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Human Mutation

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# $A_1$ATVar: A Relational Database of Human *SERPINA1* Gene Variants Leading to $\alpha_1$-Antitrypsin Deficiency and Application of the VariVis Software

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Communicated by Stylianos E. Antonarakis

Received 9 April 2008; accepted revised manuscript 5 June 2008.
Published online 19 November 2008 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/humu.20857

**ABSTRACT:** We have developed a relational database of human *SERPINA1* gene mutations, leading to $\alpha_1$-antitrypsin (AAT) deficiency, called $A_1$ATVar, which can be accessed over the World Wide Web at www.goldenhelix.org/A1ATVar. Extensive information has been extracted from the literature and converted into a searchable database, including genotype information, clinical phenotype, allelic frequencies for the commonest AAT variant alleles, methods of detection, and references. Mutation summaries are automatically displayed and user-generated queries can be formulated based on fields in the database. A separate module, linked to the FINDbase database for frequencies of inherited disorders allows the user to access allele frequency information for the three most frequent AAT alleles, namely PiM, PiS, and PiZ. The available experimental protocols to detect AAT variant alleles at the protein and DNA levels have been archived in a searchable format. A visualization tool, called VariVis, has been implemented to combine $A_1$ATVar variant information with *SERPINA1* sequence and annotation data. A direct data submission tool allows registered users to submit data on novel AAT variant alleles as well as experimental protocols to explore *SERPINA1* genetic heterogeneity, via a password-protected interface. Database access is free of charge and there are no registration requirements for querying the data. The $A_1$ATVar database is the only integrated database on the Internet offering summarized information on AAT allelic variants and could be useful not only for clinical diagnosis and research on AAT deficiency and the *SERPINA1* gene, but could also serve as an example for an all-in-one solution for locus-specific database (LSDB) development and curation.
Hum Mutat 30, 308–313, 2009.
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**KEY WORDS:** $\alpha_1$-antitrypsin deficiency; AAT; *SERPINA1*; relational database; mutations; experimental protocols; populations; visualization tool

## Introduction

$\alpha_1$-Antitrypsin (AAT) deficiency is one of the most common inherited disorders worldwide, with an estimated incidence of 1 in 2,500 individuals [Luisetti and Seersholm, 2004]. It was first described by Laurell and Eriksson [1963], who reported the absence of the $\alpha_1$-band on protein electrophoresis of serum taken from a patient at a local respiratory hospital. AAT deficiency was also implicated in the death of the composer Frederich Chopin [Kubba and Young, 1997]. AAT belongs to the serine proteinase inhibitor (serpin) family and is the most important protease inhibitor (Pi), significant for normal lung function. AAT is synthesized in the liver and released in the circulation from where it is diffused in interstitial and alveolar lining fluids, constituting about 95% of all antiprotease activity [Koj et al., 1978]. Its main molecular effect is the protection of lower respiratory tract from proteolytic damage by neutrophil elastase.

AAT-deficient patients have low AAT serum, and hence alveolar levels, leading to unimpeded neutrophil elastase digestion of collagen and elastin in the alveolar walls and progressive emphysema [Stoller and Aboussouan, 2005]. Hence, AAT deficiency can predispose to or cause pulmonary disorders, while smoking, infections, and exposure to dust and fumes can deteriorate the symptoms and/or accelerate their onset [DeMeo and Silverman, 2004] AAT-deficient patients can also develop liver disease, as a result of accumulation of particular AAT variants in hepatocytes [Lomas and Mahadeva, 2002]. AAT deficiency manifests at birth or in early childhood as a molecular dysfunction of the liver and represents genetic predisposition for the subsequent development of severe liver or lung disorders later in life [Teckman, 2007]. Early diagnosis and prevention measures are

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Contract grant sponsor: Asclepion Genetics, Switzerland; Contract grant sponsor: European Commission EuroGenTest FP6 Network of Excellence; Grant number: 512148; Contract grant sponsor: Serbian Ministry of Science; Grant number: 143051.

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currently the best choice for the management of AAT deficiency patients. However, this disease often remains undiagnosed and less than 5% of severely AAT-deficient patients are currently identified and subjected to treatment. The main reason for this is the poor genotype to phenotype correlations described for this disorder.

