

# Supplementary Information for MobiDetails: Online DNA variants interpretation

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### Supplementary Method 1:

MobiDetails is a python Flask (<https://palletsprojects.com/p/flask/>) application built on top of a PostgreSQL database (Supplementary Figure 1). The database handles gene coordinates, variants and user-specific data. Many external annotations (such as ClinVar<sup>1</sup>) are stored as compressed flat files (often in VCF format) and queried via tabix (<https://www.htslib.org/>) by the Flask engine. The engine either renders HTML/CSS/JS web pages using jinja2 templates (<https://jinja.palletsprojects.com/en/2.11.x/>) or returns a JSON object, depending on the caller (web navigation or API call). The API can be accessed via a swagger application for testing purpose (<https://mobidetails.iurc.montp.inserm.fr/MDAPI/>).

Supplementary Table 1: External resources included in MobiDetails

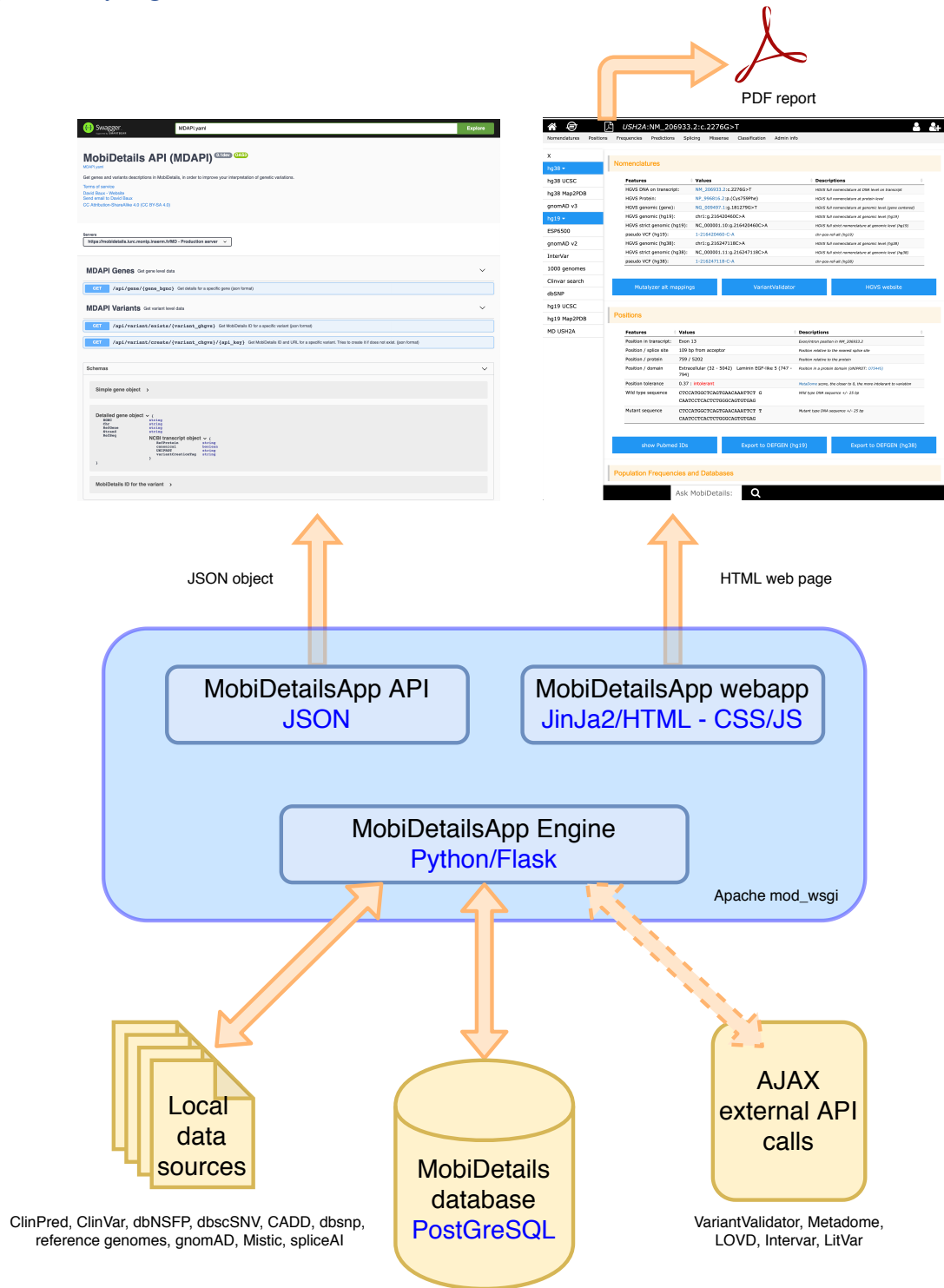
Resource	Version	Access	Reference
<b>CADD</b>	1.5	Local VCF	2
<b>ClinPred</b>	2018_hg19	Local file	3
<b>ClinVar</b>	20200830	Local VCF	1
<b>dbMTS</b>	1.0	Local file	4
<b>dbNSFP</b>	4.0a	Local file	5,6
<b>dbscSNV</b>	1.1	Local file	7
<b>dbSNP</b>	154	Local VCF	8
<b>Eigen</b>	1.1	From dbNSFP or dbMTS	9
<b>FatHMM</b>	2.3	From dbNSFP	10
<b>gnomAD exome/genome</b>	2.0.1	Local VCF	11
<b>gnomAD genome</b>	3	Local VCF	11
<b>InterVar</b>	NA	API	12
<b>LitVar</b>	1	API	13
<b>LOVD</b>	2-3	API	14
<b>MaxEntScan</b>	2004	Perl script	15
<b>MetaDome</b>	1.0.1	API – Local file	16
<b>MetaSVM-LR</b>	NA	From dbNSFP	17
<b>Mistic</b>	1	Local file	18
<b>MPA</b>	1	Internally computed	19
<b>Mutalyzer</b>	2.0.32	API	20
<b>Polyphen-2</b>	2.2.2	From dbNSFP	21
<b>REVEL</b>	NA	From dbNSFP	22
<b>SIFT</b>	Ensembl 66	From dbNSFP	23
<b>spliceAI</b>	1.3	Local VCF	24
<b>TogoWS</b>	NA	API	25
<b>VariantValidator</b>	1.0.4	API	26

