Cell Genomics, Volume *1*

Supplemental information

The GA4GH Variation Representation Specification: A computational framework for variation representation and federated identification

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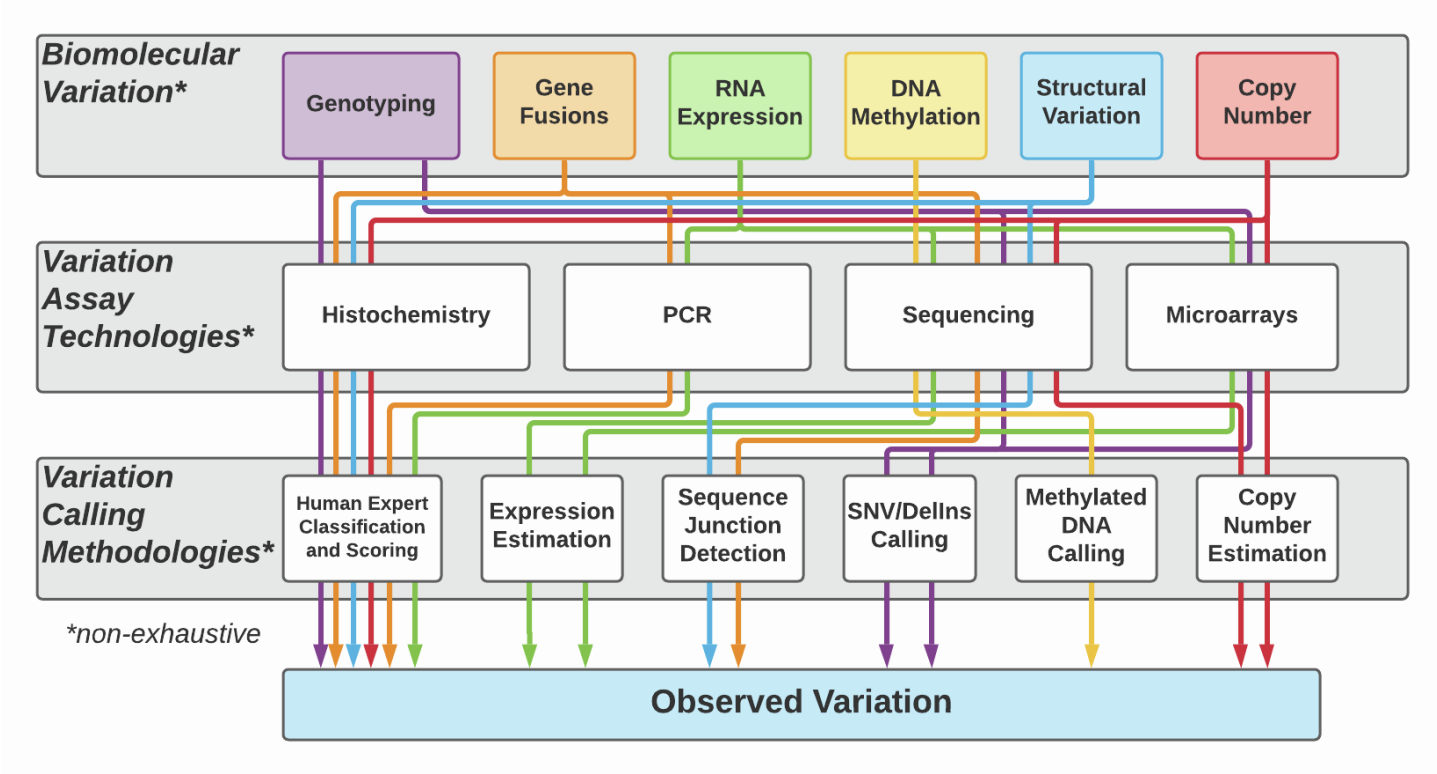
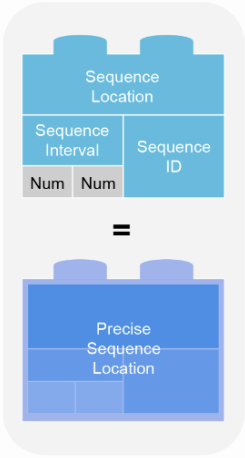
Supplemental Figures

