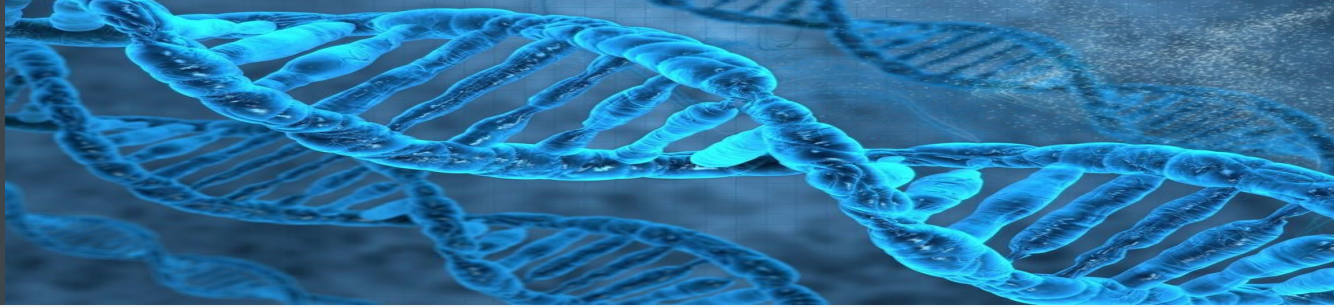


Integrating copy-number analysis with structural-variation detection in 50 ALS patients with two extreme survival phenotypes

Ahmad Al Khleifat



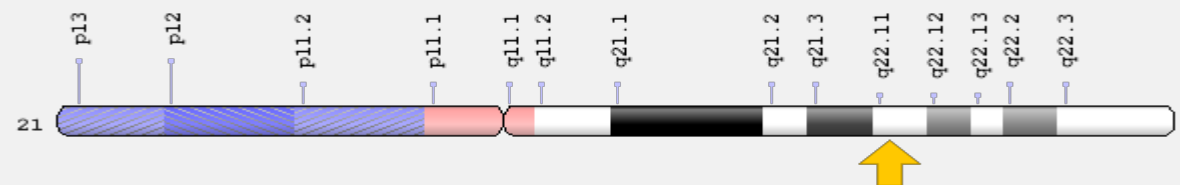
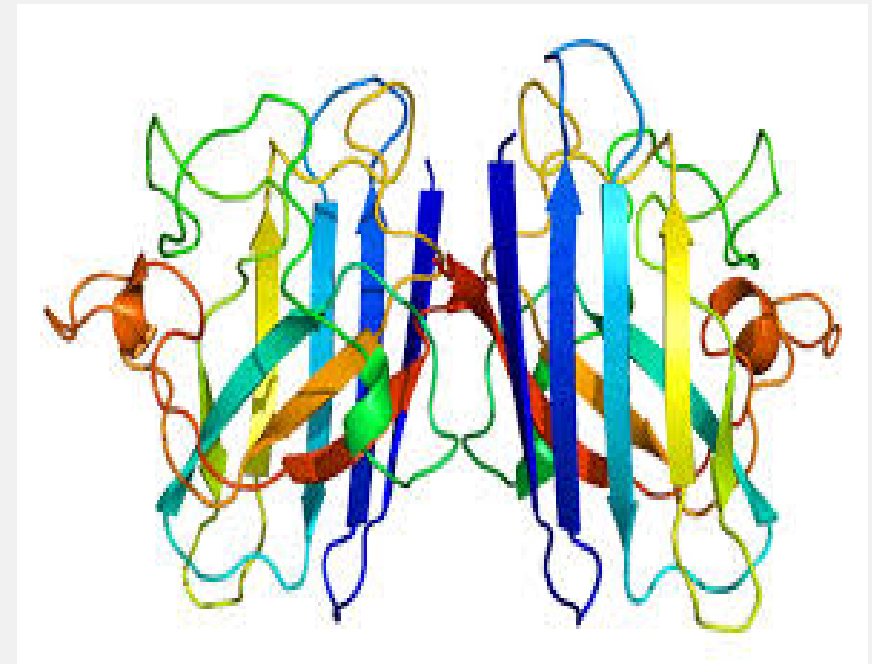
5% have a family history of ALS

