

Ethics of Mutation Databases: Correctness in Reporting Genetic Variation and its Effects

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Abstract

The reporting of genetic variation, referred to as a mutation in the clinic, and its effect, or lack of effect, is important to inform decisions in the clinic regarding prognosis, family planning and therapy. It also assists research and diagnostic strategies. However, on the one hand, there are reasons to be sensitive to the views of those who carry a deleterious mutation and on the other the views of society in need to diagnose, counsel and treat others who depend on prior information held in the literature. Discussion of ethical guidelines in human genetics and other areas has been general and difficult to decide what is applicable in the mutation database area. For this reason there has been an effort to develop practical guidelines relevant particularly to locus specific databases (LSDBs). Twelve principles have been derived on which to base activity. Currently the Chair of the Human Variome Project Ethics Working Group Professor Sue Povey, an LSDB curator, is developing a protocol for curators to put into practice on a daily basis. The practical guidelines are discussed in this article.



التطلعات الأطلاقية لقواعد بيانات الطفرات والأمراض الوراثية

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ملخص

تكمّن أهمية معرفة التنوع الجيني وتأثيره (المعروف بمصطلح "الطفرة الوراثية" في المجال الطبي) في إمكانية التنبؤ بمراحل تطور المرض وبالتالي مساعدة الأسرة في اتخاذ القرارات المتعلقة بمستقبلها ومخططاتها، كما تساعد أيضاً في اختيار العلاج الملائم. بالإضافة إلى ذلك تساهم معرفة الطفرات الوراثية المسببة للأمراض الوراثية في مجال الأبحاث والتشخيص. ولكن هناك وجهات نظر تشير إلى توشي الحذر في الكشف عن هذه الطفرات لحماية الأشخاص حاملي تلك الصفات الوراثية من التمييز. ومن جهة أخرى هناك وجهات نظر تشير إلى أن المجتمع بحاجة لمعرفة مسبقة لهذه الطفرات عن طريق ذكرها في الأبحاث المنشورة في المجالات العلمية للاستفادة منها في تشخيص وعلاج الأشخاص الآخرين الحاملين لنفس هذه الطفرات الوراثية والقدرة على اعطائهم الاستشارة الوراثية. كان النقاش الدائر حول الإرشادات الأخلاقية المتعلقة في مجال علم الوراثة البشرية والمجالات الأخرى بشكل عام ولذلك كان من الصعب تحديد ما هو المناسب تطبيقه في مجال قاعدة البيانات للطفرات الوراثية. ولهذا السبب يتم العمل على وضع إرشادات عملية لقواعد البيانات المتخصصة بأنواع الأمراض. وبهذا الخصوص لقد تم وضع اثني عشر مبدأً يقوم على أساسها عمل تلك القواعد. وفي الوقت الالي تعمل الأستاذة سو بوي، والتي تتأس فريق عمل أخلاقيات مشروع الفاريوم البشري، على تطوير بروتوكول يمكن أن يتبعه محررو قواعد البيانات المتخصصة.



Introduction

There has been much written on the ethics of the modern genetics and many guidelines established by major bodies around the world such as OECD and NIH as well as by dozens of different countries. Professional ethicists and lawyers have traditionally developed those guidelines with the assistance of medical practitioners, scientists and others. Often these have been related to general genetic problems and DNA collections and differ between countries. The initiation of the Human Genome Variation Society (HGVS; www.hgvs.org) and the Human Variome Project (HVP; www.humanvariomeproject.org) has stimulated the need for specific practical ethics guidelines developed by curators for loci specific databases (LSDB). The move in this direction was initiated by two papers: Knoppers and Laberge (2000) and Cotton *et al.* (2005). This has laid the ground work for a final document being developed by an LSDB curator and clinician, Dr. Sue Povey, (<http://www.LOVD.nl/TSC1>, <http://www.LOVD.nl/TSC2>) with an HVP Working Group and others.

General Requirements of the Community

It can be assumed that the community has an expectation as follows:

1. That the individual's mutation status be protected to avoid discrimination in the event there is no legal protection in a specific country.
2. That the mutation and its effects be available to be used by others in diagnostic strategies, assessment of the significance of a base change and research in further genes and therapy.

There clearly needs to be a balance between the protection of the individual and value to the community of mutation information and practical ethical guidelines should do this so that LSDB curators can confidently assist the users of their databases without having to wade through complex hypothetical general ethical guidelines.

Currently mutational information is gathered after consent, de-identified and published and/or directly mounted on the web in a database. It should be noted that some patient groups want their mutations and contacts public so that they may contact others to exchange details of mutation treatment, etc. This is an aspect that needs taking into account.

The ideal situation from first principles might be:

1. Consent for mutation and phenotype to be used or not and de-identified or not for:
 - a. Epidemiological studies
 - b. Assessment of disease causation by others
 - c. Publication in journals
 - d. Publication on web
 - e. Only for family diagnostics
2. Ethics committee approval of consent form and procedure.

