European Journal of Human Genetics (2021) 29:356–360
https://doi.org/10.1038/s41431-020-00755-z

BRIEF COMMUNICATION

MobiDetails: online DNA variants interpretation

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Received: 29 June 2020 / Accepted: 22 October 2020 / Published online: 7 November 2020

Abstract

MobiDetails is an expert tool, online application which gathers useful data for the interpretation of DNA variants in the context of molecular diagnosis. It brings together in a single tool many sources of data, such as population genetics, various kinds of predictors, Human Genome Variation Society (HGVS) nomenclatures, curated databases, and access to various annotations. Accurate interpretation of DNA variants is crucial and can impact the patient care or have familial outcomes (prenatal diagnosis). Its importance will increase in the coming years with the expansion of the personalized medicine. MobiDetails is specifically designed to help with this task. Exonic or intronic substitutions and small insertions/deletions related to more than 18,000 human genes are easily submitted and annotated in real-time. It is a responsive website that can be accessed using mobiles or tablets during medical staff meetings. MobiDetails is based on publicly available resources, does not include any specific data on patients or phenotypes, and is freely available for academic use at https://mobidetails.iurc.montp.inserm.fr/MD/.

Introduction

With the advent of population genomics, 2nd and 3rd generation sequencing methods, and last but not least machine-learning methods, the practice of molecular diagnosis has greatly improved over the last 5 years. DNA sequencing is becoming more and more cost and time effective, thus many more medical conditions can be analyzed using sequencing tests [1]. However, in many cases, establishing the accurate molecular diagnosis requires expert manual interpretation and classification of several DNA variants per sample [2]. Individual variant inspection is crucial, especially when genetic disorders are associated to wide phenotypic spectrum, incomplete penetrance, and/or mild phenotypes. In these particular cases, automatized annotation remains often incomplete and can lead to misinterpretation [3]. Concerning variant classification, a method is now widely recognized (American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines) [4], but, for interpretation, only a few online tools are available, such as VarSome [5], MARRVEL [6], or Variant Effect Predictor (VEP) [7]. Indeed, while more and more datasets and predictors providing valuable information on DNA variants are now available, it remains challenging to gather all the pieces of information useful for molecular diagnosis. Many invaluable tools are accessible via a Command Line Interface (CLI) (e.g., dbNSFP [8]), or one at a time by web browsing (e.g., gnomAD [9]). Hence, there is a great need for tools that simplify and curate all this data. We developed MobiDetails, a simple online data aggregator, that gives access in a few clicks to many sources of data required to properly interpret DNA variants in terms of their pathogenic effect, and in line with the ACMG classification. MobiDetails is an open-source web application accessible from most internet-connected supports. MobiDetails provides exclusive features such as the pdf export of all the annotations including the versions of all tools for traceability, a summary of LOVD [10] matches, or a detailed MaxEntScan [11] output for splicing predictions. Academics may use the application free of

Supplementary information The online version of this article (https://doi.org/10.1038/s41431-020-00755-z) contains supplementary material, which is available to authorized users.

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charge. If browsing the site and accessing the entirety of the available variants data can be performed in a public session, to improve the experience and provide a full access to the application programming interface (API), a user account can be created. MobiDetails is based on cutting edge computer technology to provide the user with a fast and robust access to what really matters: useful data for variant interpretation.

Materials and methods

Software architecture

A short description of the software is available as Supplementary Method 1 and Supplementary Fig. 1. Annotation sources are listed in Supplementary Table 1.

MobiDetails operation

The software requires that users submit the variants that will be annotated and stored in the database. This has two advantages over a precomputed-variant approach. First, it avoids the storage of millions of variants that, for the majority, will never be accessed and then alleviates the whole system. Second, an authenticated user who creates a variant in the system will be identified as "owner" or creator of this variant in the system. This may provide a useful traceability in the future, e.g., in the context of micro-attribution [12].

A variant annotation requires:

- either a RefSeq transcript accession number and the Human Genome Variation Society (HGVS) transcript nomenclature of the variant ('c.'),
- or a HGVS genomic nomenclature ('g.') coupled with a HUGO Gene Nomenclature Committee gene symbol,
- or a dbSNP [13] identifier.

Any small variants types, intronic or exonic, can be annotated (substitutions and small (<50 bp) insertions/deletions). The annotation process for a particular variant can be triggered by the end-user using:

- the search engine which can retrieve pre-exising annotations or trigger new ones,
- the form found in each gene page,
- the batch variant annotation form,
- or for long lists of variants using a dedicated script and the API.

The system is based on VariantValidator API [14] to generate the genomic, transcript and protein HGVS nomenclatures [15] (Table 1) based on the user's submission. Only validated variants are processed.

Results and discussion

Graphical user interface

Navigation in MobiDetails has been designed to be user-friendly and gives access to two types of pages, i.e., gene and variant pages. These pages can be quickly retrieved using the integrated search engine which recognizes gene symbols and HGVS variant nomenclatures (genomic, transcript, protein).

Gene pages

The main gene page displays general features concerning the gene of interest, including various accession numbers (NCBI RefSeq, Ensembl, UNIPROT) and also gnomAD gene constraints scores with confidence intervals. These scores represent for three classes of variants (loss-of-function, missense, silent variants) the ratio of number of observed/expected variants and measure the tolerance of the gene to the class of variations.

One transcript is defined as canonical, based on the RefSeq "RefSeq select" annotation available at the NCBI website. Transcripts numbering and version numbers follow those in use in VariantValidator [14]. Using the variant page, the user will be able to retrieve the mapping and the different HGVS nomenclatures in alternative isoforms via Mutalyzer [16]. A second tab on the gene page shows the variants already annotated for the gene of interest.