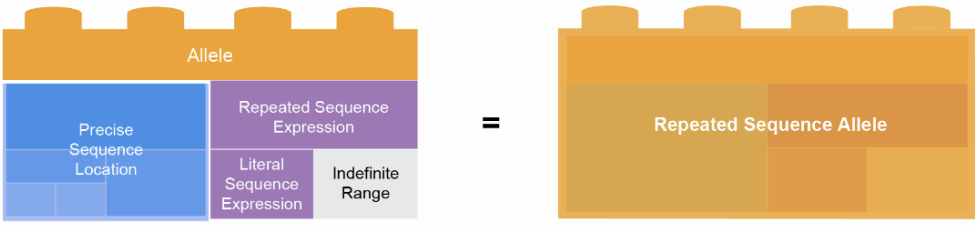


Supplemental Figure 1 - Variation Pathways
A non-exhaustive set of biomolecular variation concepts (**first row**) that are implemented or planned for the Variation Representation Specification. These variation concepts may be assayed (**second row**) and the assay signals evaluated (**third row**) to generate observed ("called") variation for downstream evaluation. Observed variation is compared to knowledgebases linking putative biomarkers to evidence informing clinical decision making. The many pathways (**colored arrows**) from variation concept through assay and evaluation result in a disparate collection of variation representations.

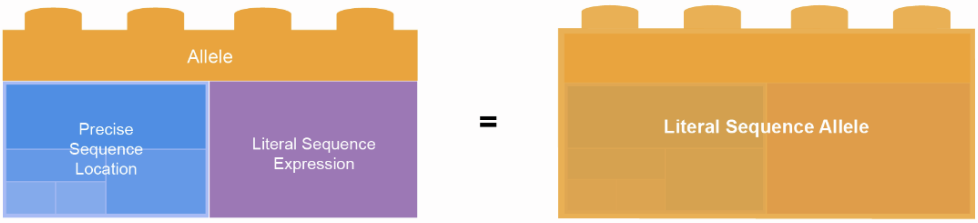
Precise Sequence Location is composed from a **Sequence Location**, which in turn is composed from a **Sequence Interval** with precise Number values



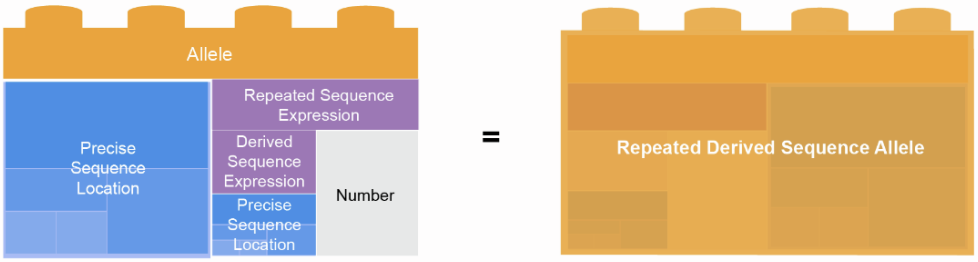
>39 'CAG' repeats in HTT is pathogenic for Huntington's Disease



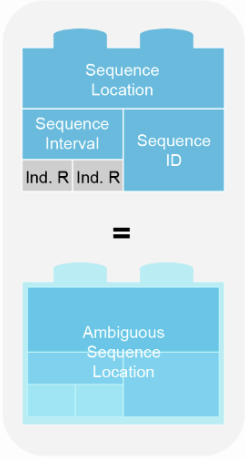
BRAF V640E confers sensitivity to Vermurafenib in melanoma



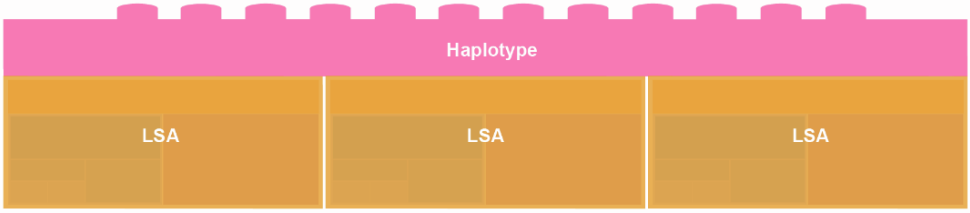
Tandem Duplication of MSH2 NM_000251.3:c.511_583 is pathogenic for Lynch Syndrome



