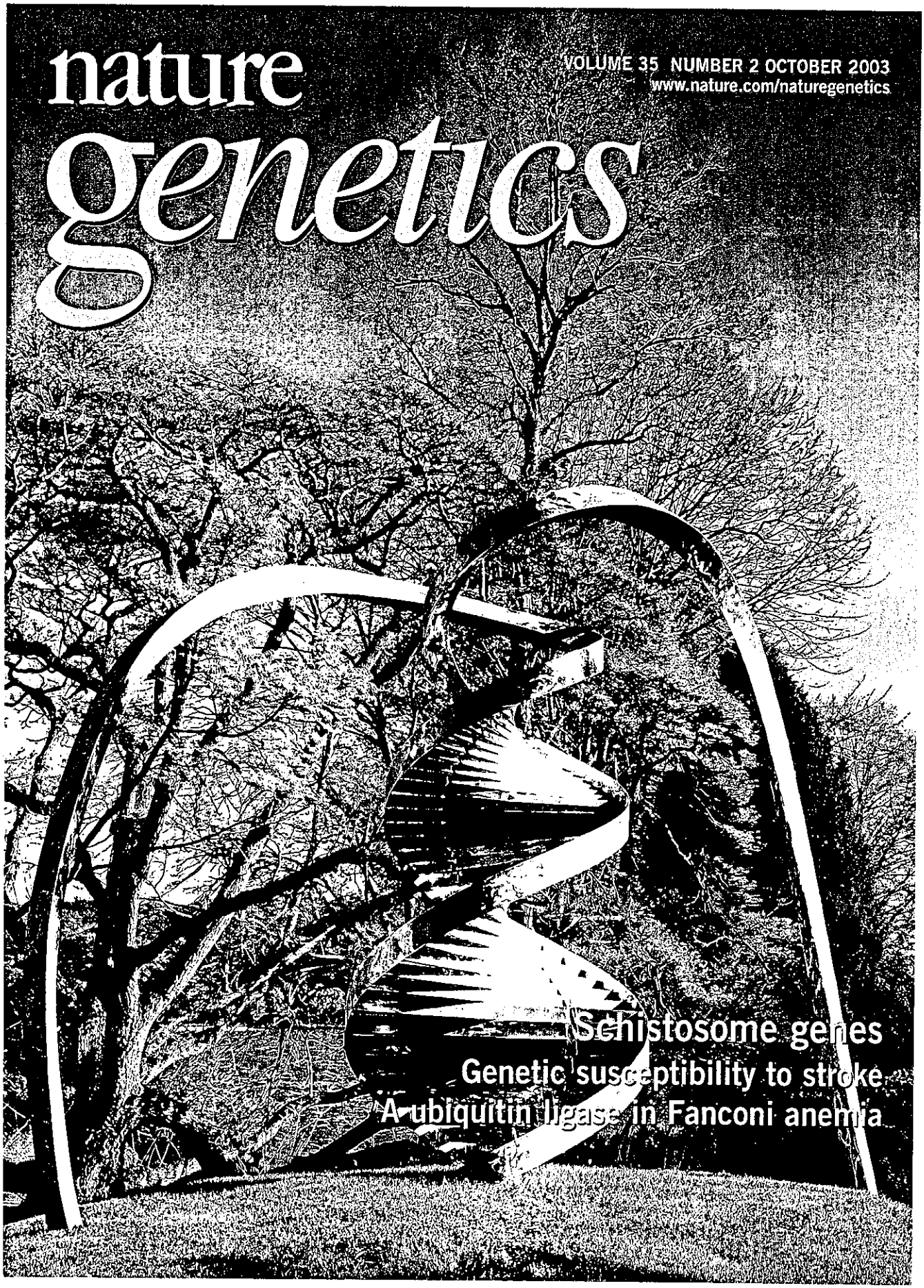

Schistosome genes

Genetic susceptibility to stroke

A ubiquitin ligase in Fanconi anemia

nature genetics

The gene encoding phosphodiesterase 4D confers risk of ischemic stroke

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We previously mapped susceptibility to stroke to chromosome 5q12. Here we finely mapped this locus and tested it for association with stroke. We found the strongest association in the gene encoding phosphodiesterase 4D (*PDE4D*), especially for carotid and cardiogenic stroke, the forms of stroke related to atherosclerosis. Notably, we found that haplotypes can be classified into three distinct groups: wild-type, at-risk and protective. We also observed a substantial disregulation of multiple *PDE4D* isoforms in affected individuals. We propose that *PDE4D* is involved in the pathogenesis of stroke, possibly through atherosclerosis, which is the primary pathological process underlying ischemic stroke.

Stroke is a common and serious disease; each year in the United States more than 600,000 individuals suffer a stroke and more than 160,000 die from stroke-related causes[1]. In western countries, stroke is the leading cause of severe disability and the third leading cause of death[2]. The clinical phenotype of stroke is complex but is broadly divided into ischemic (accounting for 80–90%) and hemorrhagic stroke (10–20%; ref. 3). Ischemic stroke is further subdivided into large vessel occlusive disease (herein referred to as carotid stroke) commonly due to atherosclerotic involvement of the common and internal carotid arteries; small vessel occlusive disease, thought to be a nonatherosclerotic narrowing of small end-arteries in the brain; and cardiogenic stroke due to blood clots arising from the heart typically on the background of atrial fibrillation or ischemic (atherosclerotic) heart disease[4,5]. Therefore, stroke does not seem to be one disease but rather a heterogeneous group of disorders reflecting differences in the pathogenic mechanisms[6,7]. All forms of stroke share risk factors, such as hypertension, diabetes, hyperlipidemia and smoking[1,8]. Family history of stroke is also an independent risk factor, suggesting the existence of genetic factors that may interact with environmental factors[7,9].

The genetic determinants of the common forms of stroke are still largely unknown. There are examples of mutations in specific genes that cause rare mendelian forms of stroke[10–16], but none of these occur on the background of atherosclerosis, and, therefore, the corresponding genes are probably not involved in the common forms of stroke, which most often occur with atherosclerosis.

The first main locus associated with stroke, *STRK1*, was mapped to 5q12 using a genome-wide search for susceptibility genes in the common forms of stroke[17]. A broad but rigorous definition of the phenotype was used, including individuals that had ischemic stroke, transient ischemic attack (TIA) and hemorrhagic stroke. The lod score after adding a high density of markers (one marker per centimorgan) was 4.40 (P value = 3.9×10^{-6}) at marker *D5S2080*.

We describe here the positional cloning of a gene associated with susceptibility to stroke in the *STRK1* locus. We finely mapped the region and tested it for association to stroke, and we found the strongest association in *PDE4D*, encoding phosphodiesterase 4D, a member of the large superfamily of cyclic nucleotide phosphodiesterases. *PDE4D* was most strongly associated with the combination of two forms of stroke related to atherosclerosis: cardiogenic and carotid stroke. Relative expression of *PDE4D* isoforms correlated with stroke and correlated with the genetic variation of stroke associated with *PDE4D*.

RESULTS

Microsatellite allelic association

We initially genotyped 864 Icelandic affected individuals and 908 controls using a total of 98 microsatellite markers. These markers are

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