Mutation@A Glance

ヒト遺伝子バリアント統合可視化ツール

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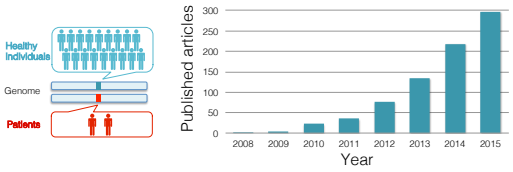
http://harrier.nagahama-i-bio.ac.jp/mutation/

Background

NGS enabled to identify novel genes/ mutations responsible for diseases

GWAS

Increasing success identifications



But the MECHANISM of the mutation for the disease in Black-box

Mutation → ? ? ? → Disease

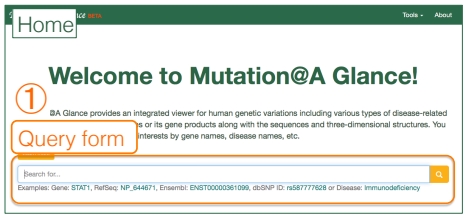
Variants/Mutations
- Genome DNA Sequences — 1D
- Amino acid Sequences — 3D
- Protein 3D Structures — 4D
- Supramolecular Structures

Mutation@A Glance
Integrative analytical platform

Decoding disease-causing mechanisms and variants unknown significance

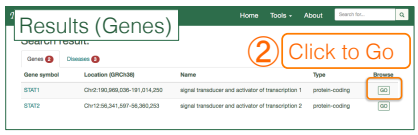
Usage

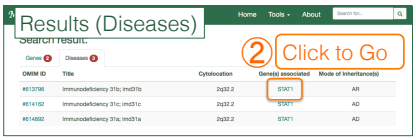
Step 1. Search for genes/diseases of interest



Search

Queries:
- ✓ Gene symbol/names
- ✓ Sequence accessions
- ✓ (RefSeq/Ensembl/UniProt) Disease names/OMIM#
- ✓ dbSNP reference ID (rsID)

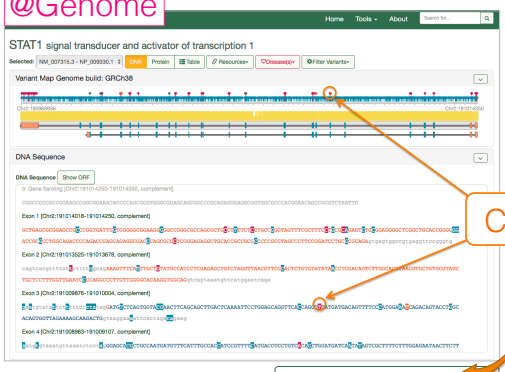




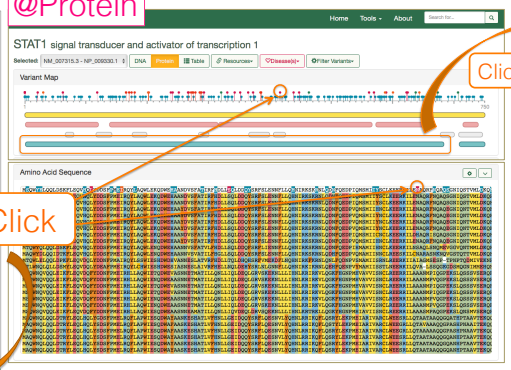
If two or more candidates hit by the query, the candidate are listed as shown above. If only one gene matched by the query, it jumps to the gene page directly. Click the "GO" button or Gene symbol to jump the gene page manually.

Step 2. Visualize variants/mutations along with the sequences/structures

@Genome

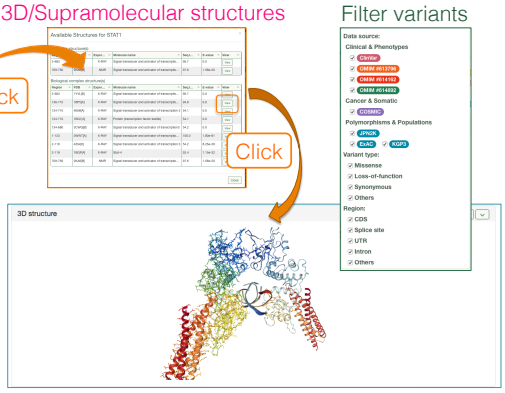


@Protein



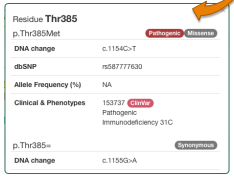
Click

3D/Supramolecular structures



Filter variants

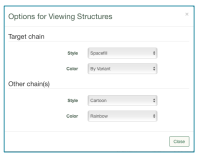
At genome level, the genetic variants are mapped on the schematic diagram (above) and also nucleotide sequences (in this case, the sequences are separated by exons). Mappability for NGS data also displayed.



If a residue of either nucleotide or amino acid in "Variant Map" or "Sequence" is clicked, detail of the residue variants is appeared with a window.

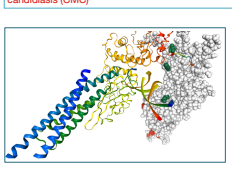
At protein level, the genetic variants are visualized on the "Variant Map" (above), multiple sequence alignment among the homologous sequences (below). The target amino acid sequence is also displayed solely.

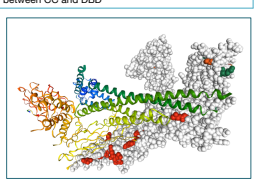
If the structure data are available for the target proteins, the 3D list is displayed by clicking the lightblue bar in the "Variant Map". By clicking the "View" button, 3D structure data is displayed. The NGL molecular viewer is implemented. The molecule can be colored by various types of features:

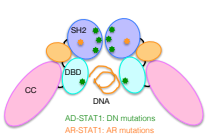


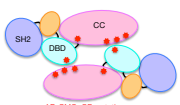
Step 3. Analyze the disease mutations (Case of STAT1)

Disease name	Inheritance	Mechanism	Mutation locations on supramolecules	Effect of mutations
Complete STAT1 deficiency (AR-STAT1)	AR	LF	Interior of STAT1 molecule	Destabilize subunit structure
AD STAT1 deficiency	AD	DN	Interface of subunit/ DNA molecules in active form	Inhibit forming active form
Chronic mucocutaneous candidiasis (CMC)	AD	GF	Interface of subunit in inactive form/Interface between CC and DBD	Destabilize inactive form/ Stable active form









Databases

Genetic variations in humans

dbSNP	(www.ncbi.nlm.nih.gov/projects/SNP/)
ExAC	(exac.broadinstitute.org)
COSMIC	(cancer.sanger.ac.uk/cosmic)
ClinVar	(www.ncbi.nlm.nih.gov/clinvar/)
KGP	(www.internationalgenome.org/)
2KJPN	(igvd.megabank.tohoku.ac.jp)

Human Genome/Gene/Protein Sequences

NCBI Gene	(www.ncbi.nlm.nih.gov/gene)
MapView	(www.ncbi.nlm.nih.gov/mapview/)
RefSeq	(www.ncbi.nlm.nih.gov/refseq/)
Ensembl	(www.ensembl.org/)
UniProt	(www.uniprot.org)

Protein Structure

PDB	(pdbj.org/)

References

Hijikata, A., Tsuji, T., Shionyu, M., Shirai, T. *Sci. Rep.* (2017)
Hijikata, A., Raju, R., Keerthikumar, S., Ramabadran, S., Balakrishnan, L., Ramadoss, S. K., Pandey, A., Mohan, S., Ohara, O. *DNA Res.* (2010)

Acknowledgements

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