Variant annotation

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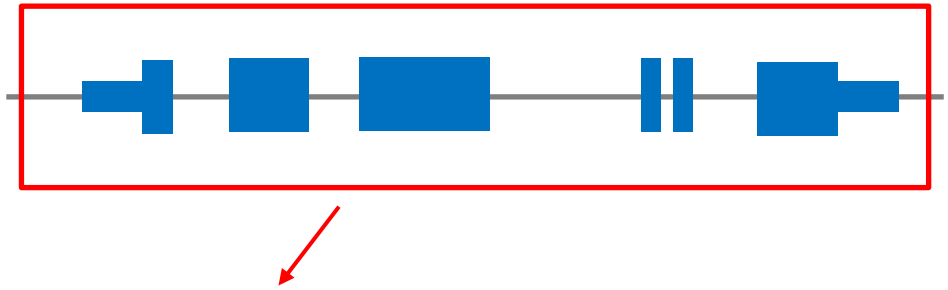
Variant annotation

Total number of variants (= differences to reference genome) detected in two example datasets:

	Whole exome (WES)	Whole genome (WGS)
Total nbr variants	106’693	4’175’605

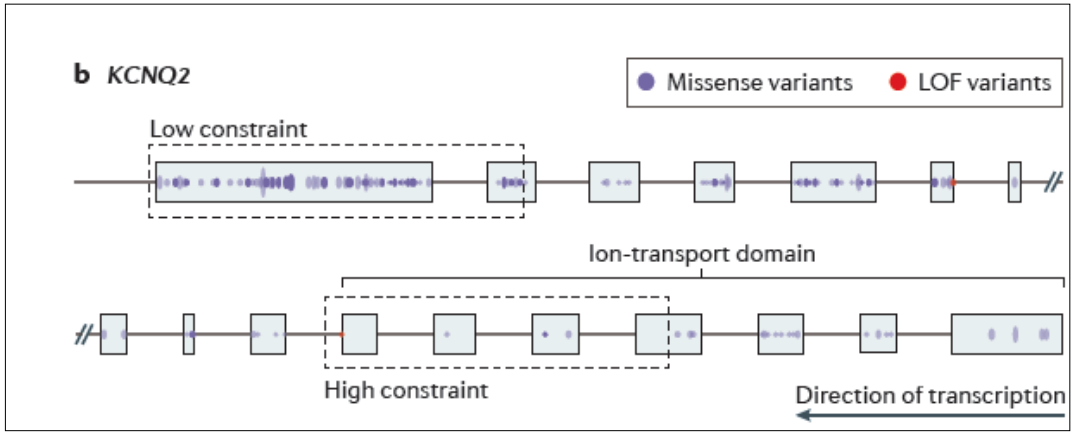
We need to prioritise these variants to be able to identify possible disease causing mutations

Gene-level annotation



Annotation for the **entire gene**. For example:

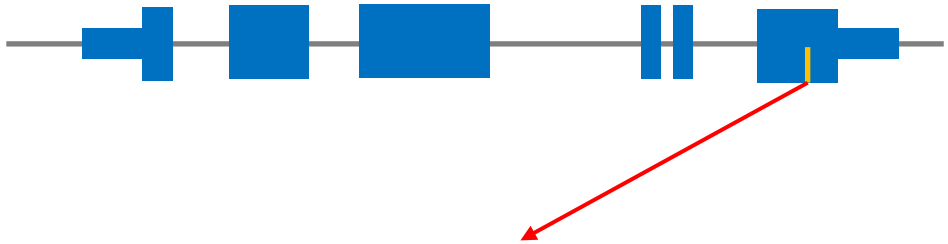
- Selective constraint: How often is the gene mutated?



