changes present in each group. These were the same criteria we used in a similar study of *MYOC* in glaucoma[8].

We observed a large degree of sequence variation in all three groups (Table 1). We identified 1,321 instances of 147 different variants in exons or near exon-intron boundaries, corresponding to a mean rate of 2.7 variants per person (range 0–11). Using non-parametric analysis of variance, the median number of total variants per person was significantly different in the three groups, being higher in the Stargardt group ($P<0.0001$). However, there was no significant difference in the median number of variants per person overall, or for each variant class separately, when comparing AMD patients with controls.

Overall, 55 different non-conservative variants were detected in the 3 groups combined. There was no significant difference between the proportion of AMD and control subjects that harboured non-conservative variants (Table 2), nor was any single class of variant or single DNA change significantly more prevalent in the AMD subjects compared with controls. In contrast, the proportion of Stargardt patients having one or more non-conservative variants was significantly higher than controls (Table 2). Three non-conservative variants (Asn1868Ile, Arg943Gln and Ser2255Ile) were very common (>4%) in all three groups. Neither inclusion nor exclusion of these common variants resulted in a significant difference in variant frequency between AMD and control patients (Table 2). Of 55 non-conservative variants, 18 would be predicted to cause protein truncation before the carboxy-terminal ATP-binding domain. All 18 of these alleles were detected only in Stargardt subjects. The majority of the other non-conservative changes were also observed primarily in Stargardt patients.

This study illustrates the difficulty of establishing the role of a candidate gene in a common complex human genetic disease without a functional assay. Although it is tempting to assume that the sequence variants found primarily in affected patients are those that cause disease, selecting a subset of variants for statistical analysis based on such a criterion will result in a biased data set, particularly when control and study individuals are not subjected to identical scrutiny (ref. 7; http://www.sciencemag.org/cgi/content/full/279/5354/1107a (Dryja *et al.*, Klaver *et al.* and Dean *et al.*)) For example, Dean *et al.* compared the number of variants found in a completely screened group of AMD patients with the number of variants found in a screen of the control group that was only about 65% complete. This is important because if even 2 additional variants had been observed exclusively in controls, their data would have shown no significant difference between AMD patients and controls by Fisher's exact test ($P = 0.064$). In our experiment, we screened all the study participants equally and we did observe 2 variants (Pro1314Thr and Thr901Ala) that were each present in only a single control subject. Neither of these changes was detected by Dean *et al.* nor did they detect a very common (15.8% overall in our study) non-conservative sequence change in exon 40 (Asn1868Ile).

In summary, the data in this report confirm that some variants in *ABCR* cause Stargardt disease. We found no evidence, however, to support the hypothesis that variation in *ABCR* has a role in age-related macular degeneration.

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# Genetics without frontiers

No human endeavour is spontaneously more international than science, but few activities are more awkward when they consciously try to be international. Geneticists encounter this paradox in four areas that transcend regional interests: nomenclature, a genome database, the legal and ethical issues raised by genetics and the infrastructure for international congresses and standing committees. They are interrelated, and perhaps painful trial and error will lead to a common solution.

Most sciences classify large numbers of objects by rules that can be applied successfully by any practitioner. The original name is conserved unless it violates a rule, and then the synonymy is clearly documented. Therefore, the role of an international nomenclature committee is primarily legislative rather than judicial. The International Standing Committee on Human Cytogenetic Nomenclature is responsible for extending the classical system to accommodate new techniques and data, so that the most complex observations can be communicated unambiguously[1]. Without a standing committee, *Drosophila* genetics has so far followed this principle, with the result that names assigned decades ago are easily traceable. Taxonomy is even more stable, giving transparent continuity from Linnaeus to the present. In contrast, the Plains Indians changed names to reflect events, and so Laughing Boy might become Sitting Bull. Human genetics follows this precedent, and we are fortunate if we can trace last year's name. Does our science really benefit when the locus controlling the JK blood groups is renamed *SLC14A1*, which signifies 'solute carrier family 14, member 1' of an otherwise empty set not recognized in other organisms or by UniGene? Why is the gene encoding dystrophin symbolized *DMD* for Duchenne muscular dystrophy, but scores of other disease symbols have been supplanted? With the greatest respect for the devotion of the two chairpersons of the HUGO committee, how can a nomenclature with ambiguous rules not be capricious? Serial replacement of a familiar symbol by one that more closely reflects evolving information about function requires enormous effort when the database has a few thousand loci, and must collapse before all 100,000 expressed loci are entered. Standardization of names for

