Commentary

RECORDING HUMAN GLOBIN GENE VARIATION

The assemble of the continuously growing amount of information on human gene variation into locus-specific mutation databases is of outmost importance not only for the better understanding of their role and function but also for their application in the accurate provision of molecular diagnostics. The creation and maintenance of such databases is powered mostly by the efforts of dedicated research teams, which make the data reported in the scientific literature available to the public to query upon. However, the input provided from the various database users, both scientists, patients or family members, is equally significant and sometimes triggers innovative steps, which are taken towards the direction of keeping these databases as updated and complete as possible. The aim of this commentary is two-fold. Firstly, it aims at informing the globin research community, in particular the readers of this journal, for the existence and continuous improvement of the HbVar database on human globin gene variants and thalassemia mutations. Secondly, and most importantly, we seek the assistance from the users of HbVar in order not only to expand and refine the contents of this database, by publishing data on human globin gene variations to this of other journals, but also to continue to provide us with ideas and comments, that will help establishing HbVar as an invaluable tool for the provision of genetic services for thalassemia disorders.

The continuous flow of information on the human genome sequence opens many opportunities for enhancing accuracy and expanding the application of information on human genomic sequence variants. However, the primary data dealing with variant alleles or more general genomic variation had long been scattered throughout the scientific literature. It was only within the last few years that information about genetic variation has begun to be organized into mutation databases for purposes of molecular, clinical, and diagnostic medicine and research, and has therefore rapidly assumed an increasing importance in all areas of health care.

Unlike the genomic variation in other loci, human globin gene mutations, leading to the various thalassemia syndromes and hemoglobin (Hb) variants, had been accumulated into two comprehensive mutation repositories, namely the syllabi of thalassemia (thal) mutations (1) and of human Hb variants (2). However, the query capacity of the information
stored in these repositories was very limited. For this reason, and based on the information contained in these two syllabi, Hardison and colleagues (3) recently developed HbVar, a relational database, which is publicly available and can be accessed at http://globin.cse.psu.edu/globin/hbvar. This database not only contains information on the human globin gene sequence variation, which can be easily queried, but also allows for the entries to be regularly updated and corrected, as new Hb variants and thalassemias are discovered.

Recently HbVar has undergone significant improvements, consistent with the requirements of its users worldwide. Among these improvements was the inclusion of the frequencies for a large number of mutations causing β-thal in at-risk populations. These data sets have been extracted from the published literature and made available for the user to query (4). Since thalassemia consists of the most common autosomal recessive disorders in populations of Mediterranean, Middle and Far Eastern, Asian-Indian and African descent with a history of malaria endemicity, each at-risk population has its own spectrum of common thalassemia mutations, usually ranging from five to 10 different mutant alleles or sometimes even more. Therefore, such information significantly simplifies mutation analysis. Carrier and prenatal diagnosis, using combined hematological and mutation analyses have made possible the population screening of women of childbearing age, and in combination with non directive genetic counseling, has resulted in a consistent decline in the birth of affected homozygotes in several at-risk Mediterranean populations [Ref. (5) and references therein].

We anticipate that the update of HbVar with the mutation frequencies for a large number of at-risk populations will substantially facilitate carrier identification, therefore contributing to thalassemia mutation detection. However, the data on the globin gene mutation spectrum for a small number of countries and/or populations were either published many years ago, or are based on a relatively small number of chromosomes, or contain incomplete information, e.g., only the frequencies of the most common mutations. Consistent with the initiated update for the thalassemia mutation frequencies in various populations, especially for those at-risk, we encourage the globin research community to submit their work on the mutational spectrum for the various types of thalassemia in different populations to HbVar (detailed contact information can be found at http://globin.cse.psu.edu/html/contact.html), as well as to specialized journals. We particularly invite those involved in the area of Hb research to submit their data on mutation distribution to the journal Hemoglobin. This journal’s continuous commitment to the recording of human globin gene variation over the years has significantly contributed to these efforts, and will continue on the same path in the future. This will definitely improve the quality of genetic testing and counseling for thalassemia disorders. Additionally, since new Hb variants and thalassemia mutations are currently added as they are discovered, this provides interested journals or books with the opportunity of publishing summaries of information from the HbVar database.

The update of HbVar has yet another interesting aspect. Until now, a substantial number (over 40) of deletional mutants in the human β-globin locus, leading to δβ- or γδβ-thal and hereditary persistence of fetal Hb (HPFH) have been reported, removing one or more globin genes, or in some cases, the β-globin locus control region (LCR). It has long been reported that critical regulatory sequences, governing the switch in expression from a fetal to an adult pattern, can potentially be identified by comparing the deletion(s) junction point(s) that do or do not allow persistent expression of the γ-globin genes in adult erythropoiesis. However, there is still some controversy
Regarding the identification of all such regulatory sequences in the human β-globin locus. So far, one of the limitations for interpreting these data has been the incomplete information about the deleted sequences. Fortunately, the DNA sequence for the human β-globin locus and surrounding regions is now complete [University of California at Santa Cruz (UCSC) genome browser, available at http://genome.ucsc.edu (6)]. This will allow for precise identification of all deletion junctions and annotation of the DNA features affected by the deletions, while yet unidentified deletional mutants now have a good chance of being characterized. Subsequently, this information will be critical for interpreting all deletional mutants, and will allow not only for better analysis and interpretation of the mutations, but also for specialized screening strategies, such as gap-polymerase chain reaction (gap-PCR) to be designed and implemented for each mutation.

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