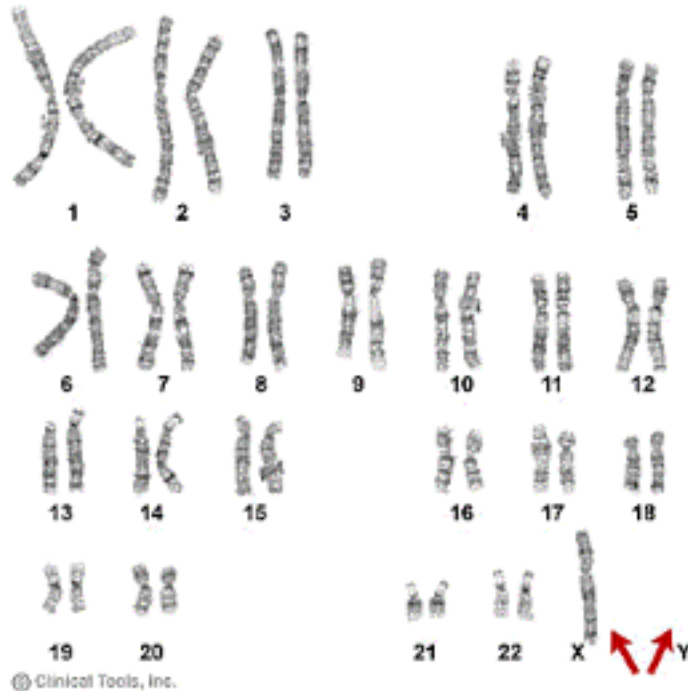


MODULE 2: Human genetic variation — structural variants

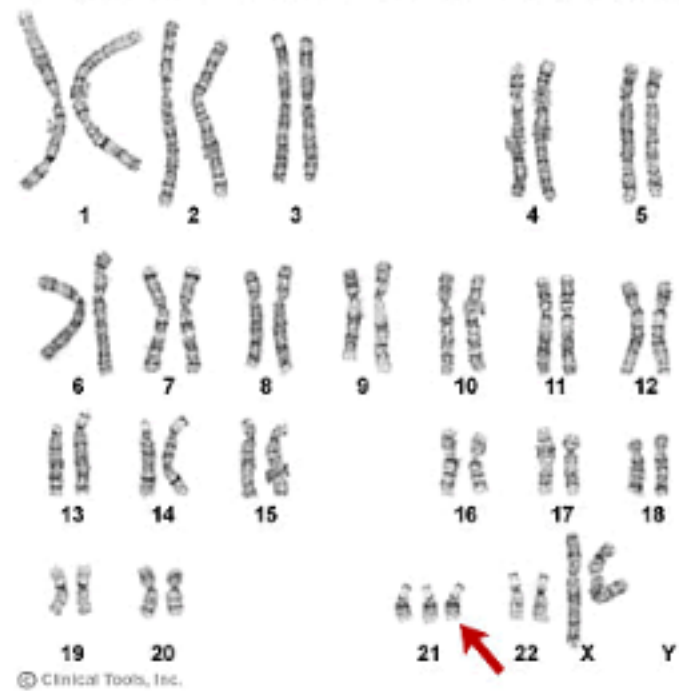
Large structural variants

Karyotype from a female with Turner syndrome (45,X)



Karyotype of Turner syndrome (45 chromosomes instead of 46)

Karyotype from a female with Down syndrome (47,XX,+21)



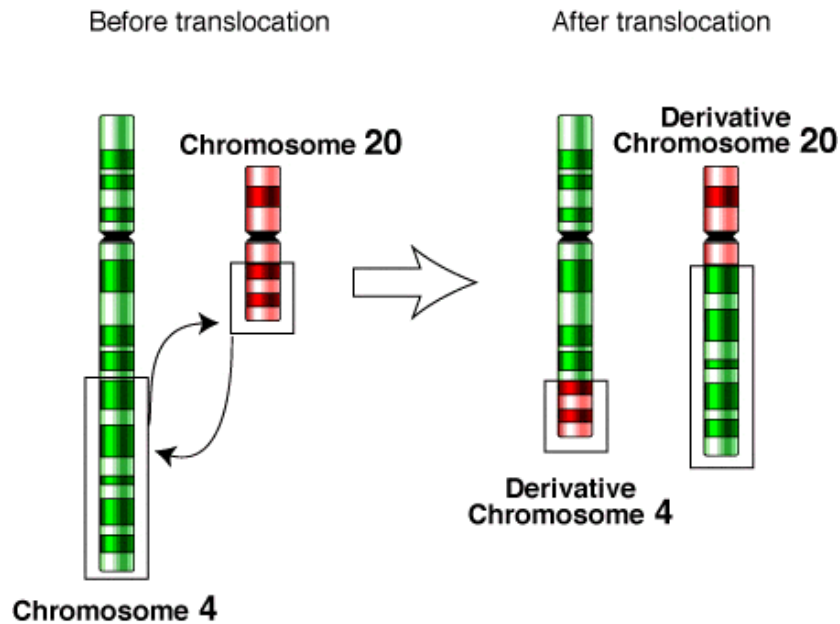
Karyotype of Down Syndrome (47 chromosomes instead of 46)

