

ClinGen Allele Registry

Protein Variants

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Current version

Last CAR release (0.10.04) is installed on the Rackspace servers.

- New User Interface (beta version)
- Production server:
<http://reg.genome.network>
<http://reg.clinicalgenome.org>
- Test server:
<http://reg.test.genome.network>
- REST API with JSON-LD responses
- Documentation for API with examples in Python and Ruby

The screenshot shows the ClinGen Allele Registry website. At the top, there is a blue header with the ClinGen logo (a stylized DNA double helix) and the text "ClinGen Clinical Genome Resource" on the left, and "ClinGen Allele Registry" on the right. Below the header, the main content area is divided into several sections. The first section is titled "Search Variants in ClinGen Allele Registry" and contains a search form with a "Type of search" dropdown menu (set to "Select One"), a "Query" input field, and a "Search" button. Below the search form, there is a link to "Supported searches". The second section is titled "Do not have transcript/HGVS expression?" and contains a paragraph explaining the service and a "Query with Gene and variation" button. The third section is titled "Bulk query" and contains a paragraph explaining the bulk query option and a "Bulk Query" button. The fourth section is titled "Create Login" and contains a paragraph explaining the login process. The fifth section is titled "What is ClinGen Allele Registry?" and contains a paragraph explaining the registry and a "Learn more" button. The sixth section is titled "API specifications" and contains a paragraph explaining the API and a "Learn more" button.

ClinGen Allele Registry

Search Variants in ClinGen Allele Registry

Type of search: Select One

Query:

Search

For example: Select type of search to load examples.

Supported searches

Do not have transcript/HGVS expression?

Please use this service to identify allele interactively if HGVS expression or transcript is not available.

Query with Gene and variation

Bulk query

This option provides a search box for entering multiple HGVS expressions (one per line). For alleles present in the allele registry, the search returns canonical allele identifiers. For valid alleles not present in the allele registry, the search results provide a button to register an allele.

Bulk Query

Create Login

Login is required to register new alleles and obtain their canonical identifiers. To create a login please send an email request to bcm.clingen@gmail.com with First name, Last name, email address, affiliation (Optional) and preferred login name. A more direct online registration process without e-mail will be available soon.

What is ClinGen Allele Registry?

The allele registry provides and maintain identifiers for variations.

Learn more

API specifications

Allele registry supports querying/registration using well documented APIs.

Learn more

Next version - in development

Next CAR release (0.11.x) will appear in ~3-4 weeks on the test server (<http://reg.test.genome.network>).

- ~250 millions of Canonical Alleles (vs. ~15 millions in 0.10.x)
- Identifiers and links to dbSNP, gnomAD, myVariant.info
- Larger & faster bulk queries & registrations
- API – new parameters to control format of output documents
- Better support for protein variants (to discuss)

Genomic alleles

Single returned page in UI (or document in API) corresponds to one Canonical Allele. It contains list of corresponding Contextual Alleles and known external identifiers (and links).

CA000123

- Type: Nucleotide
- dbSNP: [11540654](#)
- ClinVar Alleles: [NM_000546.5\(TP53\):c.329G>A \(p.Arg110His\)](#), allele ID = 133265
- ClinVar Variations: [127808](#), RCV = [RCV000122182](#), [RCV000115719](#)
- ExAC: [17:7579358 C / T](#)

Genomic Alleles

HGVS	Reference Sequence	Position	Allele
NG_017013.2:g.16511G>A, LRG_321:g.16511G>A	↗	16510-16511	A
NC_000017.9:g.7520083C>T	↗ NCBI36, chr 17	7520082-7520083	T
NC_000017.11:g.7676040C>T, CM000679.2:g.7676040C>T	↗ GRCh38, chr 17	7676039-7676040	T
NC_000017.10:g.7579358C>T, CM000679.1:g.7579358C>T	↗ GRCh37, chr 17	7579357-7579358	T

Transcript Alleles

HGVS	Reference Sequence	Position	Allele
NM_001276761.1:c.212G>A	↗	527-528	A
NM_001276760.1:c.212G>A	↗	530-531	A
NM_001276696.1:c.212G>A	↗	530-531	A
NM_001276695.1:c.212G>A	↗	530-531	A
NM_001126118.1:c.212G>A, LRG_321t8:c.212G>A	↗	647-648	A
NM_001126114.2:c.329G>A, LRG_321t3:c.329G>A	↗	530-531	A
NM_001126113.2:c.329G>A, LRG_321t4:c.329G>A	↗	530-531	A
NM_001126112.2:c.329G>A, LRG_321t2:c.329G>A	↗	527-528	A
NM_000546.5:c.329G>A, LRG_321t1:c.329G>A	↗	530-531	A
ENST00000635293.1:c.212G>A	↗	471-472	A
ENST00000622645.4:c.212G>A	↗	461-462	A
ENST00000620739.4:c.212G>A	↗	518-519	A
ENST00000619485.4:c.212G>A	↗	464-465	A
ENST00000617185.4:c.329G>A	↗	530-531	A

Protein alleles

Canonical Alleles with protein variants contain always one protein mutation (Contextual Allele). There is no link between genomic & protein alleles.