- FALS Mendelian genes

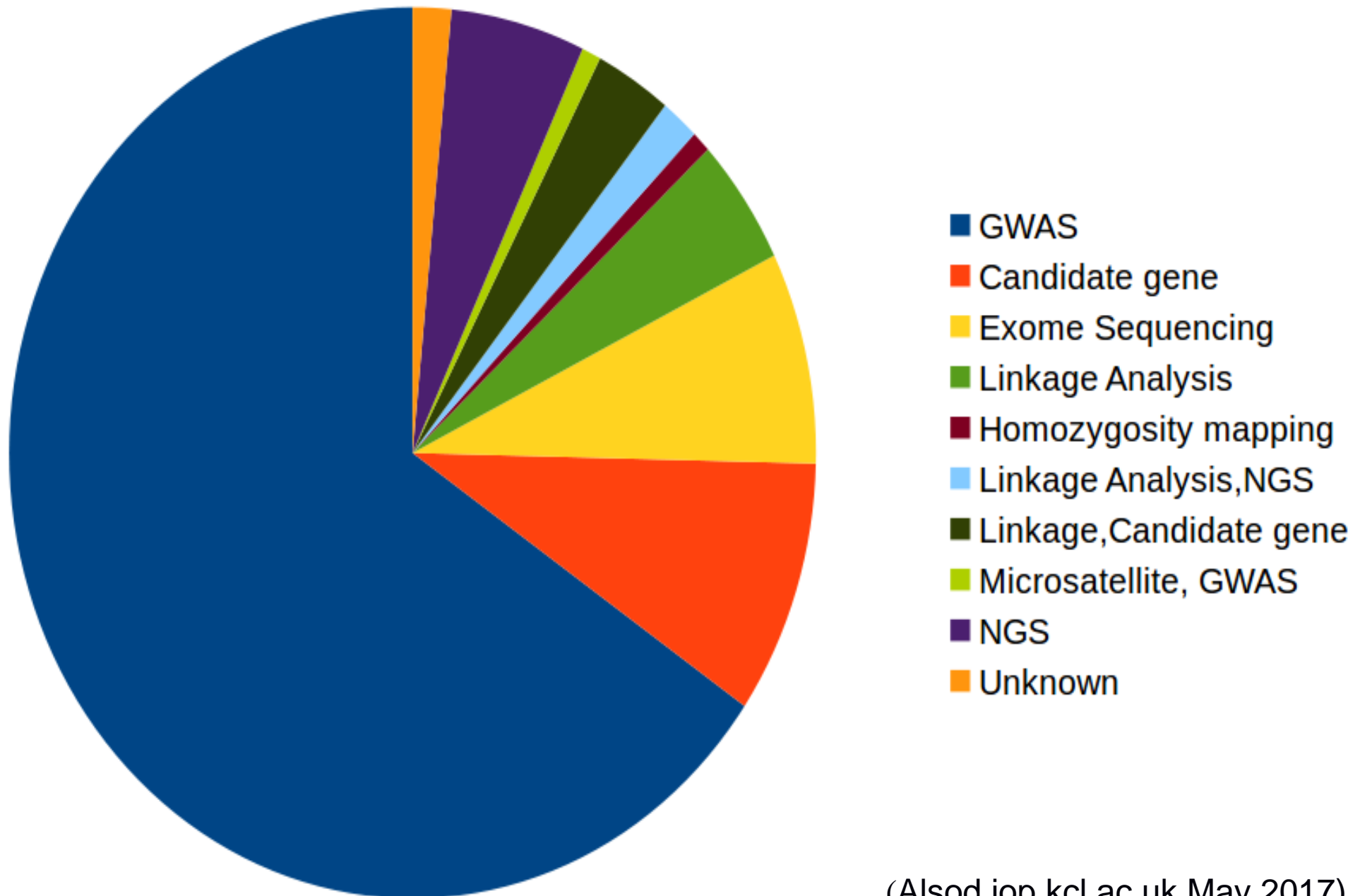
identified in about 70%

- In apparently sporadic cases, twin and population studies

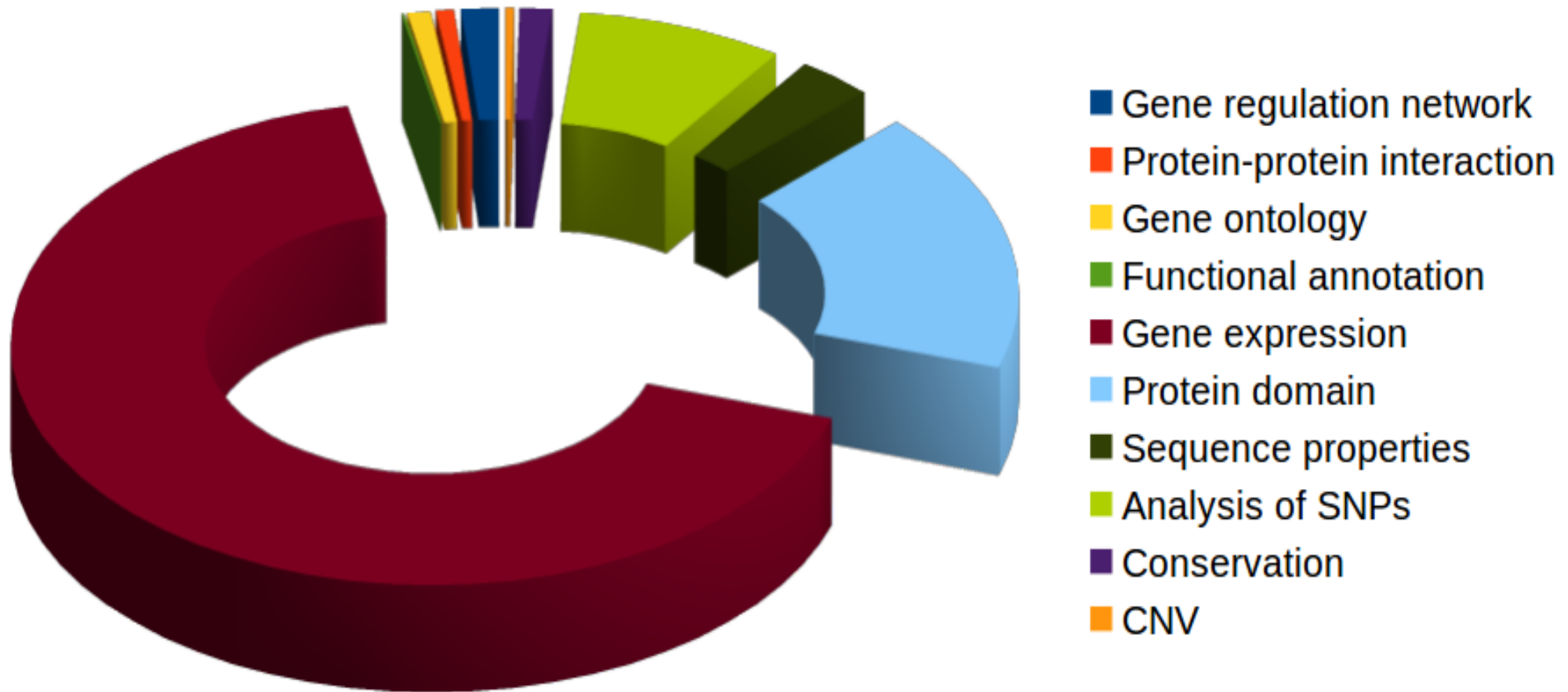
show the heritability is about 60%



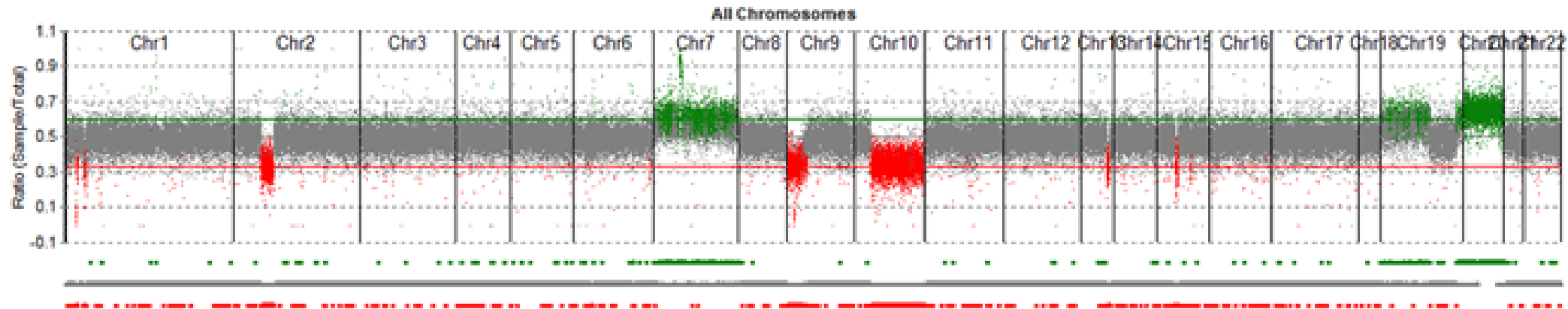
ALS Gene Hunting Methods