Variant pages

The variant page is the core of the software and allows variant interpretation. Up to 8 information sections are provided (Table 1, Supplementary Fig. 2). In addition, some complementary features are available. The LitVar API [17] from the NCBI is used to retrieve Pubmed IDs of articles mentioning the variant of interest from the dbSNP [13] identifier. Several external links can be used to directly access the hg19/hg38 UCSC genome browser, 1000 genomes browser, gnomAD [9], Intervar [18], ClinVar [19], dbSNP [13], or RegulomeDB [20] web page of the variant of interest.

All these features, in addition to variant annotation ability, are available to any public user. Registered users have access to some additional operations. The variants that they create while logged in are linked to their account. Moreover, registered users can assign an ACMG class to any variant. This is visible to all other users (including public users). Recorded ACMG classes can be easily updated or removed. Traceability is optimum as registered users can contact another user who, for example, may have assigned a class to the variant of interest.

Table 1 Different sections provided in MobiDetails.

Section	Content	References/Comments
Nomenclatures	• HGVS: genomic (hg19/hg38), DNA on transcript, protein	[15]
	• Pseudo-VCF: chr-pos-ref-alt	
Positions	• Exon/intron number	
	• Position/nearest splice site	
	• Protein domain	
	• Wild-type and mutant DNA sequences	
	• Meta Dome tolerance score	[23]
Population frequencies and databases	• gnomAD v2-v3	[9]
	• dbSNP id	[13]
	• Clinvar interpretation	[19]
	• Intervar semi automated ACMG classification	[18]
	• LOVD links	[10]
Overall predictions	• CADD score	[24]
	• Eigen	[25]
	• MPA score	[26]
Splicing predictions	• MaxEntScan	[11]
	• dbscSNV	[27]
	• SpliceAI	[28]
	• Radar view	Graphical view of the normalized scores
Missense predictions[a]	• SIFT	[29]
	• Polyphen-2	[30]
	• Fathmm	[31]
	• REVEL	[32]
	• MetaSVM–MetaLR	[33]
	• ClinPred	[34]
	• Mistic	[35]
	• Radar view	Graphical view of the normalized scores
miRNA target sites predictions[b]	• dbMTS	[22]
Classification history	• User provided ACMG classifications	Modification (add/remove) and ability to use the platform to contact other users. Variants submission to LOVD [10]. For registered users only.
Administrative information	• Creation user and date	

[a]Only for missense variants.

[b]Only for 3′UTR substitutions.

As well, security is provided as the contact is made via the application, and the option to be contacted or not can be modified in the user's profile page. Choosing to be contacted does not expose the user's email address unless he or she answers the query. MobiDetails is also linked to LOVD [10] and, on user action, the variants can be automatically submitted to the Global Variome Shared LOVD instance. A partnership is also running with CFTR-France [21] and all variants included in the database dedicated to rare CFTR variants are also included in MobiDetails. Finally, the results can be exported as a pdf file, including the date of access to MobiDetails, and different resources versions, in order to be added to the patient's record.

Table 2 Comparison of features between MobiDetails and similar software.

	MobiDetails	VarSome	VEP web	MARRVEL
Access and technical aspects				
Free usage for academics	y	y—limited	y	y
Free API usage for academics	y	n	y	y
Local installation	y*	n	y	n
User friendly	y	y	n—but extensive options	y
Encrypted connection by default (https)	y	y	n	n
Responsive website	y	y—limited	n	y
Specific content for interpretation				
Custom annotations	y—registered users	y—registered users	y—only on local instances	n
Selectable wild-type and mutant DNA sequence surrounding variants	y	n	n	n
gnomADv3: whole genome population variant frequencies	y	y	n	n
Extensive splice site predictions	y	n	y	n
miRNA target sites predictions	y	n	n	n
Literature search	y—LitVar	y—MasterMind	y	n
LOVD occurences	y	n	n	n
Pdf export	y	n	n	n
hg38 coordinates	y	y	y	n
All small variants type**	y	y	y	n—only substitutions

*Requires the SQL scheme available upon request.

**Substitutions and small insertions/deletions.

Comparison with other online platforms

A comparison of technical and content features of MobiDetails to VarSome [5], VEP [7] online, and MARRVEL2 [6] is detailed in Table 2. VEP is primarily a VCF annotation software, but it is able to annotate individual variants from HGVS nomenclatures, as the three others. MARRVEL2 lack several useful features such as automated literature search. MARRVEL2 and VarSome do not provide extensive splice site predictions and MobiDetails is currently the only tool to provide crucial information or options such as the wild-type and mutant sequences, detailed MaxEntScan [11] output, dbMTS [22] for miRNA target sites predictions, information on LOVD [10] matches and a pdf export of the annotations.

Conclusion

MobiDetails is an expert tool which provides the most qualitative and up-to-date data on DNA variants to assist the geneticists who face the challenge to determine whether a particular variant will or will not have a deleterious effect. These tasks require a sophisticated scientific and medical expertise, to interpret data from many sources, and time should not be wasted gathering the data. This painstaking task is performed by MobiDetails, allowing the end-user to focus on the precise interpretation of the identified DNA variants.

Acknowledgements We thank early adopters of MobiDetails for their feedback and input, especially Drs. Vuthy Ea, Luke Mansard, Mouna Barat, Aurélien Perrin, Juliette Nectoux, and Alessandro Liquori. We thank Lawrence McGuire for the careful reading of the manuscript.

Funding This work was supported in part by the French association "SOS Rétinite".

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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