Numerical variants (aneuploidies)

- Due to non-disjunction of chromosomes during meiosis
- Entire chromosome missing (monosomy) or extra (trisomy)
- Viable autosomal trisomies
 - Trisomy 21 (Down syndrome)
 - Trisomy 13 (Patau syndrome)
 - Trisomy 18 (Edwards syndrome)
- Viable sex chromosome aneuploidies

Sex Chromosome Abnormalities			
Female Genotype	Syndrome	Male Genotype	Syndrome
XX	normal	XY	normal
XO	Turner	XXY	Klinefelter
XXX	Triple-X	XYY	XYY

Translocations, for example



Example of a reciprocal translocation

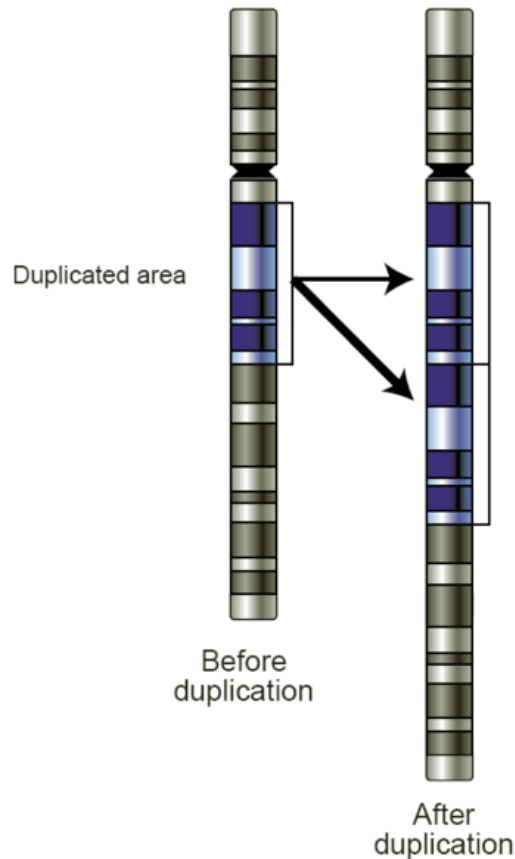
Visible by karyotype

No gain or loss of DNA,
just rearranged

Rare: e.g. translocations
~ 1/600 newborns

Usually harmless unless
breakpoint is in a gene

Copy number variants (CNVs)



