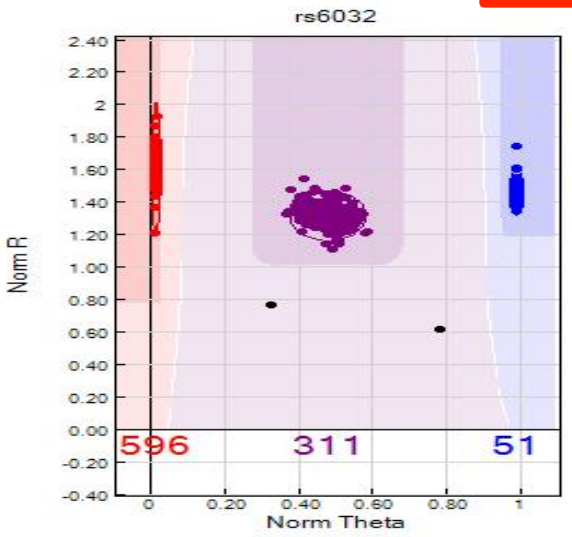
SNP Genotyping

Subject	Marker 1	Marker 2	Marker 3	Marker 4
Mom	AA	BB	AB	AB
Kid	AB	AB	BB	AA
Potential Dad #2	BB	AA	AB	AB
Potential Dad #3	AB	AB	AA	BB



Can you rule out either of these potential dads?

Important Points

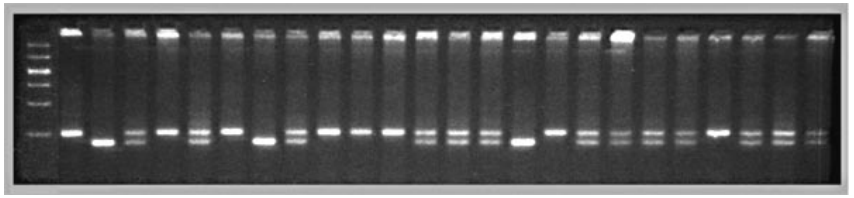
- Many markers are uninformative for identifying a person.
- A combination of markers must be used to unequivocally identify someone based on DNA.
- Errors in reporting of family relationships occur frequently!
- Before genetic analysis of families, it is important to check and verify family relationships.

Evolution of Strategies for Gene Discovery

Perceived need to be using the most cutting-edge technologies in order to be funded and get the "best" data.

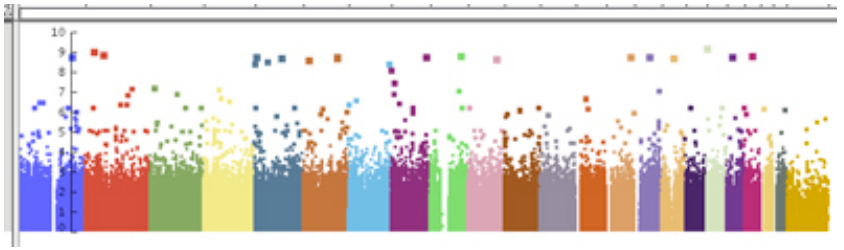
Linkage analysis

Driven by the discovery of microsatellites and the ability to run massive genotyping gels.



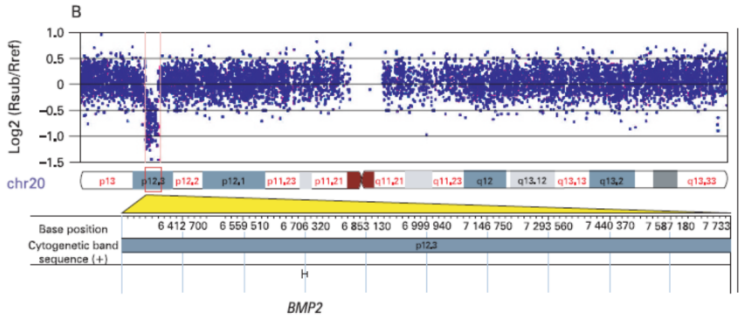
Genome-wide association studies (GWAS)

Driven by the development of ultra high throughput genotyping arrays.



The discovery of copy number variation.

A serendipitous finding from high density genotyping arrays.