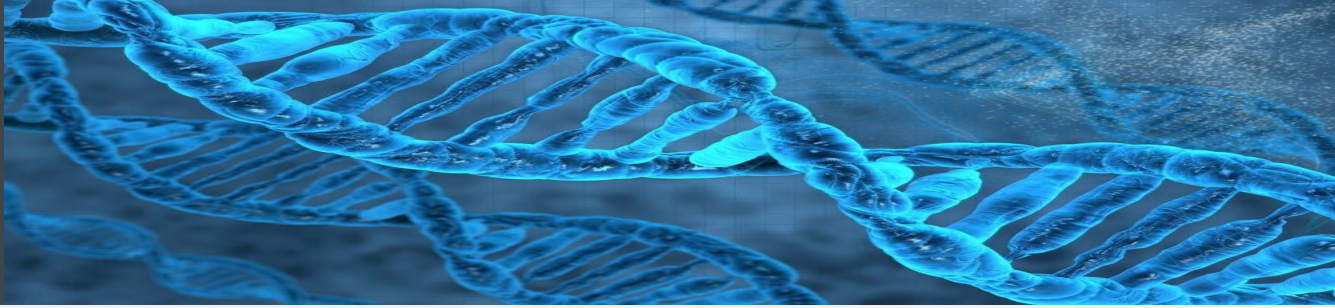


ALS Gene Study Methods

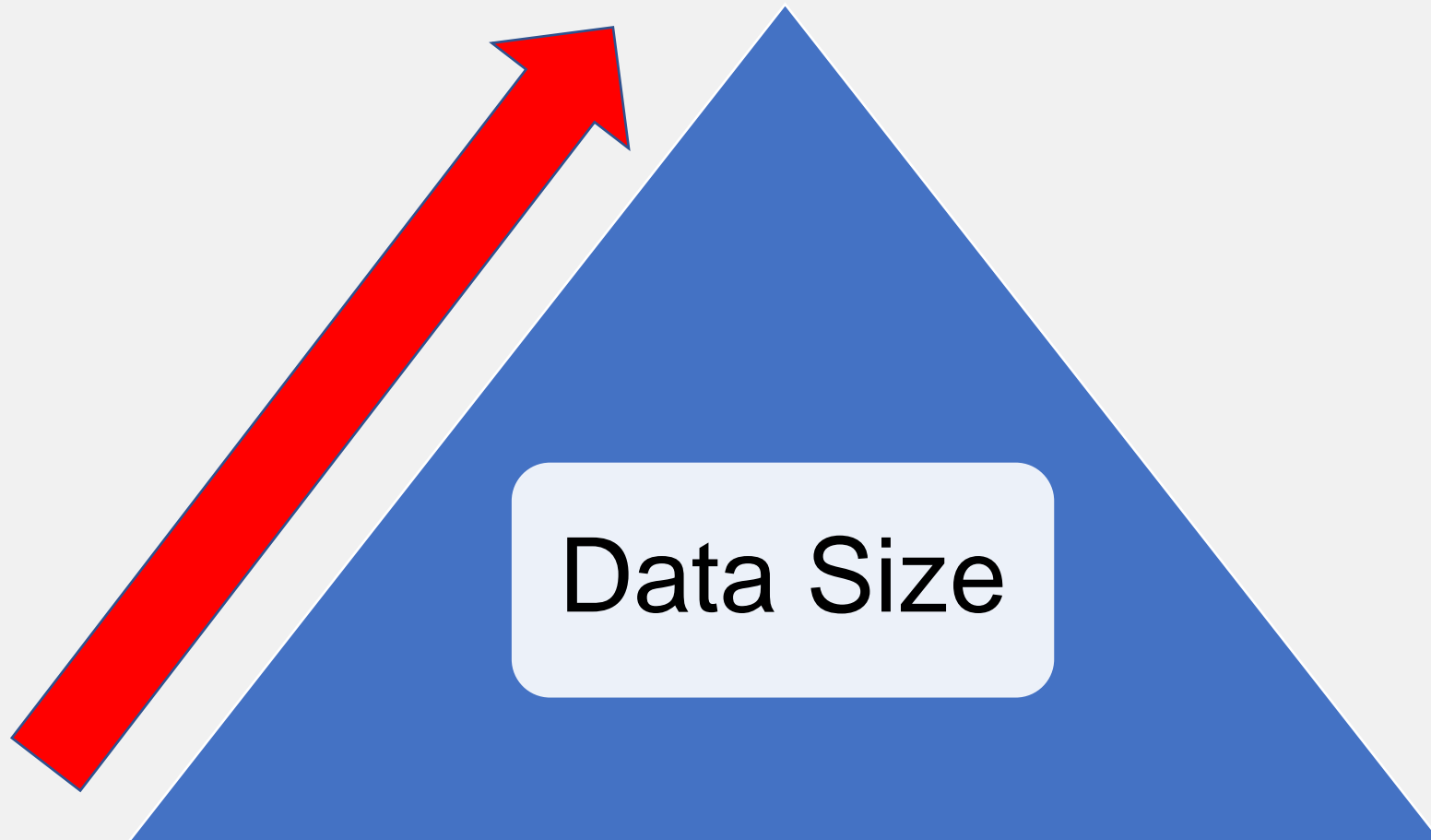


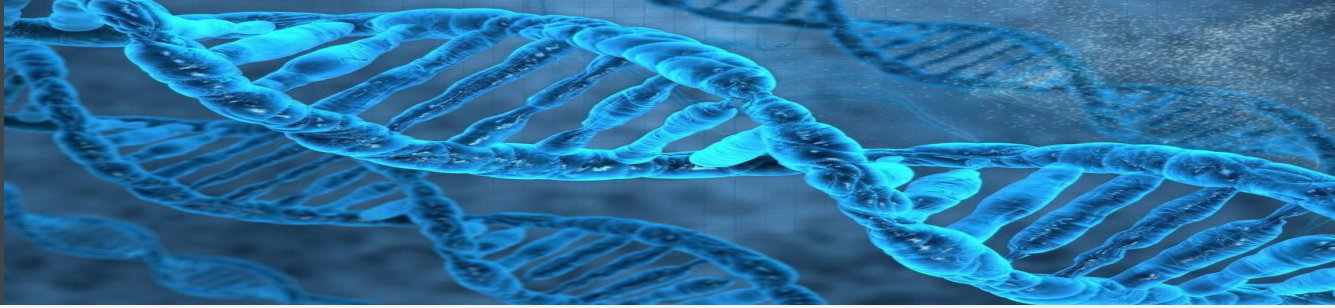
CNVs



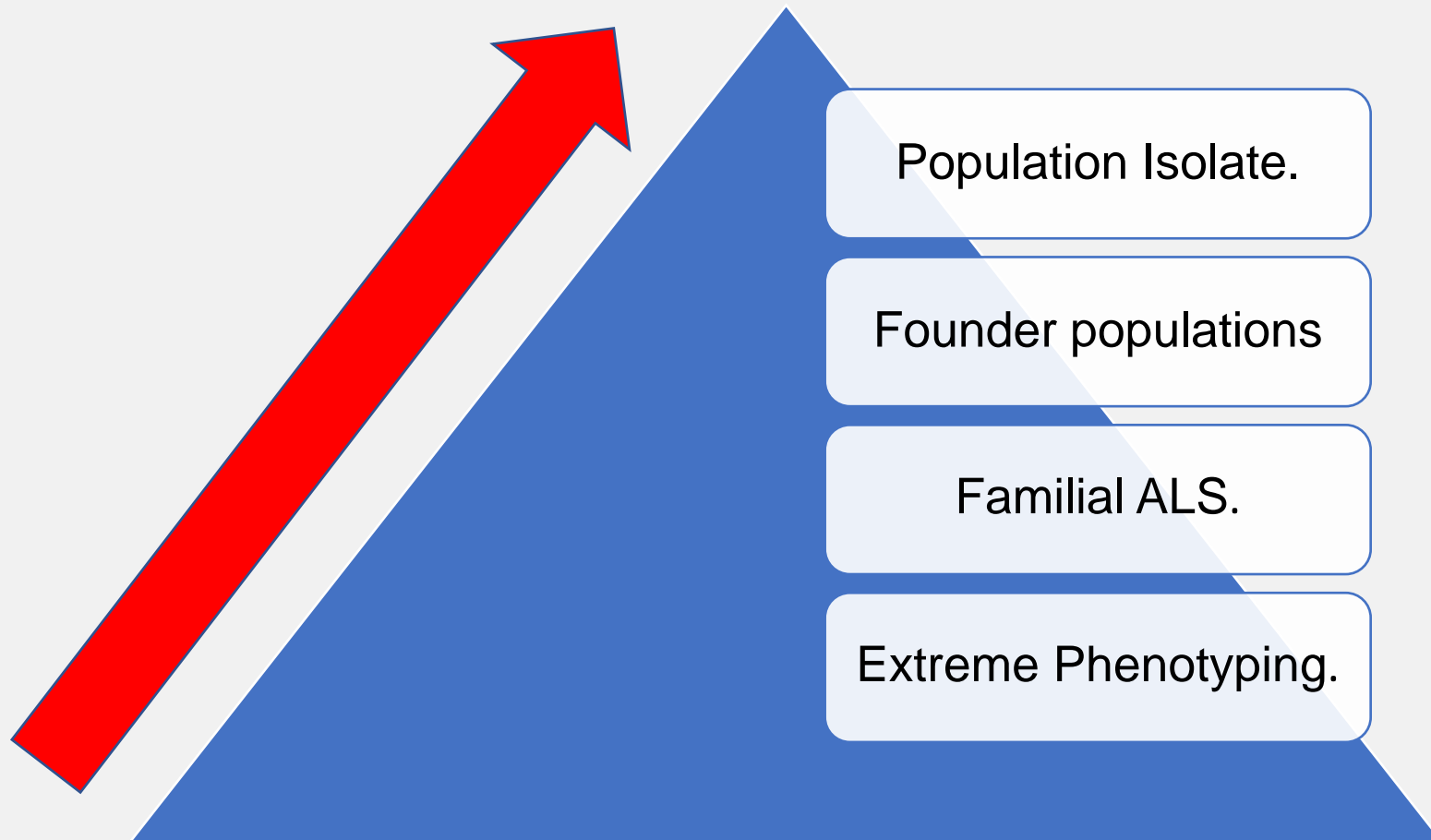


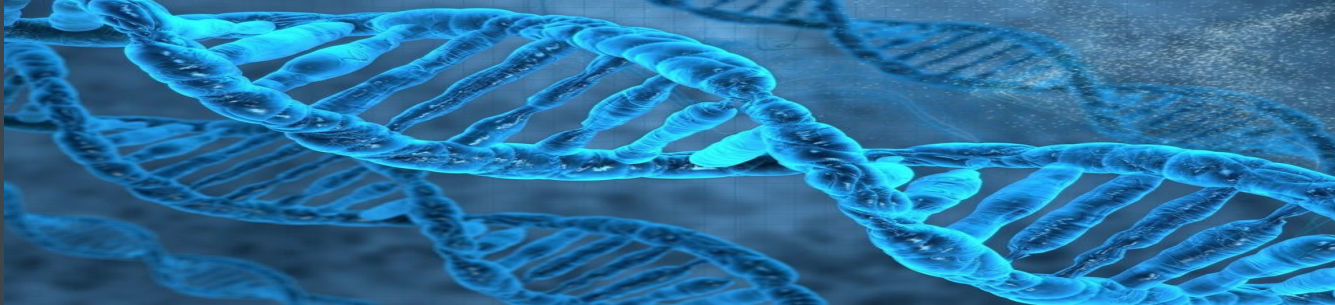
Methodological designs applied to maximize the power of detection:



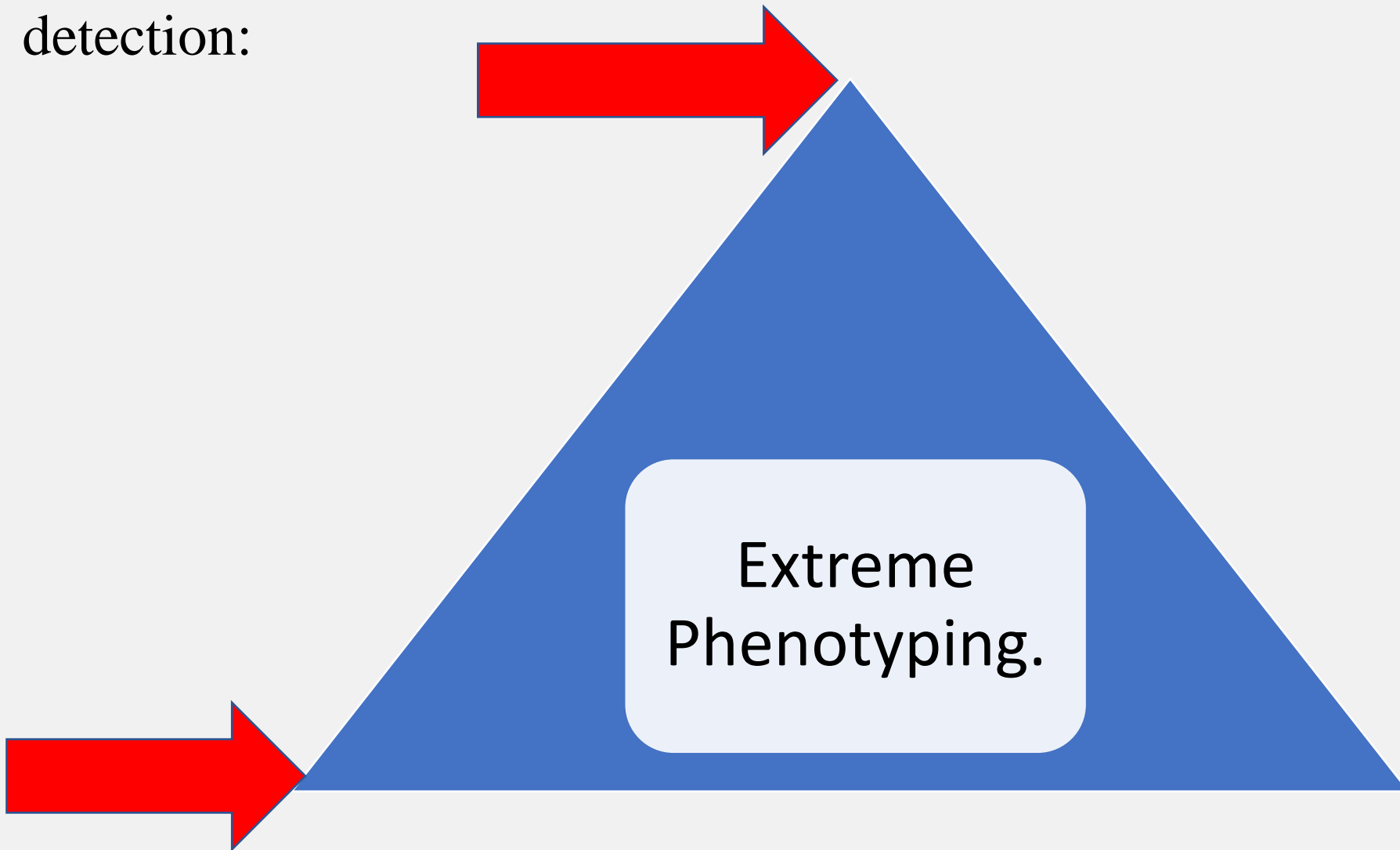


Methodological designs applied to maximize the power of detection:

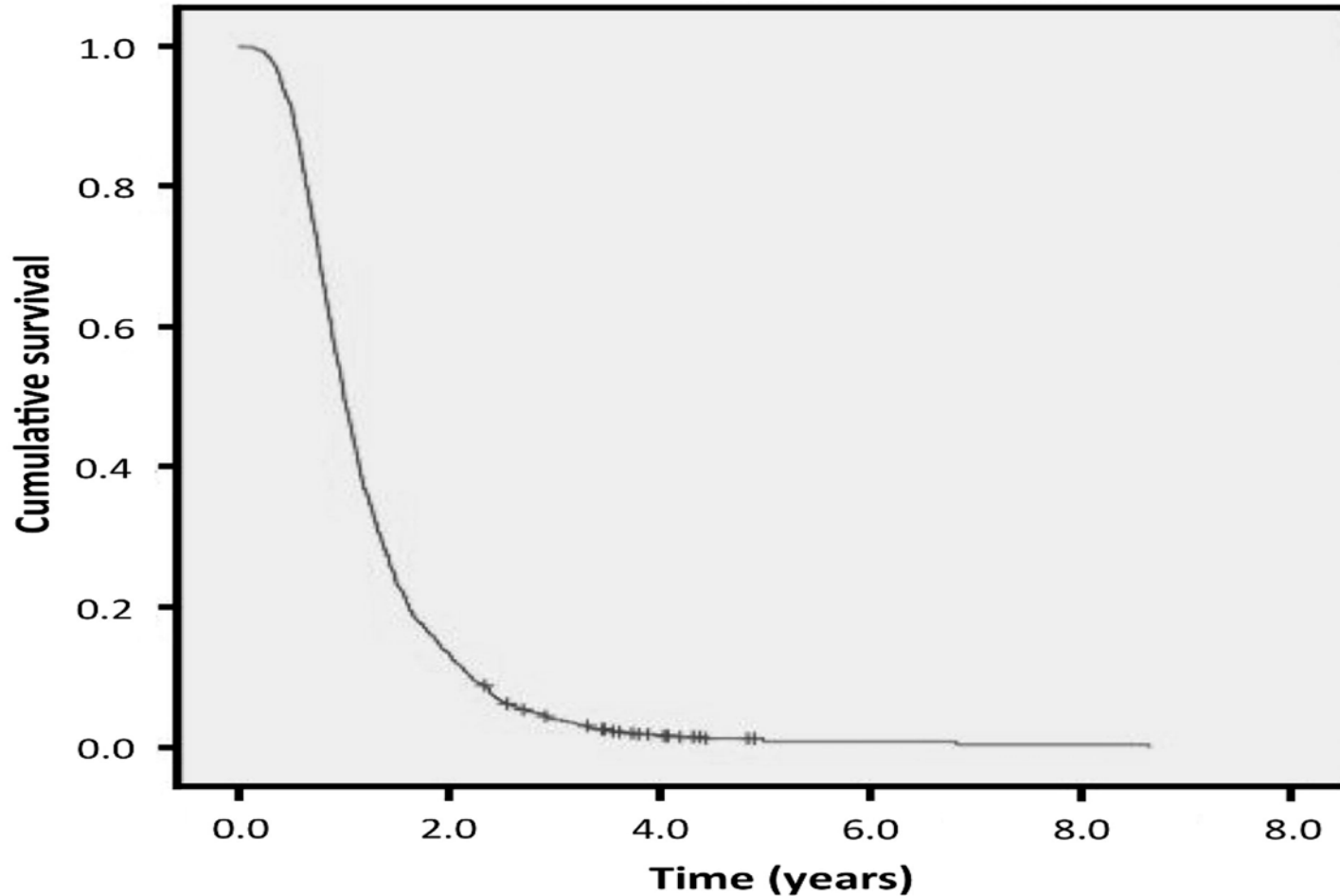




Methodological designs applied to maximize the power of detection:



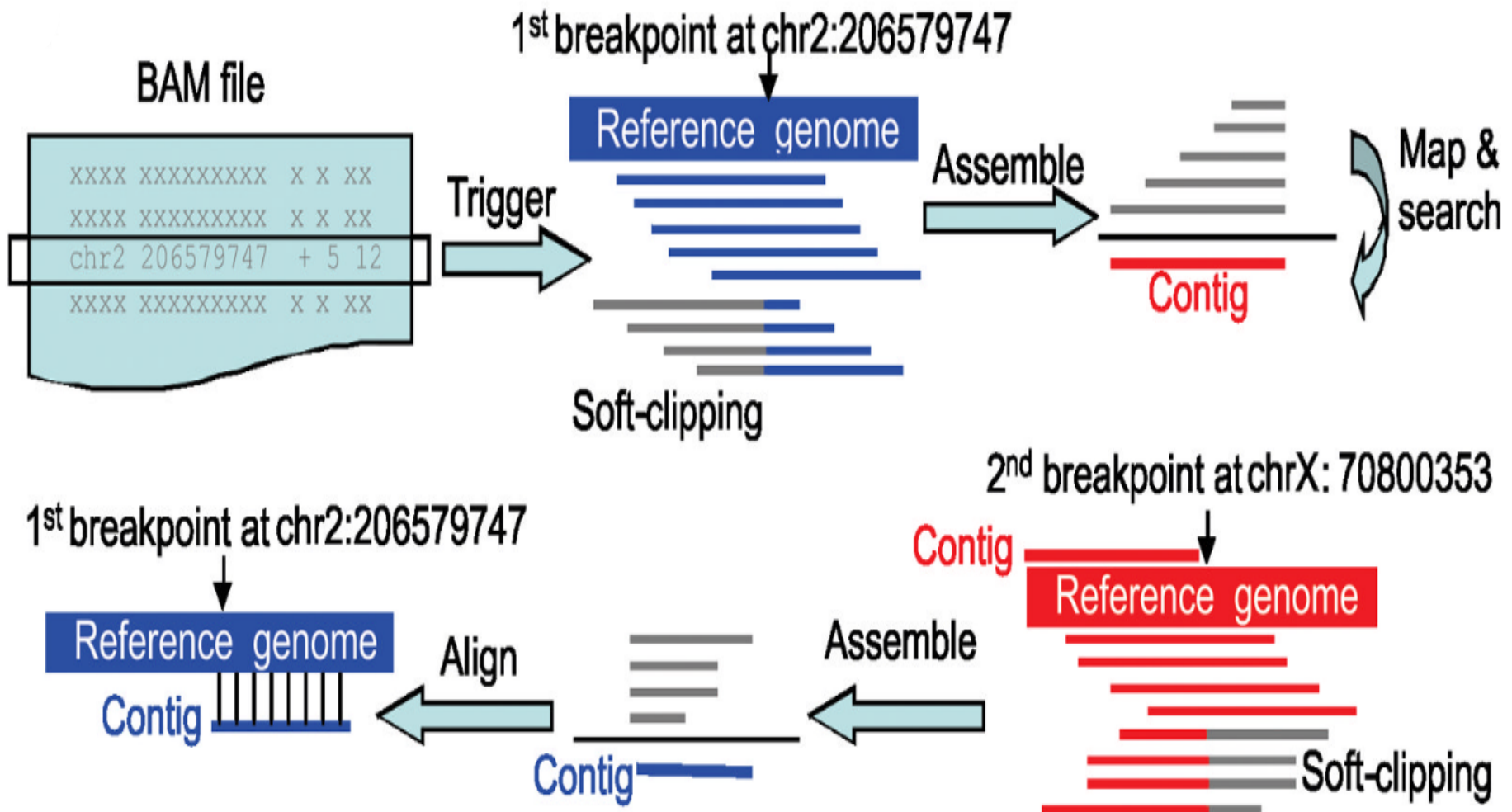
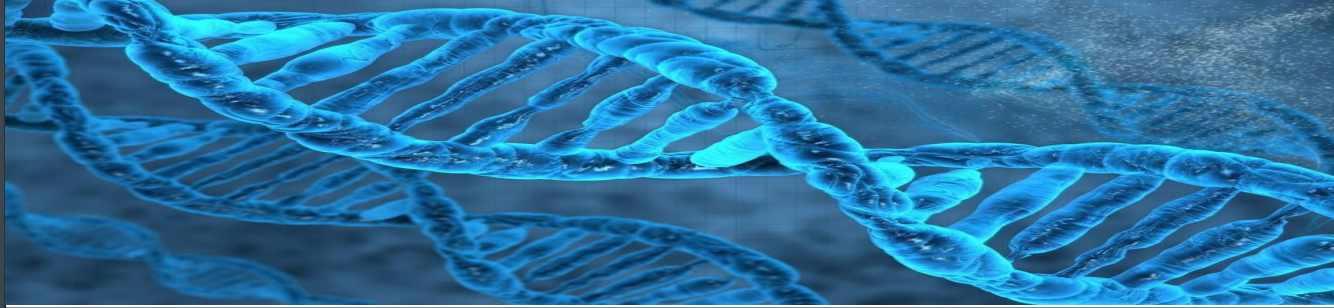
Sample Selection