expressed loci over organisms with different nomenclature conventions raises serious problems of communication among specialties, priority, degree of homology, duplication and change of function, and should not be attempted until nomenclature is coherent within organisms. Meanwhile, no effort has been made to standardize names of non-expressed sequences and clones, which are much more numerous than expressed loci. Informaticians throw up their hands and use accession numbers that vary from one database to the next, adding to the synonyms generated by inconsistent use of D numbers, underlines, hyphens, upper and lower case and abbreviations. Every geneticist who has spent hours searching for a recent symbol, now replaced by a synonym with no traceback, must envy the sciences where such unnecessary labour is recognized as not only useless but prohibitively costly. What geneticist does not address the Nomenclature Committee in the spirit and nearly the words of Oliver Cromwell, "I beseech you, in the bowels of Linnaeus, think it possible you may be mistaken."

Stable nomenclature is a *sine qua non* for a genome database that spans mapping, sequence and function. Current sequence databases are unable to handle chromosomes or even contigs[2]. For the next few years, there is no practical alternative to letting a hundred databases blossom, but a comprehensive international database should be the goal.

As the influence of genetics has grown, it confronts an increasing number of legal and ethical issues. Are there hazards in genetically engineered organisms, cloning, or physical agents that warrant legal restriction? Can patent law be interpreted so as not to hobble advances in science and medicine? Above all is the need felt by many countries to curb population growth without violating human rights and without resorting to eugenic coercion and charlatanism. Although it is inefficient for every genetics society to consider such matters independently, an international infrastructure is barely conceivable. Societies of genetics are seldom international, and the few that are (like IGES, the International Genetic Epidemiology Society) encounter the obstacle that the annual meeting cannot entirely satisfy members at great distance. Not only has the genetics community fractionated irretrievably by the formation of societies of human genetics, but within each group there are further planes of cleavage. One is represented by HUGO, reflecting not only its shifting goals[3] but also the nature of genomics, which like molecular biology is a body of techniques and data. Since the problems they address come from other sciences, there presumably will never be a 'genomicist' or *Nature Molecular Biology.* As societies of genetics and human genetics absorb genome-based research, the distinction between genetics and functional genomics becomes increasingly specious.

International congresses highlight tensions in our science. A Genetics Congress was scheduled for Moscow in 1937, despite liquidation of Soviet human geneticists the previous year. This foreign support (and the intrigues of Trofim Lysenko) proved fatal to the designated president, Nikolai Vavilov. The Congress this year in Beijing polarized genetics societies, some of which withdrew from the organizing Federation in protest. It is too early to judge whether the damage is lasting, and perhaps too much to hope that a clear resolution by a workshop of the Congress against coercive genetic counselling will moderate these practices and the laws that encourage them[4]. This is the first time that a society or congress of genetics has shown solidarity with human genetics, illustrating how much the social consciousness of geneticists has developed.

The infrastructure of human genetics is even more unsettled. One model is the World Health Organization (WHO) Hereditary Disease Programme, which developed "Guidelines on Ethical Issues in Medical Genetics" running to more than 100 pages[5]. The essence of an ethical code is that it be short enough to be memorized. If the Decalogue and Hippocratic Oath had been as verbose, they would have been forgotten long ago. Because the three authors are American and European, the Permanent Committee of the International Congresses of Human Genetics and the International Federation of Human Genetics Societies were unwilling to endorse the guidelines as a consensus. WHO lacks the resources, if it had the commitment, to provide an infrastructure for genetics. Of the alternatives, the Permanent Committee of the International Congresses of Human Genetics has a narrow mandate and at the last Congress had too many absentee members to reach a quorum. Into this vacuum stepped the new International Federation of Human Genetics Societies (IFHGS). Its full members are the presidents of the three societies bearing the names of America, Europe and Australasia, all of whom serve terms of one year. Together they organized the International Congress to be held in Vienna in 2001. Presently, Asia, Africa and Latin America are excluded from full membership because their societies are less international, whereas IGES is excluded because it is more international. National and specialty societies have delegated none of their activities to the societies that claim to be regional, and so IFHGS is neither international nor a federation, just as its predecessor is neither permanent nor able to meet as a committee. International needs must be addressed without the amorphism of HUGO, the impotence of the Permanent Committee and the elitism of the International Federation. If a solution is found, it will include congresses that are international in spirit as well as name.