Deletions or duplications

Usually too small to visualize under microscope

Typically 1-10 Kb but can be several Mb in size*

Single or multiple copies in tandem

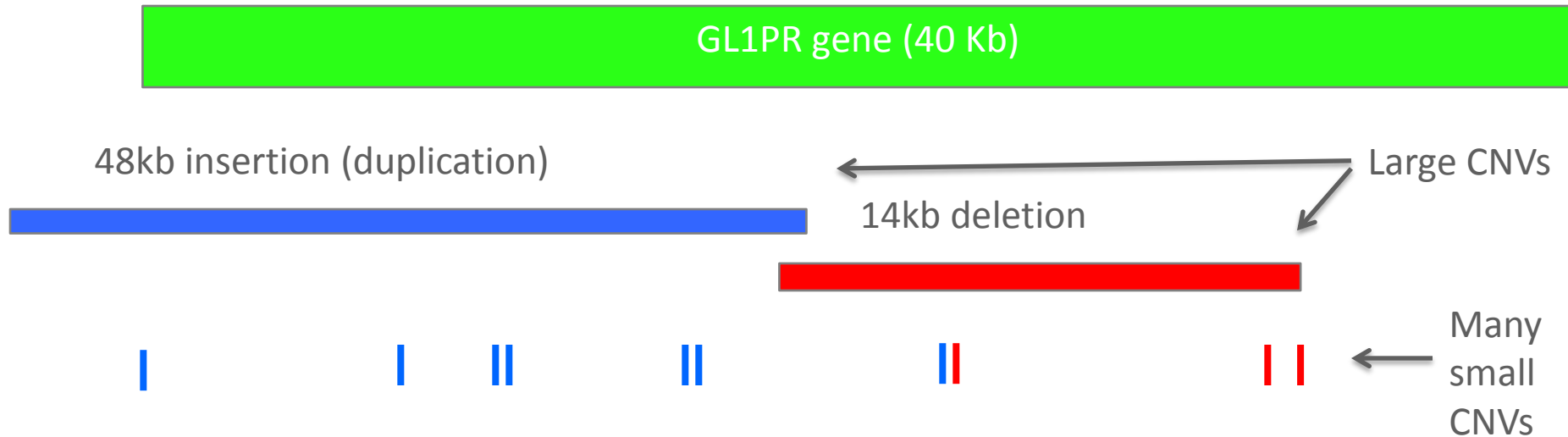
Size of this preview: 392 × 600 pixels. Other resolution: 157 × 240 pixels.

Full resolution (508 × 777 pixels, file size: 20 KB, MIME type: image/png)



This is a file from the [Wikimedia Commons](#).

CNVs can involve genes



- 33 CNVs affecting GLP1R (only 12 shown)
- Range in size from a few bp to several Kb
- 68% of CNVs overlap with genes

Large CNVs can affect multiple genes



Large CNVs

- Less polymorphic (monosomy/trisomy instead of tandem)

Normal



Deletion

Monosomy



Single duplication

Trisomy



- Less common in population
- More likely to be pathogenic (affect more genes)
- More likely to be *de novo*
- How they cause disease:
 - Too little or too much gene product
 - Unmasking of recessive trait

