

Notes

Would have two different panels for “small” variants. (Assume) one for the simple (single allele), and one for complex (multiple allele, e.g. Haplotype or compound het, etc.). This could repeat. We could collapse them into one panel with a small variation type (e.g. simple, haplotype, compound Het, etc.)

Don’t think we need an explicit node (structure) for the genotype itself, because the “whole report” describes the genotype and we already have a section for the overall report.

Have added an attribute to the Simple variant (allele) level—the allelic frequency (a number from 0 to 1) that describes the relative frequency (as a fraction) of a given allele to other alleles at the same position. (Recall there can be more than two). The content for the large (copy number) variants remains the same.

Case 1 – Single (could we have more than one?) simple variant – ask for variant ID and it can control lots and load up associated information.

Overall attributes (no repeats, no need for OBX-4)

Reason for study
Genetic disease(s) assessed
Genomic source class
Gene(s) examined
Gene mutations tested for
Ranges of DNA sequence examined
Full narrative report
Genetic disease overall interpretation

Assembly and Build – Only needed for genomic coordinates- can we say it once per study?

Simple small variant loop

1.1 Variant ID: 30880
1.2 Variant name: NM_014049.4(ACAD9):c.1249C>T (p.Arg417Cys)

Transcript specification

1.3 Allele type:
1.4 Gene: ACAD9
1.5 Transcript Ref Sequence: NM_014049.4
1.6 DNA change: c.1249C>T
1.7 Amino acid change: R417C

Genomic specification

1.8 Genomic Ref Sequence: NG_017064.
1.9 Ref allele: C
1.10 Genomic location: 31731
1.11 Alt allele: T

Other optional codes related to simple variation

1.12 dbSNP: rs368949613
1.13 COSMIC
1.14 CIGAR

Other possible attributes

1.15 Allelic Frequency NFR (new) 0.47
1.16 Cytogenetic location: 3q21

Allelic state and interpretive attributes

1.17 Allelic state: Heterozygous
1.18 Pathologic state: Pathologic
1.19 Possible associated phenotype: Acyl-CoA dehydrogenase family, member 9, deficiency of

Case 2 – Complex small variants (those with multiple alleles) -- structure can repeat because there can be more than one complex small variant within one study (e.g. two haplotypes).

Overall attributes for the whole study

Reason for study
Genetic disease(s) assessed
Genomic source class
Gene(s) examined
Gene mutations tested for
Ranges of DNA sequence examined
Full narrative report
Genetic disease overall interpretation

??Assembly and Build – Only needed for genomic coordinates- can we say it once per study?

First complex variant consisting of more than one simple variant -- could have more than one

1	Complex small variant ID:	217737
2	Complex small variant name:	NM_014049.4 (ACAD9):c.[1249C>T];[1030-1G>T] Compound heterozygote (Choices of)
3	(Maybe) complex variant type	

First contained simple variant

1.1	Simple variant ID:	39837
1.1.1	Simple variant type:	SNV

Transcript specification

1.1.2	Gene:	ACAD9
1.1.3	Transcript Ref Sequence:	NM_014049.4
1.1.4	DNA change:	c.1249C>T
1.1.5	Amino acid change:	p.Arg417Cys

Genomic specification

1.1.6	Genomic Ref Sequence:	NG_017064.1:
1.1.7	Ref allele:	C
1.1.8	Genomic location:	31731
1.1.9	Alt allele:	T
1.1.10	Allelic frequency	

[Etc. repeat attributes down to 1.19 in the simple small variant as selected by senders.]

Second contained simple variant

1.2	Simple variant ID:	214385
1.2.1	Simple variant type:	SNV

Transcript specification

1.2.2	Gene:	ACAD9
1.2.3	Transcript Ref Sequence:	NM_014049.4
1.2.4	DNA change:	c.1030-1G>T
1.2.5	Amino acid change:	-

Genomic specification

1.2.6	Genomic Ref Sequence:	NG_017064.1:
1.2.7	Ref allele:	G
1.2.8	Genomic location:	29896
1.2.9	Alt allele:	T
1.2.10	Allelic frequency	0.48

[Etc. repeat attributes down to 1.19 in the simple small variant as selected by senders.]

Allelic state and interpretive attributes for the complex variant (may also need some on each simple variant)

3	Allelic state:	Heterozygous
4	Pathologic state:	Pathogenic
5	Possible associated phenotype:	

Case 3 – Structural (copy number) variationsOverall attributes for the whole study

Reason for study
 Genetic disease(s) assessed
 Genomic source class
 Gene(s) examined
 Gene mutations tested for
 Ranges of DNA sequence examined
 Full narrative report
 Genetic disease overall interpretation

1.1	Structural variation name:	CMT1A duplicated region transcript 8
1.2	Gene symbol:	CDRT8
1.3	Reference Sequence ID:	NC_000017.11
1.4	Structural variant reported start-end:	
1.5	Precision of boundaries:	
1.6	Structural variant reported aCGH ratio:	
1.7	DNA sequence variation type:	Duplication
1.8	Structural variant length:	1203
1.9	Structural variant outer start-end:	14947741-15265357
1.10	Structural variant inner start-end:	
1.11	Structural variant HGVS:	
1.12	Structural variant ISCN:	
1.13	Structural variation cytogenic location:	17p12

Questions – Discussion points

1. Think it would be simpler to combine the loop for simple small variants with the complex small variants and indicate whether simple small or complex as another attribute. What are the thoughts?
2. We only need the assembly and build for genomic coordinates – and there is more than one way to specify. Presume we would only have to specify the assembly and build once in the overall report section. That would make things simpler if so.
3. We presume there is no need for an explicit node (level) for genotype, because the whole report is the genotype and we have an overall report section where we could put any needed “genotype” information without adding another level.
4. The HGVS of the complex small variants really “says it all” and one could conceive of reports that did not carry the detailed information about each contained Allele. In that case, would not have a place for the amino acid level definition or the genomic specification or the allelic frequency. Just something to think about.