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In reply—We are glad to have this opportunity to respond to the important concerns of Dr Newton Morton regarding gene nomenclature. We share his wish for good international communication between scientists, and agree that problems of nomenclature make map integration in human genetics an extremely frustrating task. We are, however, surprised to find that he singles out for attack an effort which is actually having some success in solving these problems, especially as we cannot understand what alternative is proposed. So far approximately 8,000 human genes have approved names and symbols (short-form abbreviations), approximately 10% of the total. Although some speeding up is required, the task is finite. As more gene families are defined, more groups working on them find a need for standard nomenclature and naming the remaining genes becomes easier.

We do not agree that nomenclature in one species should be entirely sorted out before any cross-species collaboration is attempted. The excellent relationships

between the human and the mouse databases ensure that the overwhelming majority of genes have the same symbol in human and mouse, and that no approved symbol in one database clashes with an approved symbol in the other. These common symbols are used throughout the mammals and have allowed the construction of comparative maps which have played a role in the identification of the cause of many human genetic diseases.

The primary concern of the Nomenclature Committee, authorized by HUGO, is to agree with authors on a symbol and name which must be unique and which will be accepted by the majority of people working on that gene. It is actually rather rare these days for only one group to be working on one gene, and if this is the case the author can insist on virtually any name and symbol which does not conflict with published minimal guidelines, although we do often make suggestions which experience has shown will make the name more useful. Ideally, a scientific community gets together and comes up with an agreed nomenclature. Some communities, like those working on HLA, have done this for many years; others, such as those working on the cytochrome P450s, 'the CYPs', and on the CASPases, are more recent successes. Many are still being negotiated. *DMD* is an example of a symbol well supported in the community.

With respect to the other example singled out for attack, *SLC14A1*, denoting one of 79 human genes coding for solute carrier proteins, there is no problem in tracing the change of this symbol. Searching by 'JK' on GDB, OMIM or the Nomenclature database will immediately retrieve it, as will a search on 'KIDD' or 'urea transporter'. *SLC14A1* can also be found in SWISSPROT, which is a much more stable source of information about genes than Unigene, which is recompiled at frequent intervals. The Nomenclature Committee is currently working with NCBI on the development of a 'REFGEN' selection of UNIGENE, which will contain authoritative information on sequence with links to SWISSPROT, OMIM and to approved nomenclature.

Are there really sciences in which these problems do not occur? In which, in the absence of bureaucracy, all participants follow a simple set of guidelines resulting in rapid (compatible with, say, the publications schedule of *Nature Genetics*) and universal agreement of a permanent name. The Linnaean system quoted is not such an example. Many systematic names change as more is learned, and these changes are not without controversy. The agreement on the definition of human karyotypes mentioned by Dr Morton is not comparable. No one feels the passion for naming a chromosome band that a scientist has for his/her favourite gene, and a numerical solution was obvious and easy to remember.

It is infuriating and obstructive to current research that there is little consistency in the naming of clones, STSs and other anonymous bits of sequence. Much time has been spent devising conversion programmes which frequently are still defeated by the chaos, and the most reliable maps are often those where all data originate from one source. However, in the end these problems will be overtaken by complete DNA sequence, and it is uncertain whether the massive effort needed to coordinate such nomenclature difficulties could now be justified.

The understanding of genes, as well as being an immediate need, is a long-term goal for the whole of biology. With appropriate support from scientists and from journals like *Nature Genetics*, gene nomenclature, slowly evolving while retaining full referencing to the past, can make a substantial and international contribution to this understanding.

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