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A call for mutations

To the Editor:

We believe that an important scientific resource of identified gene variants (pathogenic, uncertain significance, and silent) is currently being lost to the research and medical community: the mutations and variants determined by commercial genetic testing laboratories.

Identification of sequence variants in genes associated with specific genetic disorders was initially accomplished by academic research laboratories. Previously, hundreds of research laboratories each analyzed a limited number of genes. Principal investigators in these laboratories had a scientific interest in the gene(s) that they analyzed, and as part of their laboratories' research protocol, they analyzed these genes in patients with the specific genetic disorder being studied. Identified DNA variants, particularly pathogenic variants, were then published in scientific articles, and in many cases, the variants for a given genetic disorder were accumulated, reported in review articles, and stored in internet-accessible databases. For an example, see the Phenylalanine Hydroxylase Locus Database (http://www.pahdb.mcgill.ca/) curated by Dr. Charles Scriver, McGill University, Canada. In this database, 485 sequence variants of the phenylalanine hydroxylase gene are available for review, as well as supporting information on phenylketonuria. Resources such as this provide information on the different gene variants associated with specific genetic disorders and can be used by other researchers and medical professionals. Due to changes in the regulatory and legal landscape for genetic analysis and diagnosis, mutational analysis has now been largely transferred to clinical/pathological molecular diagnostic laboratories. With the passage of time, the interests of some of the research laboratories move on and mutational analysis is no longer available. Furthermore, novel sequence variants that are identified by diagnostic laboratories are no longer being consistently collected and published in the scientific literature. We feel that this is a loss of important information, both for the general scientific community as well as for all clinical molecular diagnostic laboratories. In particular, this loss of information will directly impact the ability of the health professional to assist in interpretation of a variant, having either no, pathogenic, or uncertain consequences. Furthermore, allelic frequency information, which can be important in setting up targeted screening sets, is not collected. These gene mutations can also be used for structure/function analysis or to answer other basic research questions.

The Human Genome Variation Society (HGVS) has been instrumental in creating a network of locus-specific databases (LSDBs) used to accumulate, edit, and report mutations in genes associated with specific genetic disorders. This network was originally organized by the Mutation Database Initiative within the Human Genome Organization (HUGO). This resource is now administered by the HGVS. The URLs to web sites for specific LSDBs can be found at http://www.HGVS.org/dblist/glsdb.html. It has also provided standards and entry forms for mutation submission. We wish to encourage molecular diagnostic laboratories to release any or all novel mutations and DNA variants that they identify so that this information can be made available to the scientific and medical community. It would be even more desirable if such submission was part of activities required by accreditation. We suggest that diagnostic laboratories contact the curators of specific LSDBs, who are identified on the HGVS LSDB web site, and collaborate in including these novel mutations into the existing databases. The HGVS web site (http://www.HGVS.org) also contains recommendations for the correct nomenclature guidelines for reporting a specific nucleotide change. In cases where there is no LSDB for a given gene, a system is currently being put in place to publish such mutations. Where a database is not currently being curated, offers to the curator or a new curator to assist could be made. Mutation databases are increasingly being consulted by clinicians and those in the diagnostic arena, and the more complete these databases are, the better for making accurate genetic diagnoses.

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