Kaplan–Meier survival curve from which the study groups were derived.

Demographic features of the long and short survival groups

	Long survival group	Short survival group
Number	25	25
Male:Female	10: 15	8: 17
Mean age of onset (y)	53.7	60.2
Proportion alive	0.6	0.04
Median survival (KM method) (y)	9.16	1.04



Pipeline

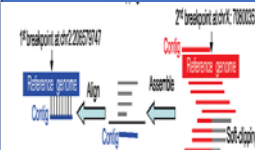


BAM files from WGS

Computer analysis



CNV results



Statistical analysis

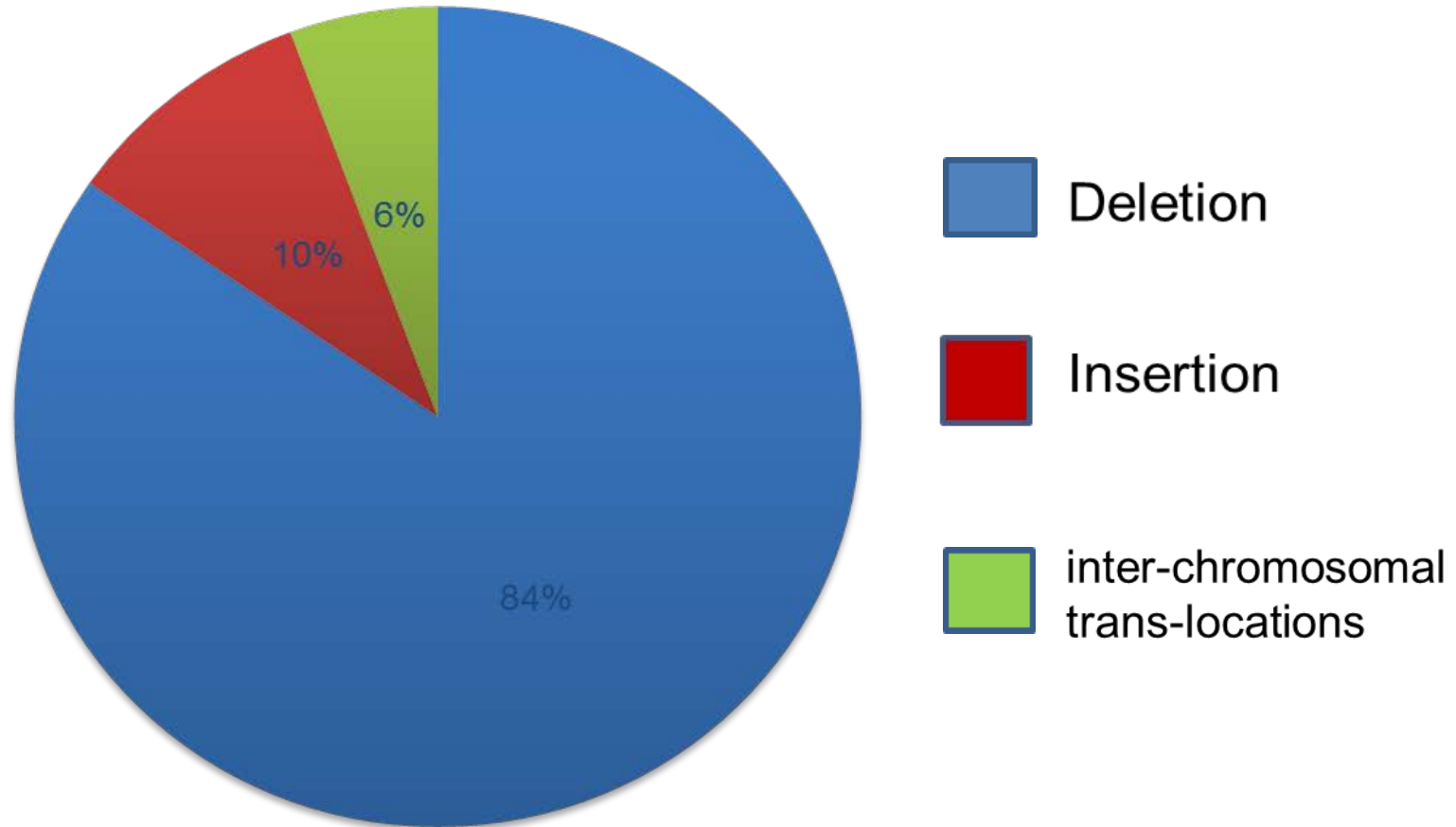


Mapping Copy Number Variations



Alignment of next-gen reads in both long survival (top panel) and normal (bottom panel) at A- Inter-chromosomal translocations spanning chr20:18591542-1859588. B- Deletion spanning chr20: 14466308-14466371

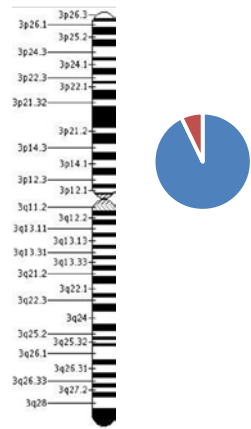
Copy Number variation analysis



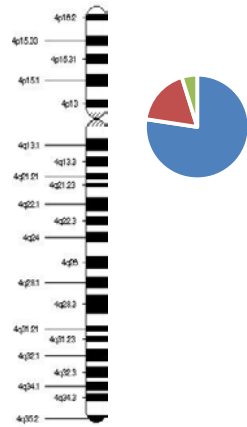
983 Copy number variations were identified in 50 samples