The AAT protein is 394–amino acids long and encoded by *SERPINA1* gene (MIM♯ 107400). The gene is mapped on the long arm of chromosome 14 (14q32.1) and contains seven exons and six introns [Long et al., 1984]. AAT alleles are expressed in a codominant manner and, therefore, the combined effect of these alleles leads to certain levels of AAT protein. The normal AAT allele is M (PiM), accounting for almost 90% of all AAT alleles and with AAT serum levels of 20 to 53 μmol/L, while the most common AAT-deficient alleles are PiS and PiZ, the latter being the most severe AAT allele [DeMeo and Silverman, 2004]. Homozygous ZZ patients present with only 3.4–7 μmol/L of AAT serum levels (approximately 10–15% of normal levels). Additionally, a relatively large number of other rare AAT variants have been described, accounting for 2 to 4% of the total number [DeMeo and Silverman, 2004].

Although there are several patient-oriented websites offering summary information on AAT deficiency, a locus-specific database (LSDB) that would document existing knowledge for research, genotype/phenotype correlation, and disease diagnostics at the protein and/or DNA level is currently missing. LSDBs are extremely useful tools, as they can contribute toward identification of causative mutations, provide information about phenotypic patterns associated with a specific mutation, and enable researchers to define an optimal strategy for mutation detection [Patrinos and Brookes, 2005].

We report here the development of $A_1$ATVar, a relational LSDB, which captures most of the information available on the genetic basis of AAT deficiency, documentation of AAT variant alleles (together with epidemiological data), and protein and DNA experimental protocols for *SERPINA1* mutation screening. This work also describes the first application of a model visualization tool for LSDBs [Smith and Cotton, 2008]. We describe the construction and curation of the database and give examples of its use.

## Data Sources and Database Design

The primary source of information in $A_1$ATVar is the PubMed literature database (www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?db = PubMed), and proper variant nomenclature and annotation is done by the curators. Where DNA information is missing, the predicted DNA change is provided. $A_1$ATVar contains information on 91 AAT variant alleles, accounting for the vast majority of the variant alleles reported in the literature, and 13 experimental protocols for AAT variant and *SERPINA1* gene mutation screening protocols.

The main menu of $A_1$ATVar is located at the left side of each page, where buttons are shown that depict the database functionalities. Each selected page is highlighted. A "User Guide" provides simple instructions on how to navigate and query $A_1$ATVar. The main database content, i.e., all AAT variant alleles, can be accessed and queried on the "Search" page (see also below) and sorted by exon. Automated summary listings are also provided at the end of the "Home" page, grouped according to exon, and by allelic variant category. Frequencies of PiM, PiS, and PiZ, representing the three most frequent AAT alleles, are provided on the "Frequencies" page for 58 populations/ethnic groups, and the VarisVis visualization tool [Smith and Cotton, 2008] is available in the "Graphical Display" page, allowing for the graphical display of the $A_1$ATVar contents in the context of the *SERPINA1* gene sequence. Links to patient organizations and societies, as well as contact information, are provided on the corresponding pages. Finally, the "Data Submission" page includes an online data submission tool that allows registered users to directly submit novel AAT variant alleles and experimental protocols.

Finally, $A_1$ATVar fulfills all the required quality criteria, by including copyright and disclaimer notices and the date when the resource was last updated, and all mutation entries comply with the official Human Genome Variation Society (HGVS; www.hgvs.org) nomenclature [Antonarakis et al., 1998].

## Database Design, Implementation, and Access

$A_1$ATVar is a relational database, implemented by the PHP hypertext preprocessor scripting language and MySQL (MySQL AB, Uppsala, Sweden; www.mysql.com) open source software. This choice was guided partly by the desire to facilitate easy creation and maintenance and, most importantly, to support efficient interfaces for AAT variant allele frequency data, experimental protocol archiving, and sequence analysis output with other databases, such as FINDbase (www.findbase.org) [van Baal et al., 2007]. Data are stored in a single table format. Database design follows all content criteria and HGVS recommendations [Cotton et al., 2008]. Finally, $A_1$ATVar design follows certain database guidelines to conform to quality requirements.