Some practical guidelines for LSDB curators have been published (Cotton *et al.*, 2005) and were derived from ethical principles endorsed by international instruments (see: Cotton *et al.*, 2005). It should be noted the principles are not legally binding but should be adopted everywhere if possible. Four principles were selected as relevant for Curation of LSDBs.

1. Scientific and ethical responsibility and competence
2. Confidentiality and security of data
3. Ethical supervision
4. Care of vulnerable persons and societies

Difficulties in the area that need to be taken into account are that "Genetic databases" dealt with in the literature, etc often refer to sample/DNA repositories; the degree and wording of "de-identified" varies between WHO, OECD, etc – this wording needs to be agreed and standardized; there is often the time consuming need for re-consent and potential discrimination or stigmatization. These difficulties need to be addressed in any guidelines for LSDB Curation. However, the need and next step now is for actual protocols to be derived from the current 12 practical guidelines (below).

Develop a common ethical framework: Complete collection of all mutations causing inherited disease worldwide is the ideal aim of the Human Variome Project in the first instance. Thus,



overarching principles need to be developed which allow for nation/country specific collection as well as disease specific efforts which will be worldwide. Thus, the principles should ideally be compatible with application in all countries.

Define ethical principles and scientific approach: Curators need to be free of concerns as to whether they are proceeding correctly in an ethical sense. Thus, a “recipe” or “standard operating procedure (SOP)” needs to be developed for curators to follow from the start. This would then allow for correct consent and confidentiality aspects to be dealt with in a routine way day to day.

Clarify the purpose and limits of the LSDB: The purpose and limitation should be defined for the LSDB. In a general sense, this should be similar for all “standard” LSDBs, but there may be special cases where some diseases have complex phenotype. Thus for each LSDB the following should be stated:- mission, objectives, goals and limits.

Create an ethics review board: Whilst an agreed SOP may allow confidence that the actions of the curator are legitimate, extra confidence would be engendered by the appointment of an ethics committee from the local institution or HUGO. This could then validate officially the SOP, ensuring transparency and act as a monitor of activities.

Foster international standardization: International standards need to be agreed on. For example, when the terms single or double coded and anonymized (unidentifiable) need to be agreed on.

Anonymize prior to submission: Discussion should commence as to whether anonymization prior to submission should be pursued as is sometimes the case for publication, although in many cases patient ID numbers/codes are given. The meaning of anonymized has been defined as being “practicably impossible for an individual using reasonable manpower and time to identify the source” of data. In the USA, the HIPAA standards dictate a “minimum of 18 identifiers should be removed such as Name, Hospital, discharge, post code, etc.”

Protect confidentiality: If samples are not anonymized, a maximum should be done to protect confidentiality. A practical situation to avoid might be that a particular very rare mutation and location of the author of the report might allow patient identification. It should be noted that increasingly families of patients wish to publish their identity, so that those with a similar affliction can be contacted for community and morale building. It has also been suggested that data transmission to a database or publication should not be recorded in the medical record.

Inform donors of transmission to LSDBs: When patients present, they, as part of the consent process, should be told that coded or an anonymized data might be sent to journals or databases. This allows queries and refusal.

No disclosure without consent: Colleagues may ask data submitters for further information not provided in the database to inform their prognostic or treatment decisions. In this case no personal ID should be provided without consent. Thus only coded data should be exchanged.

Take vulnerable persons into account: Particularly incapacitated individuals (or young children) unable to consent should be given special care. In this case more stringent review of data included from them should occur.

Take specific communities/cultures into account: Data from individuals from identifiable groups such as Amish or Ashkenazi Jews should be especially treated by prior engagement of spokesperson from the group. This is because interpretation of the case of one individual may affect the whole community.

No virtual “Medical Advice” relationship: Clinical advice should not be offered by databases and readers should be referred to specialist clinicians. However, a listing of frequently asked questions (FAQ) is acceptable.

Regarding the balance of individual protection and benefit and community value, the WHO guiding values published in 2003 stated that ethical guidelines should allow:

1. The pursuit of human well-being.
2. The quality of human dignity, including fundamental human rights and the principle of non-discrimination.
3. The principle of respect for persons, including the imperatives of beneficence and non-maleficance.
4. The principle of respect for individual autonomy.



These should be acknowledged in any future ethical protocols for curation of mutations and their effects on individual patients.

Conclusion

It is acknowledged that LSDBs have an essential role, but curators are nervous about their ethical responsibilities so agreed protocols are needed which need to be endorsed and authorized by OECD, UNESCO, WHO, and others. Proliferation of general ethical guideposts currently inhibit vital data flow. Lack of knowledge of them also inhibits data listing. We hope work by the HVP in the next months will provide a draft of the desperately needed LSDB ethical curator protocol which derives from OECD, UNESCO and WHO guidelines.

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