NA: not available

Local resources are either automatically updated (ClinVar), i.e. a script periodically checks whether a more recent version of the resource has been released, or must be updated manually, when updates are quite rare (gnomAD, dbNSFP...). The Metadome API returns for each transcript a JSON file containing all the scores for each position of the encoded protein: MobiDetails calls it the first time a gene is visited and keeps a local copy of the JSON file for each gene. Then when a variant page is called, the data is retrieved from the local copy.

VariantValidator API is called when a variant is annotated for the first time. Mutalyzer API is called when a variant is annotated for the first time from its dbSNP identifier (rs id).

# Supplementary Figure 1: Global architecture of MobiDetails



The main engine manages the PostgreSQL relational database which stores the genes and variants data. On query, it uses tabix (<https://www.htslib.org/>) to retrieve data from compressed files, and sends AJAX http requests to selected external APIs. Data sources are listed in Suppl. Table 1. SQL queries and data extracted from the files are treated to be rendered as JSON objects (REST API calls) or web pages.

Supplementary Figure 2: Full view of the variant web page

The screenshot shows a variant web page for **USH2A:NM\_206933.2:c.2276G>T**. The page is divided into several sections:

- Navigation:** Home, about, all genes; PDF export; Variant; Profile; Logout.
- Shortcuts to different categories:** Nomenclatures, Positions, Frequencies, Predictions, Splicing, Missense, Classification, Admin info.
- Nomenclatures:**