Information for each AAT variant is summarized in three different sections in the query outcome table, and is depicted in different colors (Fig. 1). The section pertaining to the structure of the AAT variant alleles (depicted in blue) include the variant's name, the genomic region that is located (e.g., exon, intron), the position and alteration in the amino acid and DNA sequences, according to the official HGVS nomenclature, and the corresponding RS number from the dbSNP database (www.ncbi.nlm.nih.gov/projects/SNP), where available.

The section on clinical presentation (depicted in yellow) is a summary of published results. In this section, considerable effort was made to enforce a uniform, controlled vocabulary, i.e., using descriptions such as "inspiratory capacity (IC) accumulation," "IC degradation," "deficient," etc. Hence, to enforce this controlled vocabulary, data entry and queries can be performed primarily via menus and lists. For each AAT variant, information on the RNA levels, the clinical phenotype, the AAT variant allele category, and the organ affected is available, while in the "Comments" column, additional comments can be added, if needed. Additional information on laboratory findings, such as AAT serum levels, is recorded quantitatively for some published cases.

Techniques used to identify each AAT variant are recorded, and categorized as protein- and DNA-based. Where applicable, the restriction enzyme (RE) used to identify the presence of absence of an AAT variant is also provided. For some variants, a quantitative scale is made available to describe their mobility in isoelectric focusing (IEF) electrophoresis, and is shown on the "Links" page. In the "Graphical Display" column, the system redirects the user to the corresponding exon, where the respective AAT variant is located. Finally, additional fields record references, hyperlinked to the corresponding URL in the PubMed literature database. This last section is depicted in gray.

$A_1$ATVar is a freely-available online resource that can be accessed on the World Wide Web at the Golden Helix Server