Structural variations and CNVs observed in ALS short survival group

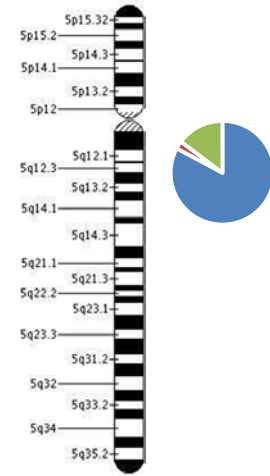
Chr3-15



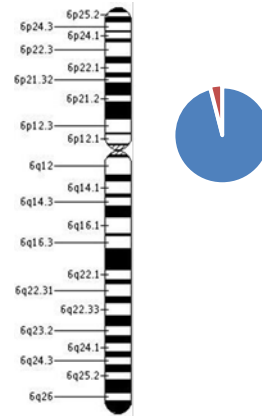
Chr4-60



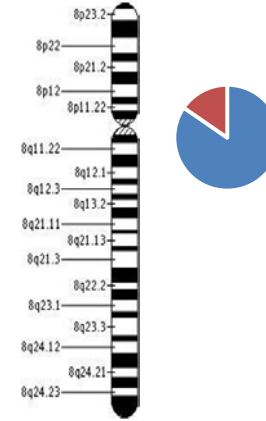
Chr5-122



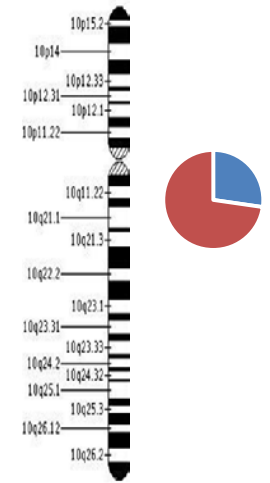
Chr6-80



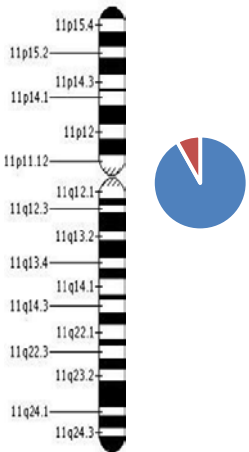
Chr8-15



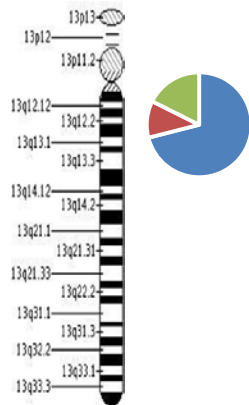
Chr10-11



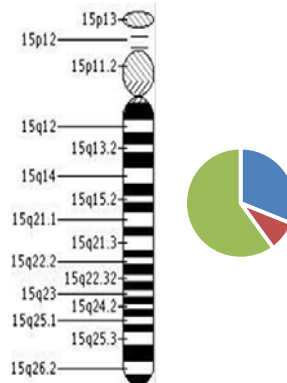
Chr11-39



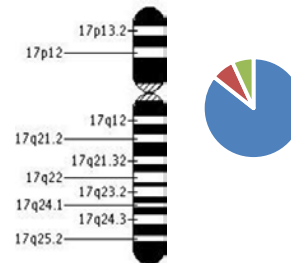
Chr13-171



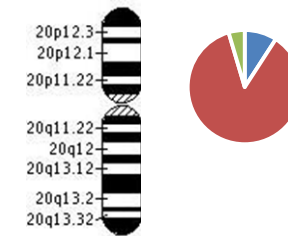
Chr15-45



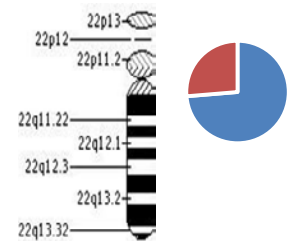
Chr17-146

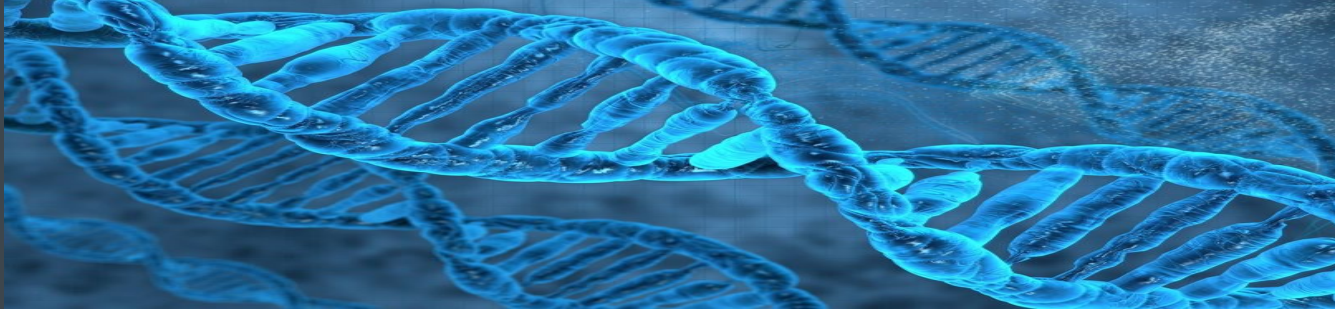


Chr20-131



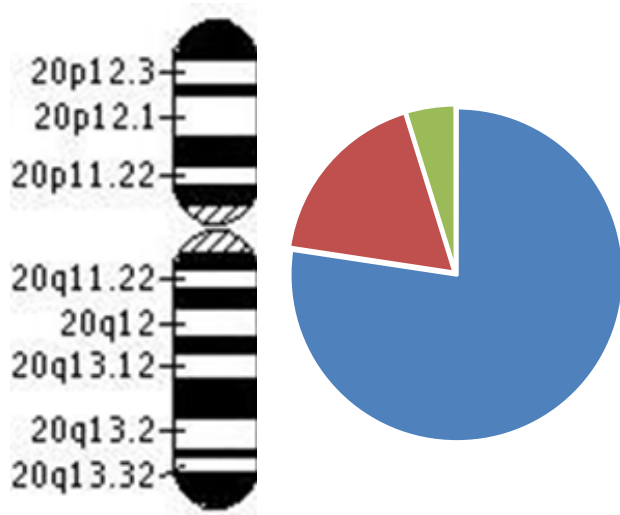
Chr22-38





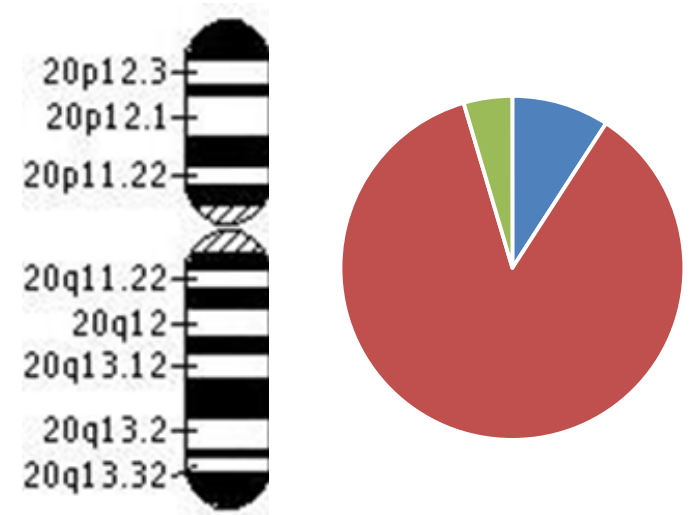
Comparison between CNV observed in chromosome 20 between the long and short survival groups

Chr20-67

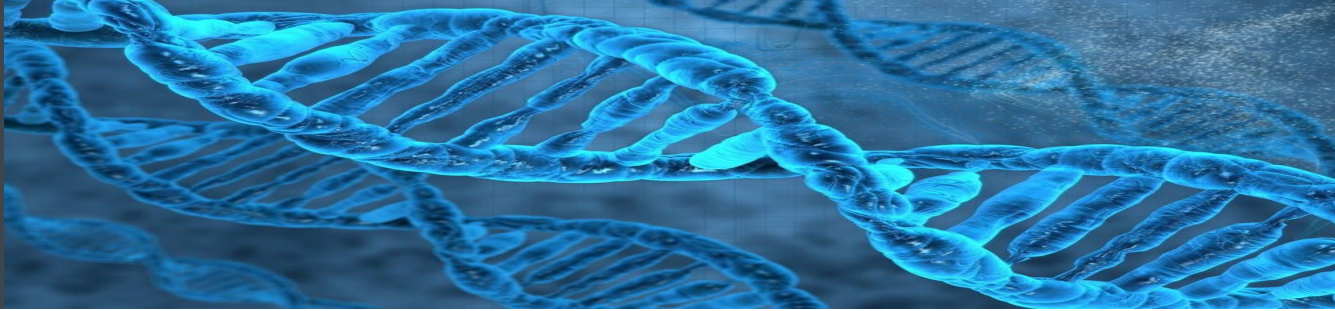


Long survival group

Chr20-131



Short survival group



Conclusions

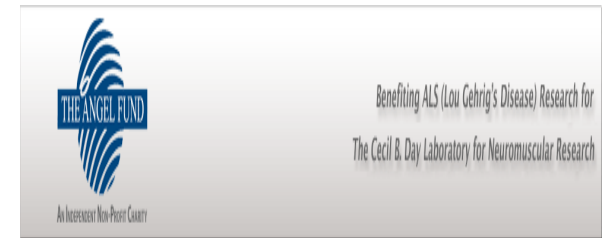
- Deletion is the most common CNV observed in ALS in the two extreme survival groups
- Chromosome 13 and 17 show the highest structural variations in the ALS short survival group
- Further analysis and validation is needed