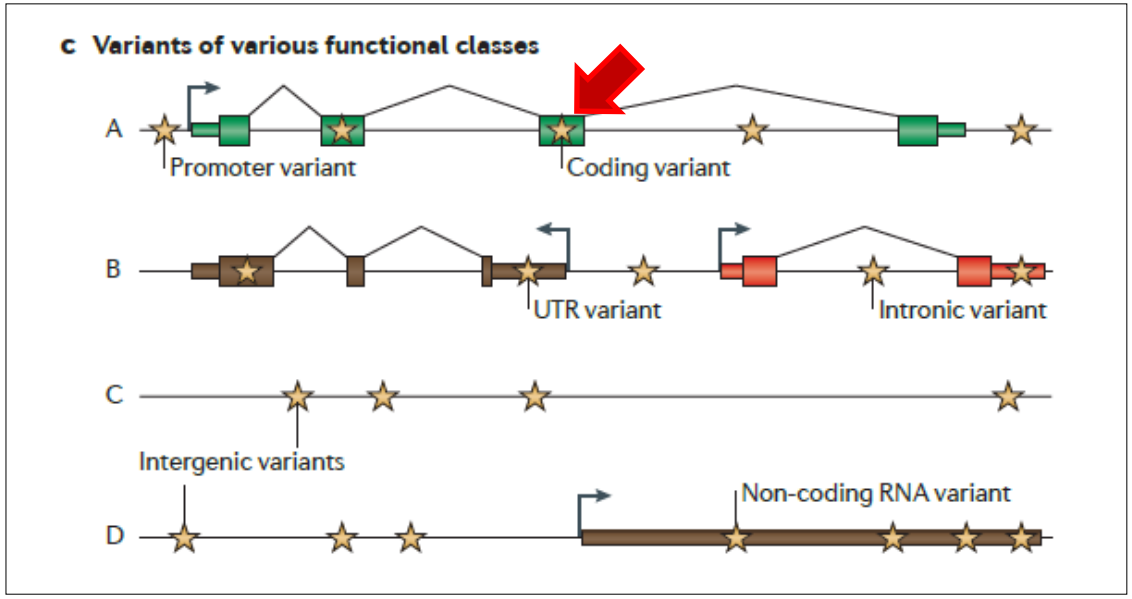
From Eilbeck et al. 2017 Nature Methods

- Is the gene known to be associated with a particular (disease) phenotype?