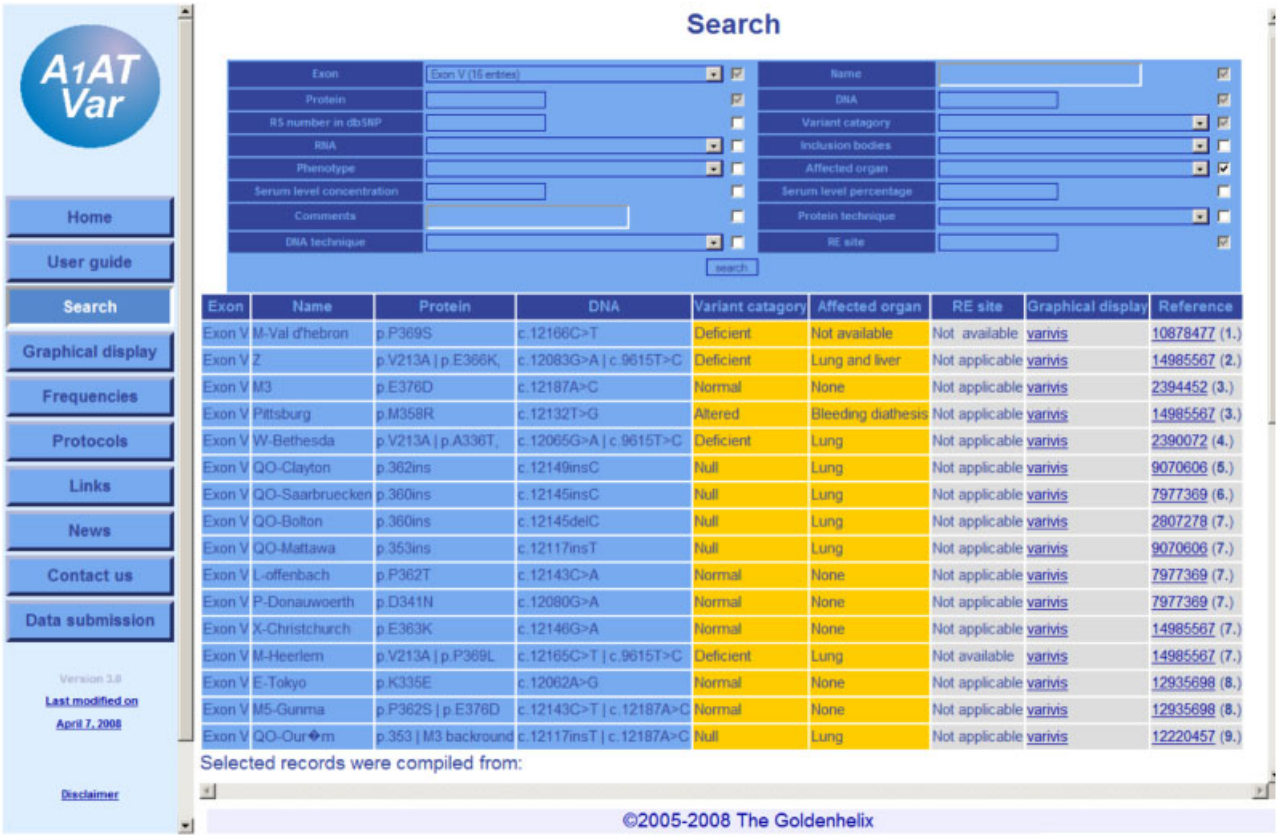


**Figure 1.** Querying the $A_1$ATVar database for all AAT variants located in exon V. Query output includes 16 records (also indicated in the dropdown menu) for which the desired information is provided (for RNA levels and phenotype) in addition to the standard column display (selected by default and shown in light gray). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

(www.goldenhelix.org/A1ATVar). Detailed instructions for both using and querying the database are also available from the same site ("User Guide" page). There has been no claim of ownership of the information stored in this database by anyone involved in this initiative. However, this compilation and representations of it are subject to copyright and usage principles, to ensure that $A_1$ATVar and its contents remains freely-available to all interested individuals.

## Querying the Database

$A_1$ATVar data can be queried through user-generated queries. Data querying not only includes the AAT allelic variants but also their frequencies in various ethnic groups and the experimental protocols used to detect them, both at the protein and/or the DNA level. $A_1$ATVar does not yet provide a function to formulate ad hoc queries.

$A_1$ATVar also allows the user to submit highly specific queries. For example, one can query for all of the AAT alleles identified in exon V. This requires selecting "Exon V" as the exon (Fig. 1). A total of 16 AAT variants are retrieved, which are indicated in the respective dropdown menu. The user can select the columns to be displayed in the query output table by selecting them at the right-hand side of the respective querying options (Fig. 1). The "Exon," "Name," "Protein," and "DNA" nomenclature and RE site are preselected, and the graphical display and reference columns are shown by default. Documentation of AAT variant properties is not as comprehensive as in other LSDBs, i.e., HbVar [Hardison et al., 2002; Patrinos et al., 2004; Patrinos and Wajcman, 2004], since the information available for the vast majority of AAT variant alleles is limited. One can imagine a query similar to this being useful in a clinical setting as a source of data to help reach a diagnosis. For example, one such query would be to collect all the AAT variants displaying IC degradation.

In addition, $A_1$ATVar can be used to query allele frequencies for the most common AAT alleles, namely PiM, PiS, and PiZ, in 58 populations and ethnic groups worldwide. This information is bidirectionally linked with the FINDbase database for frequencies of inherited disorders (www.findbase.org) [van Baal et al., 2007]. Bidirectional linkage implies that once a FINDbase record on AAT variant allelic frequencies is updated, the corresponding record in $A_1$ATVar is automatically updated. The automatic updating is facilitated by the fact that both the AAT-specific information and FINDbase operate under the same software [Patrinos et al., 2005; Patrinos, 2006], which allows for maintaining updated versions of the linked databases using a very simple server task tool (Sjozef van Baal, unpublished results).