Features	Values	Descriptions
HGVS DNA on transcript:	NM_206933.2:c.2276G>T	HGVS full nomenclature at DNA level on transcript
HGVS Protein:	NP_996816.2:p.(Cys759Phe)	HGVS full nomenclature at protein level
HGVS genomic (gene):	NG_009497.1:g.181279G>T	HGVS full nomenclature at genomic level (gene centered)
HGVS genomic (hg19):	chr1:g.216420460C>A	HGVS full nomenclature at genomic level (hg19)
HGVS strict genomic (hg19):	NC_000001.10:g.216420460C>A	HGVS full strict nomenclature at genomic level (hg19)
pseudo VCF (hg19):	1-216420460-C-A	chr-pos-ref-alt (hg19)
HGVS genomic (hg38):	chr1:g.216247118C>A	HGVS full nomenclature at genomic level (hg38)
HGVS strict genomic (hg38):	NC_000001.11:g.216247118C>A	HGVS full strict nomenclature at genomic level (hg38)
pseudo VCF (hg38):	1-216247118-C-A	chr-pos-ref-alt (hg38)
- Positions:**

Features	Values	Descriptions
Position in transcript:	Exon 13	Exon/intron position in NM_206933.2
Position / splice site	109 bp from acceptor	Position relative to the nearest splice site
Position / protein	759 / 5202	Position relative to the protein
Position / domain	Extracellular (32 - 5042) Laminin EGF-like 5 (747 - 794)	Position in a protein domain (UNIPROT: O75445)
Position tolerance	0.37 : <b>Intolerant</b>	MetaDome score, the closer to 0, the more intolerant to variation
Wild type sequence	CTCCATGGCTCAGTGAACAAATCT G CAATCCTCACTCTGGGCAGTGTGAG	Wild type DNA sequence +/- 25 bp
Mutant sequence	CTCCATGGCTCAGTGAACAAATCT T CAATCCTCACTCTGGGCAGTGTGAG	Mutant type DNA sequence +/- 25 bp
- External Resources:** Mutalyzer alt mappings, VariantValidator, HGVS website.
- Pubmed Links:** show Pubmed IDs, Export to DEFGEN (hg19), Export to DEFGEN (hg38).

Callouts highlight: Navigation, PDF export, Variant, Profile, Logout, Shortcuts to different categories, Direct links to external resources/mark/unmark favorites (star), and Display links to Pubmed articles citing this variant (obtained from Litvar API).

## Population Frequencies and Databases

Features	Values	Descriptions
gnomAD exome:	0.0009	v2.0.1 Exomes global MAF
gnomAD genome:	0.0009	v2.0.1 Genomes global MAF
gnomAD v3:	1.34030e-03	v3 Genomes global MAF
dbSNP rsid:	rs80338902	Identifier for NCBI dbSNP
Clinvar:	Pathogenic	Clinvar interpretation
Intvar:	Pathogenic	Semi-automated ACMG classification - click on the interval link to adjust
LOVD Matches:	<ul style="list-style-type: none"> <li>Whole genome datasets</li> <li>Global Variome shared LOVD</li> <li>Retinal and hearing impairment genetic mutation database</li> <li>MSeqDR-LSDB Mitochondrial Disease Locus Specific Database</li> </ul>	LOVD match in public instances
LOVD Effect Reported:	<ul style="list-style-type: none"> <li>unknown: 1</li> <li>functionProbablyAffected: 16</li> <li>functionAffected: 178</li> <li>functionNotAffected: 2</li> </ul>	Effects reported by LOVD submitters
LOVD Effect Concluded:	<ul style="list-style-type: none"> <li>functionAffected: 175</li> <li>notClassified: 20</li> <li>functionNotAffected: 2</li> </ul>	Effects concluded by LOVD curators

Direct links to various LOVD instances containing the variant

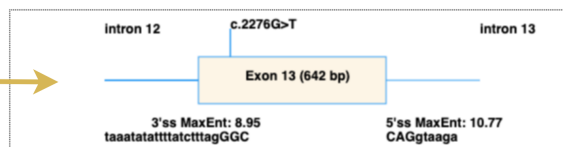
## Overall predictions

Features	Values	Descriptions
CADD raw:	3.924570	[-6.41;35.5] The higher the less likely to be observed
CADD phred:	25.4	Phred-like scaling of raw score
Eigen raw:	1.04852691810073	[-3.33;6.84] The higher the less likely to be observed
Eigen phred:	15.52217	Phred-like scaling of raw score
MPA score:	10	Raw score [0;10], 10: high impact
MPA impact:	Clinvar pathogenic	Impact type