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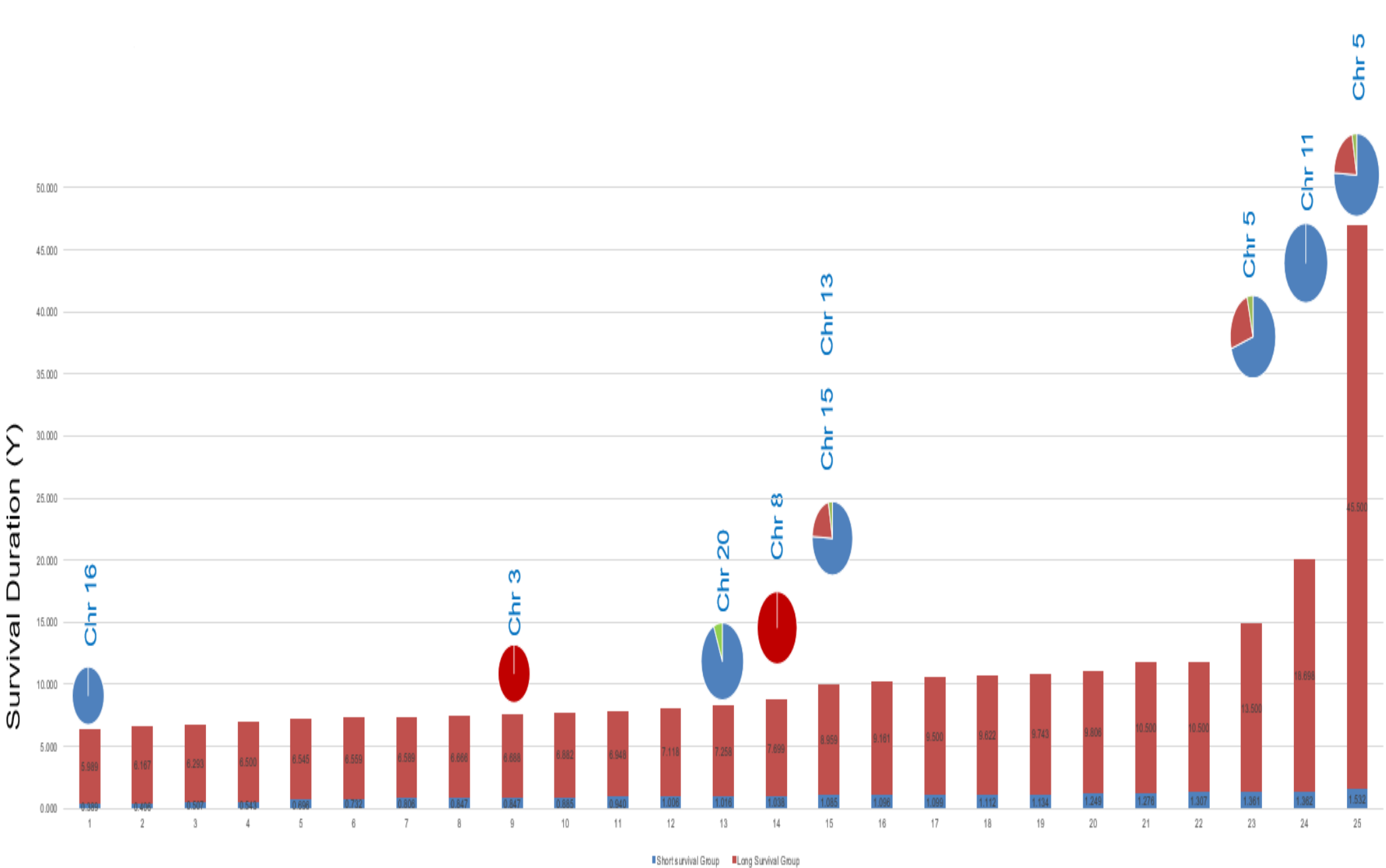


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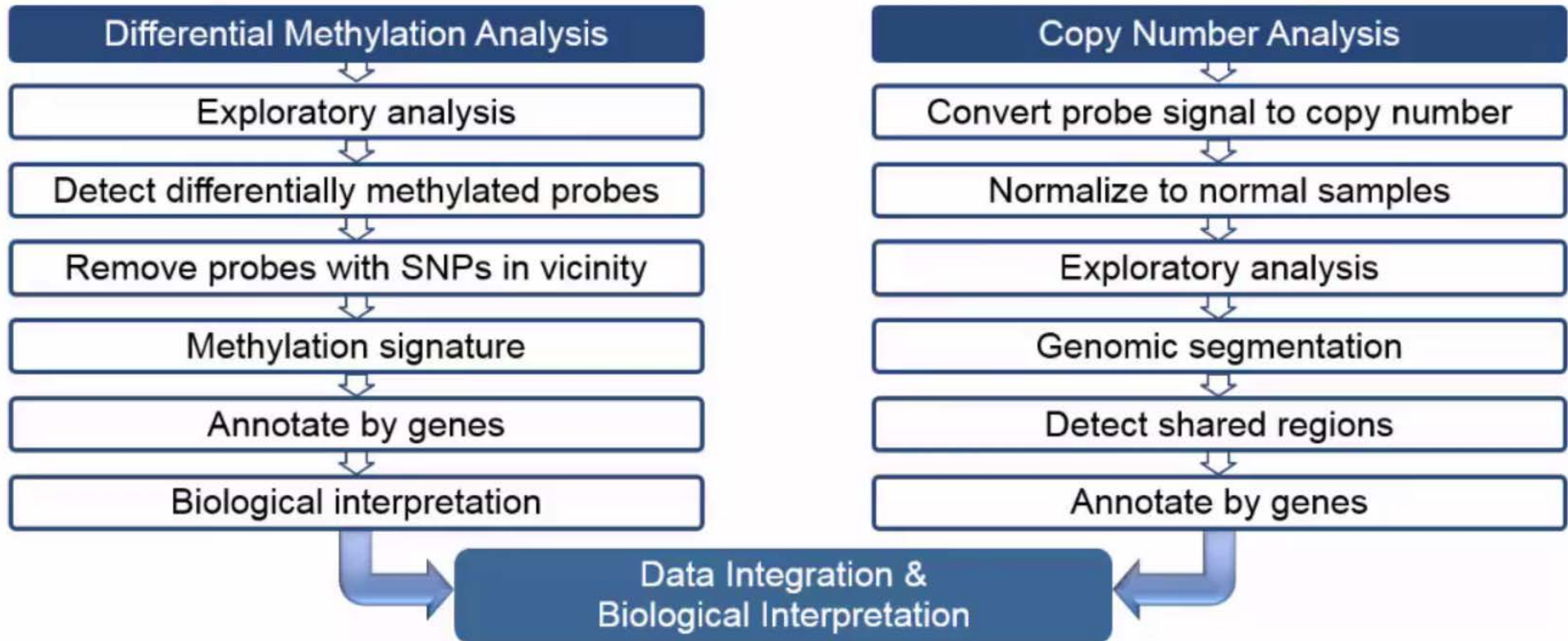
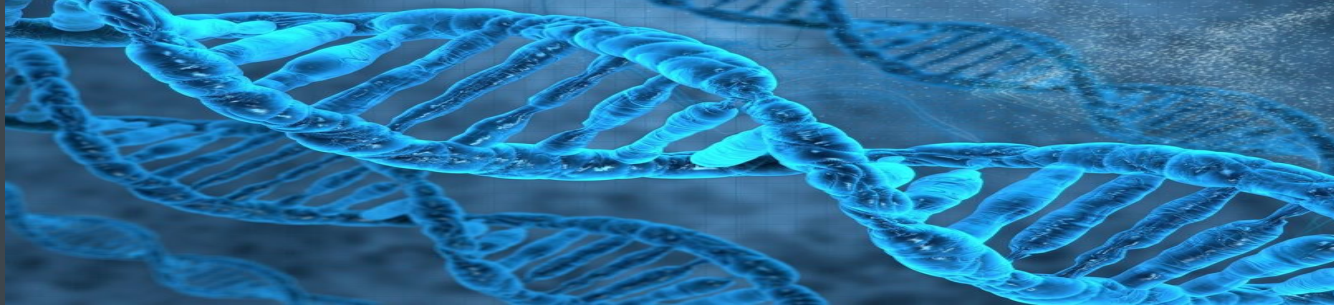