$A_1$ATVar includes a separate archive, based on a flat-file database, to provide a succinct listing of the protocols available for AAT variant detection at the protein level and for *SERPINA1* gene mutation screening. This archive can be accessed from the "Protocols" button and currently contains 13 experimental protocols. These protocols are listed as protein- or DNA-based methods, and are named after keywords from the method itself, e.g., IEF, denaturing gradient gel electrophoresis (DGGE), etc., and can be retrieved by following the corresponding hyperlinks. These protocols also include hyperlink(s) to the respective citation, describing the method in question. Detailed instructions

for both using and querying this archive are also available from the "User Guide." In this archive, all screens are based on hypertext markup language (HTML) with some JavaScript scripts and rely on Cascading Style Sheet (CSS) support. They are built using a custom-made PHP script that comprises the archive's core engine, not only for menus and basic screens that display and parse files, but also for handling data queries. Although the structure of this database resembles the XPRbase database for human globin gene experimental protocols (www.goldenhelix.org/xprbase) [Giardine et al., 2007], protocol querying is done on a different and much simpler way, i.e., keyword-based rather than gene-based querying.

Protocols can be added by registered users through the "Data Submission" page. Modifications are only possible by the administrator through a dedicated administrator module. When a new protocol is added to this file, a separate file named for the first author of the protocol is automatically created. To modify an existing protocol, the administrator only needs to select the desired protocol from the list and modify its contents in the designated area. These examples show only a fraction of the querying possibilities of the $A_1$ATVar database.

The $A_1$ATVar database and associated resources are currently in use worldwide. In December 2007, $A_1$ATVar was accessed 624 times from 238 unique IP addresses, despite the fact that it is only now being announced.

## Graphical Display

From the 683 LSDBs available to date (www.hgvs.org), few possess graphical displays, especially of a dynamic nature [Claustres et al., 2002]. We have therefore selected VariVis, a system designed to provide a basic set of sequence variation visualization tools specifically for LSDBs. VariVis is designed to work in parallel with a database's existing user interface and storage and retrieval backend. The *SERPINA1* gene sequence is automatically retrieved from GenBank (NC_000014) and displayed in color: white (introns) and blue (exons).

In $A_1$ATVar, VariVis can be accessed from the "Graphical Display" button. Two different conceptual views based on the sequence and variation data are provided. The first (Standard view) displays the gene sequence and overlays positions where variation is present (Fig. 2). Clicking the variant symbols provides the user with a brief overview of the data extracted from the database, from which the user can link to the variant entry in the database, or perform simple PubMed and Google Scholar searches to find published articles on the variant. The second (Gel View) has the same functionality as the first viewing option, but with the sequence orientated vertically, with all four possible nucleotide possibilities for each nucleotide position, including deletions and insertions between positions, and highlighting, in contrasting colors, the nucleotides present in the reference sequence and any variations. In both views, the software also displays any structural annotations, such as promoter sequences, polyadenylation sites, and untranslated regions that are present in the sequence file being used, and the exon sequences are underlined. The software also provides access to the raw sequence data, allowing users to copy or download the entire sequence or specific chunks, negating the need to navigate to a dedicated sequence database [Smith and Cotton, 2008].

## Data Submission

In $A_1$ATVar, data entry and modification is only possible for registered users. The data submission page can be accessed through the "Data Submission" button. Once logged in (Fig. 3A), the registered user connects with the publication data editor for further guidance through the data entry procedure (Fig. 3B). Each entry contains empty fields in a table format, through which the registered user enters the requested information, according to the regular table output. Experimental evidence to support the data entered can be uploaded separately with the main submission. Once the data are reviewed by the database administrators and judged appropriate, they become part of the main data collection.

Furthermore, experimental protocols for AAT variant identification or *SERPINA1* gene mutation screening can be also entered through the same page, by selecting the corresponding data entry field. Data submitters may also be contacted for clarifications regarding their submission, through the contact details they provided when they requested an account.


**Figure 2.** VariVis visualization tool for variants located in exon III using the standard view. Note that the total number of mutants also includes complex AAT variants, i.e., variants with two mutations in different exons. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

## Future Prospects

In this work, we report the construction of the $A_1$ATVar database for AAT allelic variants that lead to AAT deficiency. This database is expected to provide assistance for clinical diagnosis and for fundamental studies of AAT deficiency and the *SERPINA1* gene, to offer summarized information on AAT deficiency and


**Figure 3.** $A_1$ATVar variant submission module, including data definition (**A**) and data entry (**B**) steps. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

causative mutations, and to draw attention to AAT deficiency, which is a more common disorder than is currently thought.