CA162562

[See this allele in the new user interface \(beta\)](#)

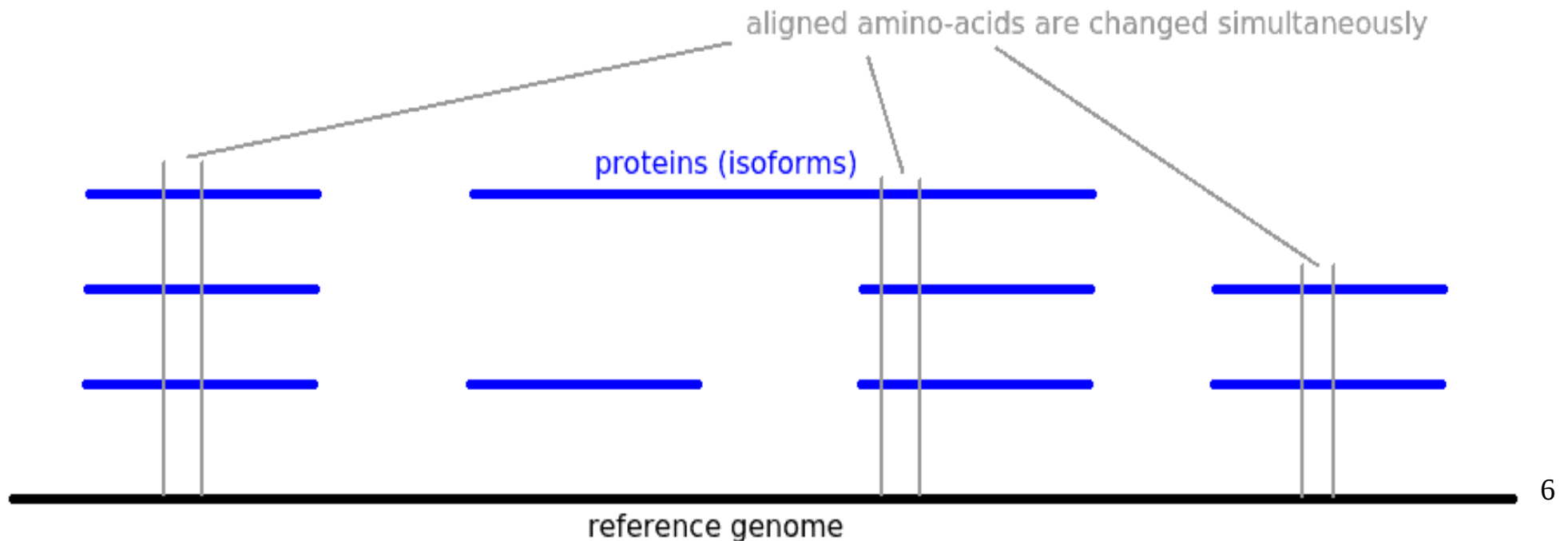
- Type: Amino-acid

Amino-Acid Alleles

HGVS	Reference Sequence	Position	Allele
NP_001119590.1:p.Arg71His	↗	70-71	H

Grouping together protein alleles

- For each protein's amino-acid we can find corresponding codon on the reference genome
- For this codon we can find all proteins, that contain amino-acid produced from this codon (no frameshift is allowed)



Grouping together protein alleles

- Using this approach we can calculate alignment between proteins (isoforms).
- For given protein variant, a list of corresponding protein variants can be calculated.
- For given protein variant CAR can return page (document) with corresponding variants on different proteins, that always co-occur together (Canonical Protein Allele).
- Two Contextual Protein Allele belong to the same Canonical Protein Allele => they occur simultaneously (it does not work in the opposite direction).

Protein variant (modification) definition

- Protein variant (modification) definition:
 - Sequence modification (minimal, right aligned)
 - Range of replaced amino-acids (may be empty)
 - New amino-acids (may be empty)
 - Frameshift
 - 0 – no frameshift
 - 1 – skip 1bp
 - 2 – skip 2bp
- Complex Alleles can be aligned between proteins
- Several different protein variants with frameshifts can be translated to the same HGVS

Links between genomic & protein alleles

- Contextual Genomic Allele may have link to single Contextual Protein Allele (exception: two “active” start codons)
- Canonical Genomic Allele may have link to single Canonical Protein Allele
- Contextual Protein Allele may have links to several Contextual Genomic Allele
- Canonical Protein Allele may have links to several Canonical Genomic Allele

Others

- Change prefix of identifiers of Protein Alleles
- What should have unique ID?
 - Canonical Protein Allele
 - Contextual Protein Allele (this is probably needed)
 - both
- Where to bind external identifiers?
 - Canonical Protein Allele
 - Contextual Protein Allele
 - Both
- Can Contextual Protein Allele belong to two Canonical Protein Alleles?