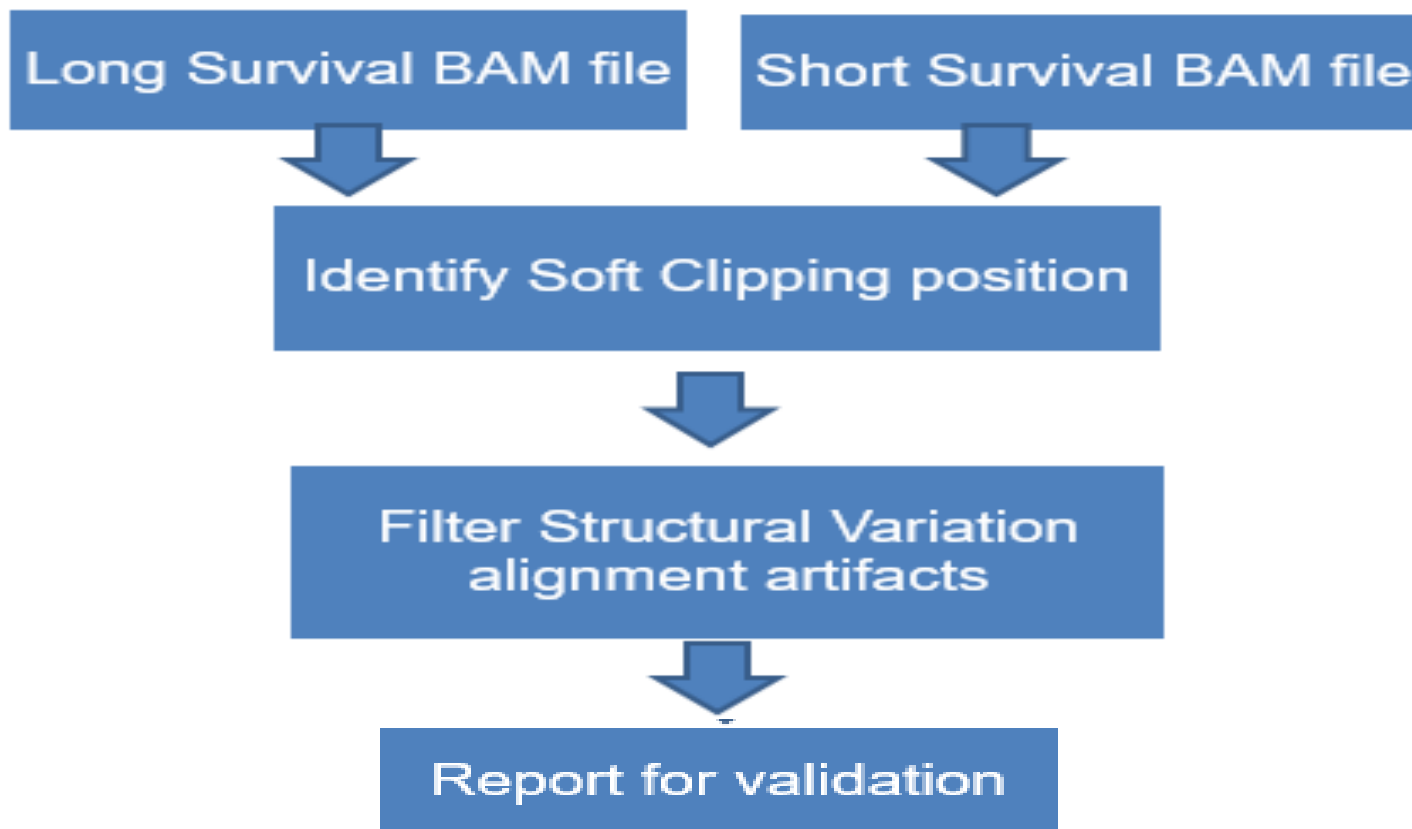
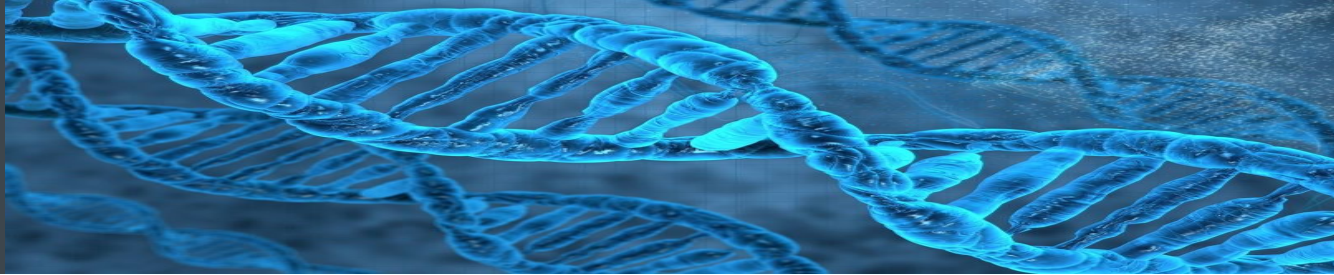
Economic and Social Research Council
Shaping Society





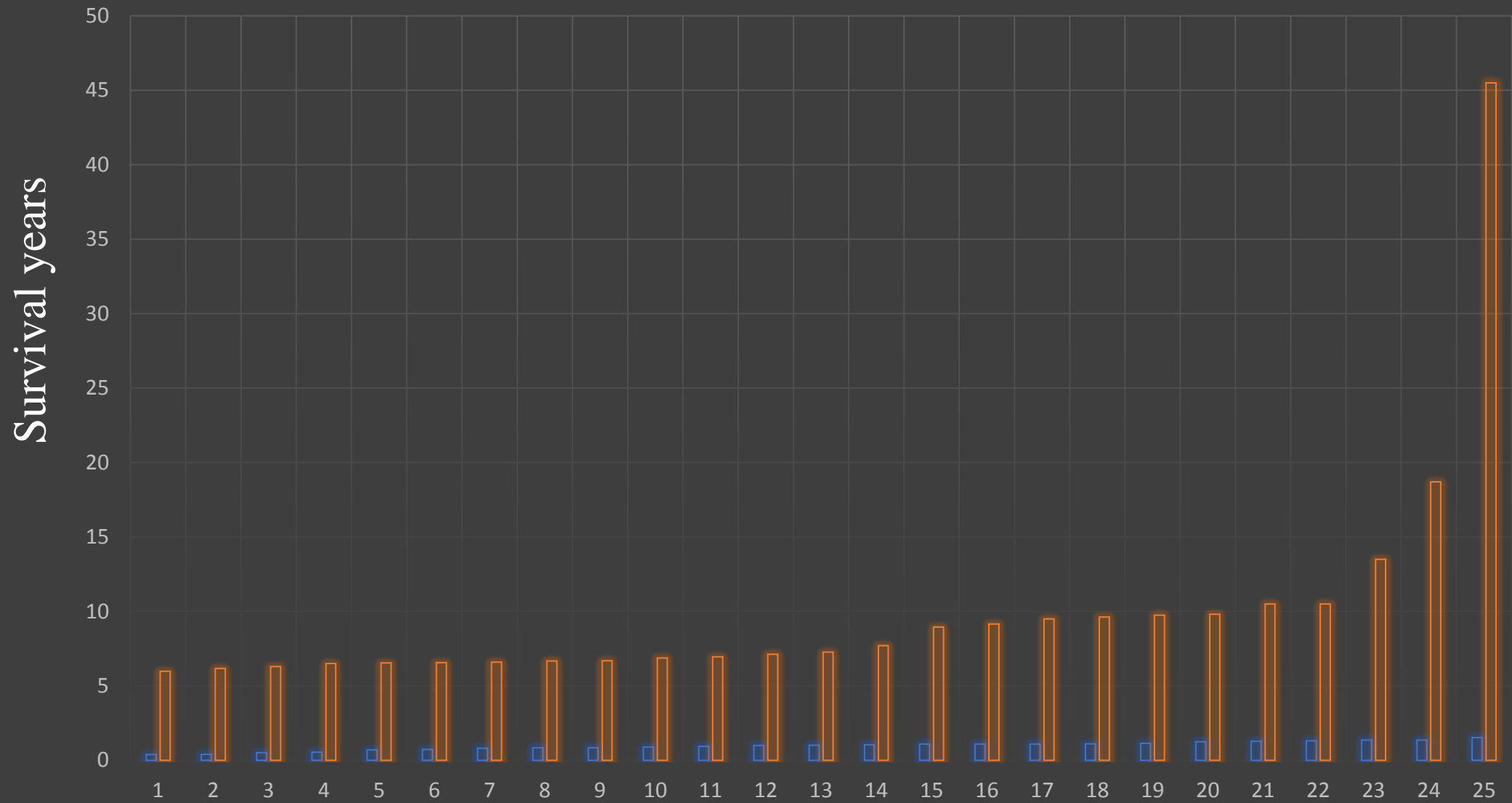
■ Deletion
 ■ Insertion
 ■ inter-chromosomal translocations
 Chr Chromosome
■ ■ Matched long and short survival cases.
● Pie chart shows the ratio of CNVs





Comparison between the two extreme survival groups

Short survival Long Survival



AAAGTATTCACTTTAAAGAAACAACGTTGGGCCAGGTG* TGGTGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCCAAGGC GGG
AAAGTATTCACTTTAAAGAAACAACGTTGGGCCAGGTG* TGGTGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCCAAGGC GGG
AAAGTATTCACTTTAAAGAAACAACGTTGGGCCAGGTG* TGGTGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCCAAGGC GGG
AAAGTATTCACTTTAAAGAAACAACGTTGGGCCAGGTG* TGGTGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCCAAGGC GGG
AAAGTATTCACTTTAAAGAAACAACGTTGGGCCAGGTG* TGGTGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCCAAGGC GGG
TTGGTTCTCTTCCCCAAAGGAAAAGTCAGTCCAGTGA* TGCCGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCCAAGGC GGG
TTGGTTCTCTTCCCCAAAGGAAAAGTCAGTCCAGTGA* TGCCGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCCAAGGC GGG
TTGGTTCTCTTCCCCAAAGGAAAAGTCAGTCCAGTGA* TGCCGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCCAAGGC GGG
TTGGTTCTCTTCCCCAAAGGAAAAGTCAGTCCAGTGA* TGCCGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCCAAGGC GGG

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integrating copy-number analysis with structural-variation detection