We elected to build this database using a custom-made SQL-based platform, mainly to allow easy and efficient intercommunication with databases related to $A_1$ATVar; e.g., FINDbase and the *SERPINA1*-related experimental protocols archive for mutation screening. Alternative possibilities to the chosen platform would have been the use of already-available LSDB creation programs, such as the Universal Mutation Database (UMD) [Béroud et al., 2000], Mutation Storage and Retrieval (MuStaR) [Brown and McKie, 2000], and Leiden Open (source) Variation Database (LOVD) [Fokkema et al., 2005] systems; however, they do not presently accommodate our needs. We have attempted to maintain a layout for the $A_1$ATVar data output that is similar to that of LOVD-derived LSDBs, not only to contribute to LSDB uniformity but also to facilitate possible migration to the LOVD platform in the future.

Plans for further development include addition—preferably direct submission—of new AAT variants from interested parties and building tighter links to other resources. Such resources would be patient organizations, e.g., the Alpha-1 Association (www.alpha1.org), the AlphaNet (www.alphanet.org), and the AlphaOne Foundation (www.alphaone.org), in an effort to make this resource known to a more patient-related audience. Users who would like to have new variants entered should register themselves in the system (through the "Data Submission" button) or should contact us to receive more detailed guidance, if needed (contact information is available from the corresponding button).

At present, $A_1$ATVar is the primary repository for information on AAT variant alleles, and a regularly-updated document containing summary listings of the available AAT variant information is available in the "Search" page. Such information could be used as part of a book or a publication on *SERPINA1* mutation summaries or the database itself. Ultimately, $A_1$ATVar's scope could be expanded to include variants of additional serpin protein superfamily members, such as $\alpha_1$-antichymotrypsin, C1 inhibitor, antithrombin, and plasminogen activator inhibitor-1, which have key regulatory functions in the inflammatory, complement, coagulation, and fibrinolytic cascades, and when mutated lead to various types of serpinopathies [Lomas, 2007]. So far, there are only two LSDBs for serpin family members, namely *SERPINC1* (www1.imperial.ac.uk/medicine/about/divisions/is/haemo/coag/antithrombin) and *SERPING1* (http://bioinf.uta.fi/SERPING1base), encoding for antithrombin and C1 inhibitor, respectively. The rationale for such an attempt to expand the scope of $A_1$ATVar is that the serpin protein family members share more than 30% sequence homology with AAT and conservation of their tertiary structure.

Information on human polymorphisms that do not cause a change in the amino acid sequence of the *SERPINA1* gene is not currently recorded in $A_1$ATVar. Addition of these polymorphism data in an organized manner, so it could be queried, could be useful for genetic mapping of novel or complex traits and for evaluation of the role of selection in conserved sequences. In addition, inclusion of SNPs that have been shown to act as modifiers on AAT deficiency phenotype, e.g., NOS3 polymorphisms associated with severe airflow obstruction in PiZ individuals [Novoradovksy et al., 1999], is also part of the future update plans. Currently, a hyperlink to the dbSNP database of single nucleotide polymorphisms (SNPs) is provided on the "Links" page so the user can access information on SNPs recorded for the human *SERPINA1* gene (www.ncbi.nlm.nih.gov/sites/entrez?db = snp&cmd = search&term = SERPINA1%20homo). Finally, $A_1$ATVar contents have been contributed to the Ensembl genome browser (www.ensembl.org), to maximize human gene variation data distribution into major genome browsers.

As with every database project, user input is fundamental for improving the overall database quality and data accuracy. Therefore, we encourage $A_1$ATVar users to frequently communicate their opinions and notify the administrator of erroneous

entries or incomplete information. This will certainly contribute toward keeping the database as complete and up-to-date as possible.

Finally, $A_1$ATVar development provides another example of an all-in-one solution for database development and curation. Such off-the-shelf solutions, such as UMD, LOVD, etc., are useful to keep database content uniform in existing and/or new database projects, particularly in the LSDB field, which suffers from vast content heterogeneity [Patrinos, 2006; Cotton et al., 2007]. Also, further suggestions for the use and further development of the VariVis "open source software," which allows a more ready inspection and access to variant information in LSDBs, is welcome.

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