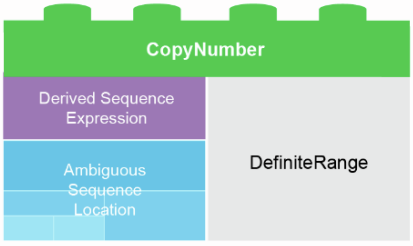
Ambiguous Sequence Location is composed from a **Sequence Location**, which in turn is composed from a **Sequence Interval** with Indefinite Range values



CYP2C19*34 has CYP2C19: uncertain function. It is comprised of 3 Literal Sequence Alleles: 1) **NM_000769.4(CYP2C19):c.7C>T (p.Pro3Ser)**, 2) **NM_000769.4(CYP2C19):c.10T>C (p.Phe4Leu)**, and 3) **NM_000769.4(CYP2C19):c.-13G>A**



GRCh38/hg38 14q32.33(chr14:105224887-106877229)x6 (NC_000014.9:g.(?_105224887)_(106877229_?)dup (6 to 8 copies) Uncertain Significance



Supplemental Figure 2 - Building Blocks of the Variation Representation Specification
Components of the specification can be used in many different constructs. Sequence Locations can be defined once and added as a component by reference in larger constructs. Haplotypes, for example, are composed from Alleles. Shown here, a Haplotype (pink brick) is constructed of three Literal Sequence Alleles (LSA; orange bricks). Literal Sequence Alleles are in turn composed from Literal Sequence Expressions (purple bricks) and Precise Sequence Locations (blue bricks) or Ambiguous Sequence Locations (light blue bricks), which in turn are composed from Intervals, Sequence IDs, and supporting primitive concepts. These same underlying components are used to support other VRS variation types, such as Copy Number (green bricks).

Supplemental Table 1 - Features of Variation Representation Specifications

Specification	Purpose	Reference Types	Sequence Coordinates	Allele Normalization	Reference
HGVS	Human readable variant descriptions	Sequences	Residue	3-prime shifted	http://varnomen.hgvs.org/
ISCN	Human readable cytogenomic events	Cytobands	N/A		https://www.karger.com/Book/Home/271658
SPDI	Human readable variant descriptors	Sequences	Inter-residue	Full-justification	https://www.ncbi.nlm.nih.gov/variation/notation/
PGx	Human readable CYP haplotype descriptors	CYP Alleles	N/A		https://www.pharmvar.org/criteria
VCF	Flat-file variant records	Chromosomal Sequences	Residue	Left-shifted	https://samtools.github.io/hts-specs/VCFv4.3.pdf
MAF	Multisample flat-file variant records	Chromosomal Sequences	Residue	Left-shifted	https://docs.gdc.cancer.gov/Data/File_Formats/MAF_Format/
VRS	Inter-system variation exchange	Sequences, Cytobands, Genes	Inter-residue	Full-justification	https://vrs.ga4gh.org/

Supplemental Table 2 - VRS Implementations

Resource	Usage	Language	Status	Example / documentation
BRCA Exchange	Allele search	Python	Live	https://brcaexchange.org/backend/data/vrid/?vr_id=ga4gh:VA.Z6PI2AKspOXLbCgmyw6JYQxRAoF_qi92
ClinGen Allele Registry	Allele translator	C++	Live	https://reg.clinicalgenome.org/vrAllele?hgvs=NC_000007.14:g.55181320A>T
ELIXIR Beacon Network	Variation search	Python	In progress	
NCBI	Allele id constructor (POST)	C++	Live	https://api.ncbi.nlm.nih.gov/variation/v0
VICC MetaKB	Variation search	Python	Live	https://search.cancervariants.org/api/v1/associations?size=10&from=1&q=ga4gh:VA.mJbjSsW541oOsOtBoX36Mppr6hMjbjFr
VICC Variation Normalizer	String parsing to VRS	Python	Live	https://normalize.cancervariants.org/variation
vrs-python	Open Python Implementation	Python	Released on PyPI	https://pypi.org/project/ga4gh.vr/
AnyVar	Variant Registration Service	Python	In progress	
MyVariant.info	Variation search	Python	Planned	
Ensembl	Variant Recoder and VEP	Perl	In progress	