Variant-level annotation

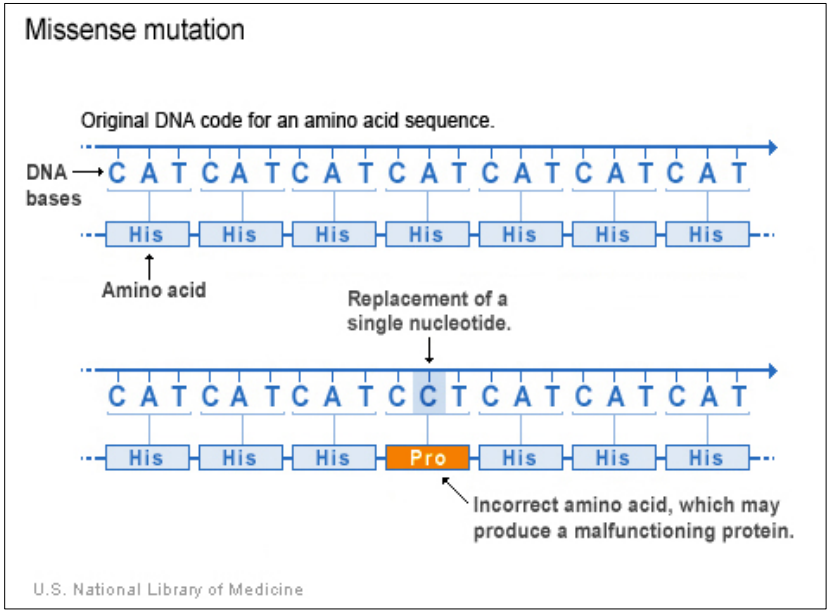


Annotation for individual variant, e.g. SNP



From Cooper & Shendure 2011 Nature Reviews Genetics

Identify coding variants



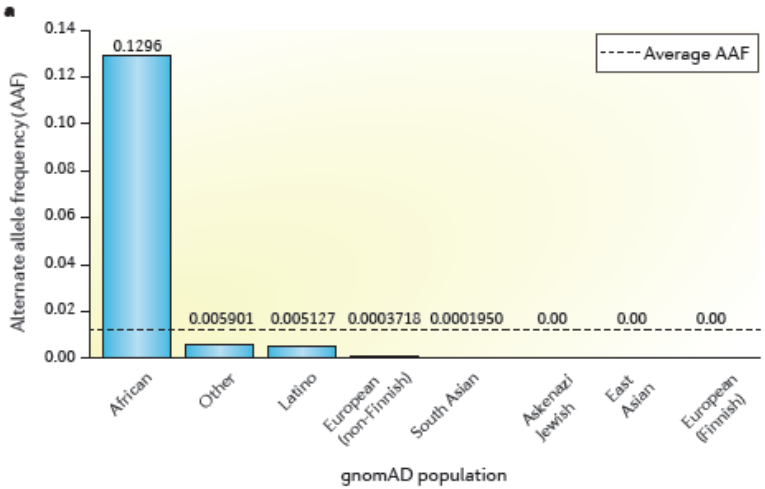
	WES	WGS
Total nbr variants	106’693	4’175’605
Coding variants	10’494	10’263

Of course, non-coding variants can also have functional effects but these are, in general, more poorly understood

Variant ranking

Based on **allele frequency in the general (healthy) population**. Important to consider the correct reference population!

Allele frequencies for rs79444516

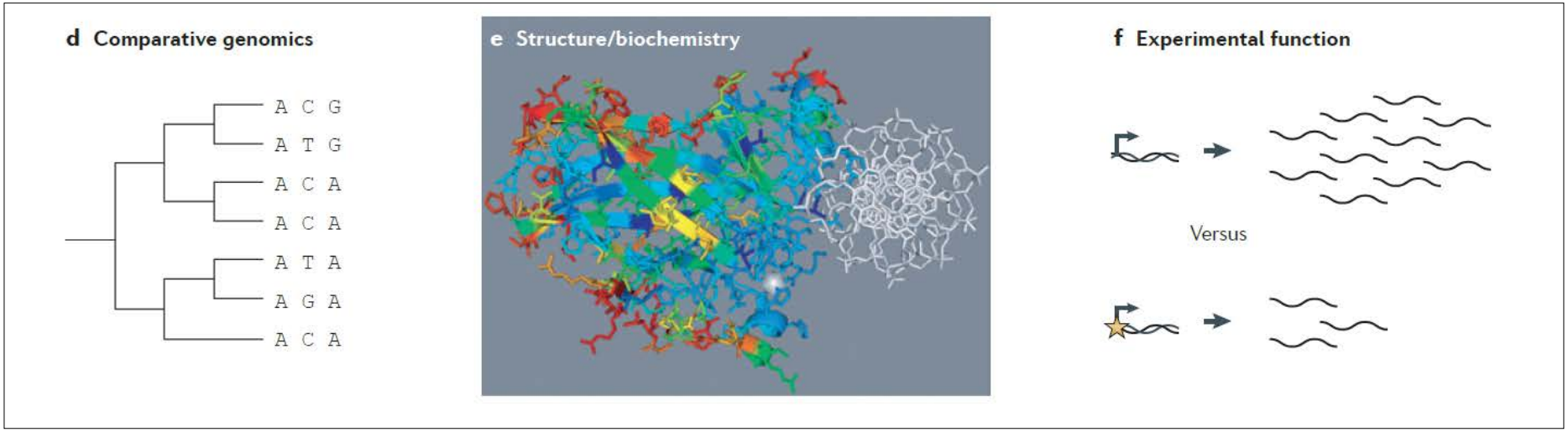


Eilbeck et al. 2017 Nature Methods

	WES	WGS
Total nbr variants	106’693	4’175’605
Coding variants	10’494	10’263
Coding, rare (<1%) variants	411	

Variant ranking

Based on **effect prediction scores** (see Ritchie & Flicek 2014 Genome Medicine for a very good overview)