## Splicing predictions

The exonic splicing context of the variant including natural splice sites scores is summarized in the graph below:

Representation of the exon, the variant position within the exon and natural 3' and 5' splice sites sequences and MaxEntScan values



MaxEntScan scores are presented in the two following tables. Selected scores have:

- a |variation| > 15% and
- a raw score for mutant or wild-type of at least 3

The upper sequence shows the variation site in red, and the lower sequence the putative splice site considered by MaxEntScan (putative introns are shown as lower case and exons as upper case).

MaxEntScan 5'ss scores

Wild-type sequence	Score	Mutant sequence	Score	Variation(%)
No significant MaxEnt 5'ss scores found.				

MaxEntScan 3'ss scores

Wild-type sequence	Score	Mutant sequence	Score	Variation(%)
No MaxEnt 3'ss score performed (exonic variant far from 3'ss).				

This last table present dbcsSNV and spliceAI scores, when available.

Features	Values	Descriptions
dbcsSNV ADA:	No match in dbcsSNV v1.1	Raw score (0-1), threshold > 0.8 for impact
dbcsSNV RF:	No match in dbcsSNV v1.1	Raw score (0-1), threshold > 0.8 for impact
spliceAI AG:	0.00 (-20)	Acceptor Gain, 0-1 (distance in bp), thresholds > 0.2 0.5 0.8 for impact
spliceAI AL:	0.00 (12)	Acceptor Loss, 0-1 (distance in bp), thresholds > 0.2 0.5 0.8 for impact
spliceAI DG:	0.01 (-20)	Donor Gain, 0-1 (distance in bp), thresholds > 0.2 0.5 0.8 for impact
spliceAI DL:	0.00 (46)	Donor Loss, 0-1 (distance in bp), thresholds > 0.2 0.5 0.8 for impact

Show radar chart

### Missense predictions

Click to display a radar chart of splicing or missense predictions

Features	Values	Prediction	Descriptions
SIFT:	0.0	Damaging	Threshold < 0.05 for Damaging
Polyphen 2 HumDiv:	1.0	Probably Damaging	Thresholds > 0.454 0.957 for Possibly and Probably Damaging
Polyphen 2 HumVar:	0.999	Probably Damaging	Thresholds > 0.447 0.909 for Possibly and Probably Damaging
REVEL:	0.902	Damaging	Thresholds 0.2 0.5 for Benign, Uncertain, Damaging
ClinPred:	0.88	Damaging	Threshold ≥ 0.5 for Damaging
Fathmm:	-3.4	Damaging	Threshold ≤ -1.5 for Damaging
Meta SVM:	1.0888 (9)	Damaging	Threshold ≥ 0 for Damaging (reliability index: 0-10), 10:high
Meta LR:	0.9471 (9)	Damaging	Threshold ≥ 0.5 for Damaging (reliability index: 0-10), 10:high
Mistic:	0.88	Damaging	Threshold ≥ 0.5 for Damaging

Show radar chart

### Classification History

User	Date	ACMG Classification	Comments
No classification defined yet for this variant			

Add your classification

### Administrative information

Features	Values	Descriptions
Creation user:	mobidetails	User who created the variant
Creation date:	2019-11-19	Date of creation in MD

Search engine

Ask MobiDetails:

Full view of a MobiDetails variant page for *USH2A* NM\_206933.2:c.2276G>T variant (<https://mobidetails.iurc.montp.inserm.fr/MD/variant/7>). Up to 8 categories can be displayed



on the center panel depending on the nature of the variant (i.e. not all insertions/deletions have splicing predictions, non-missense variants do not present missense predictions, 3'UTR variants present miRNA target sites predictions...). The left panel is dedicated to direct external links and to the button star used to mark/unmark a variant as favorite when logged in. The header is used to present links for navigation (home, about...), for pdf export and administrative tasks (login/logout, register, profile page). Finally, the footer is dedicated to the search engine.

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