Recessive – both copies of gene affected

2 mutations

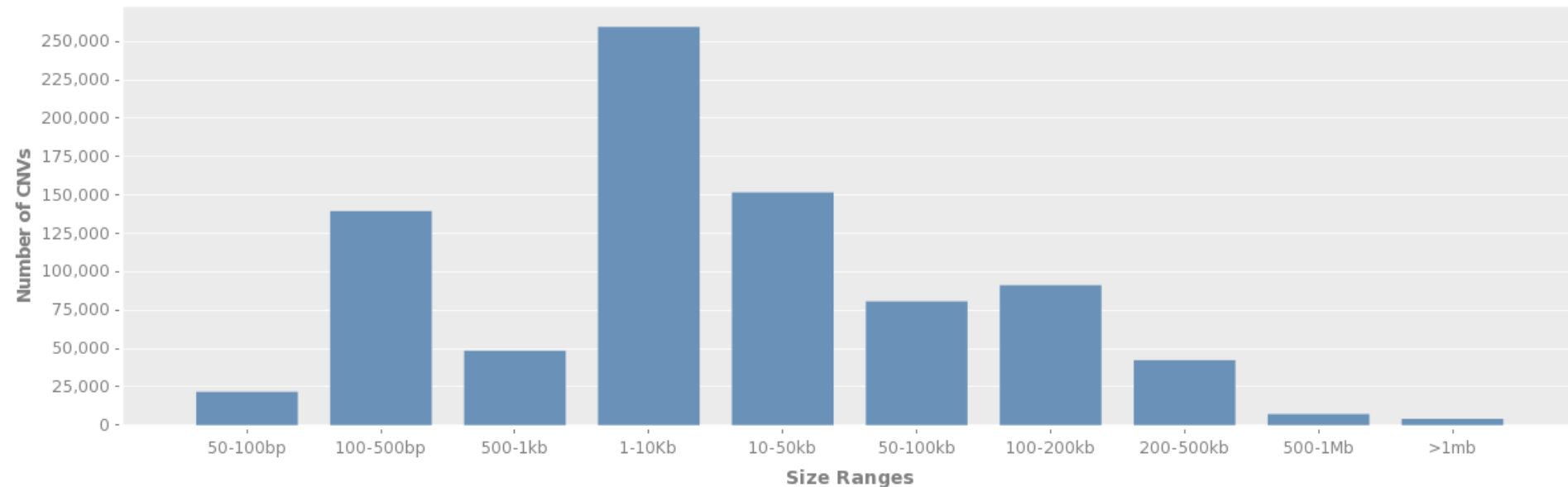


mutation and deletion

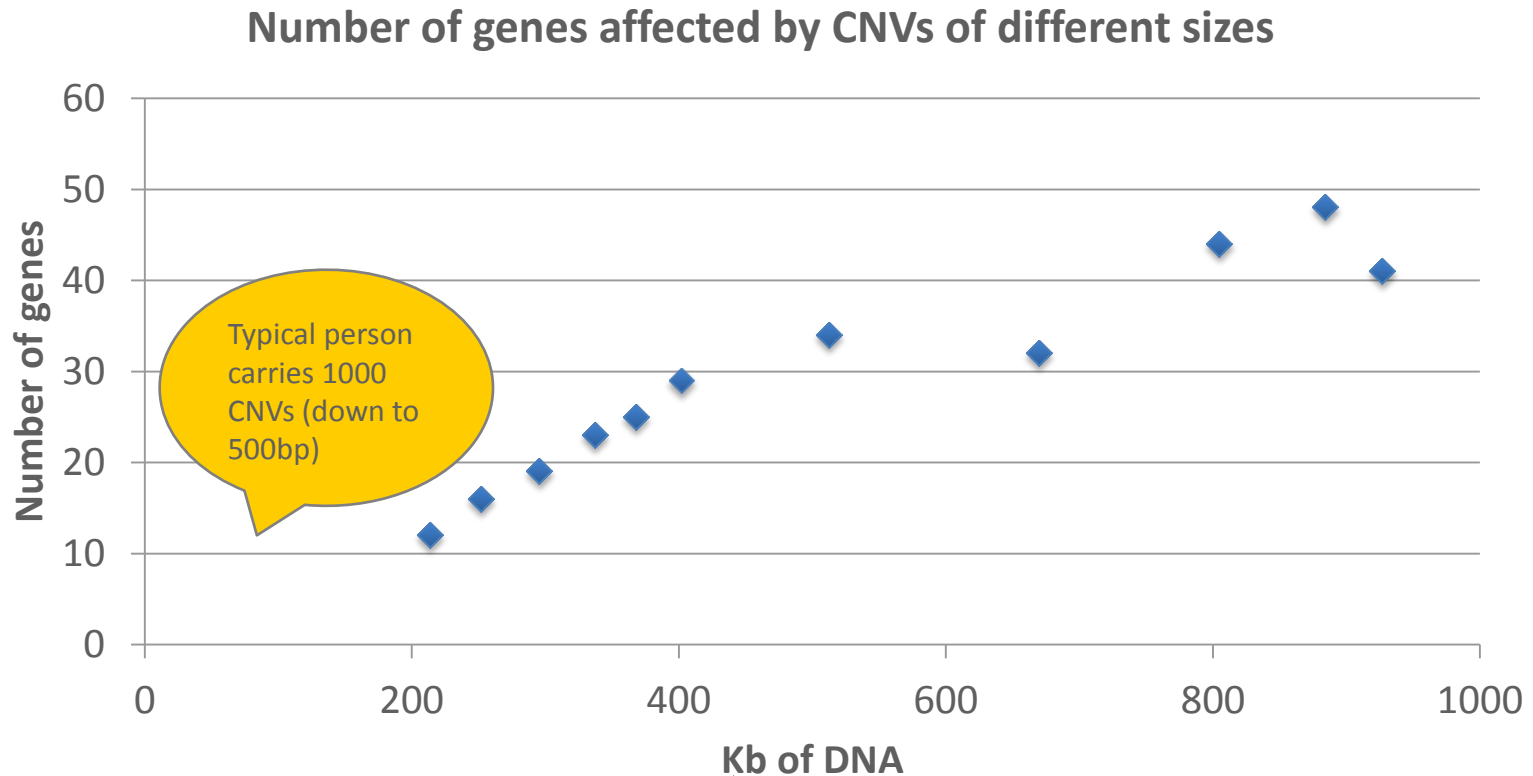


How many CNVs in the population?

*D*atabase of *G*enomic *V*ariants



How many CNVs in an individual?



How many individuals carry one of these?

65-80%

5-10%

1%

Question

The pathogenicity of CNVs is a function of which of the following:

- A. Size
- B. Location
- C. Both size and location

Answer

C. Both size and location

Size... large CNVs are usually more pathogenic than small CNVs

Location... intergenic CNVs are usually not pathogenic, while those that encompass genes are