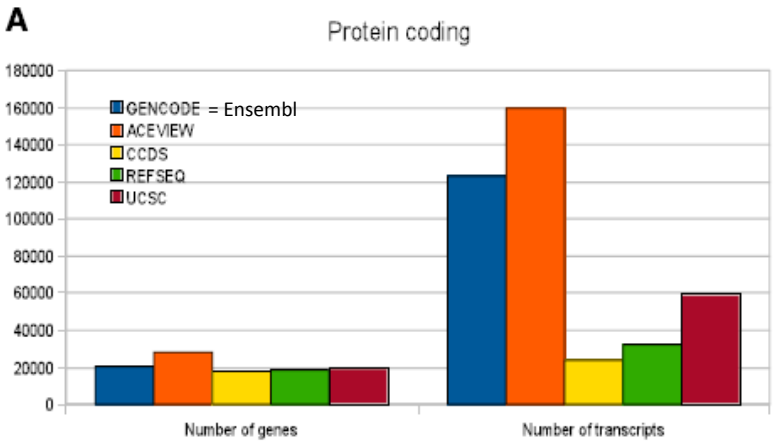


Cooper & Shendure 2011 Nature Reviews Genetics

- For the human genome, many of these scores have been precomputed: https://sites.google.com/site/jpopgen/dbNSFP
- Important: For many of these predictors, it has been shown that the average scores differ between known deleterious and putatively neutral variants but, often, there is quite some overlap and individual variants may be misassigned

Issues/difficulties with variant annotation

- **Different annotations** for the same species, for example Ensembl, RefSeq etc



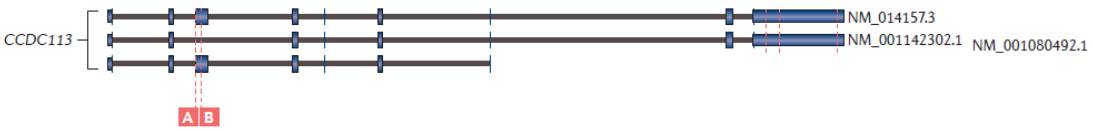
From Harrow et al. 2012

- Annotations are regularly updated

→ It is critical to keep track of exact annotation + version used in each project!

Issues/difficulties with variant annotation

- Many genes have **multiple isoforms**
- Annotation may differ between isoforms



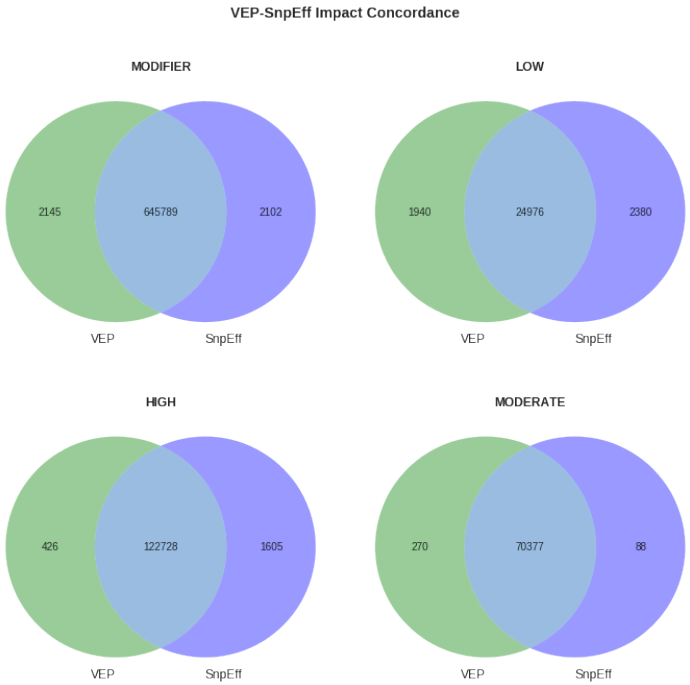
	Variant allele	Gene	Transcript change	RefSeq	Protein change	Molecular consequence
A rs765957496	G	*CCDC113*	c.228+1143A>G	NM_001142302.1	—	Intron variant
	G	*CCDC113*	c.229•2A>G	NM_014157.3	—	Splice acceptor variant
B rs775877153	A	*CCDC113*	c.228+1182T>A	NM_001142302.1	—	Intron variant
	A	*CCDC113*	c.266T>A	NM_014157.3	Met89Lys	Missense variant

Eilbeck et al. 2017 Nature Methods

→ Most annotation tools will select one annotation based on certain criteria, e.g. most serious effect

Issues/difficulties with variant annotation

- Annotation may depend on **tool** that is used → But big efforts to improve consistency



http://andrewjesaitis.com/2017/03/the-state-of-variant-annotation-in-2017/

Variant Effect Predictor VEP

http://grch37.ensembl.org/Homo_sapiens/Tools/VEP