Copy Number Variations (CNVs)

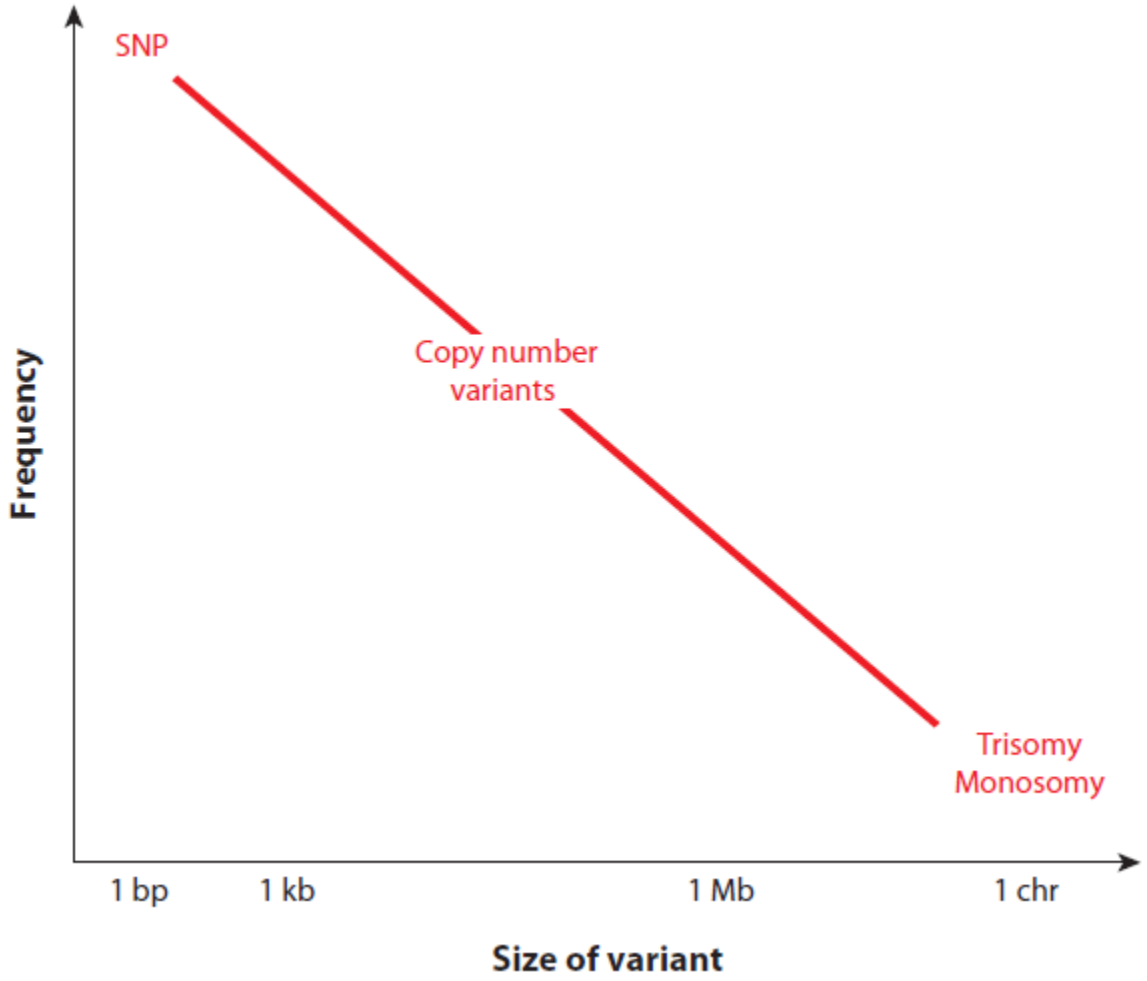
- Stretches of genomic DNA present in more than or less than two copies that can range in size from kilobases (kb) to megabases (Mb).

- Cannot be identified by conventional G-banded chromosome analysis, but can be identified by cytogenomic array methodologies and whole genome sequencing.

- Can be inherited or sporadic; large *de novo* CNVs are more likely to be disease causative.

- Recent studies have indicated that CNVs are widespread in the human genome and are a significant source of human genetic variation accounting for population diversity and human disease. Between any two individuals the number of base-pair differences due to CNVs is >100-fold higher compared with SNPs.

Size and frequency of major categories of genetic variants

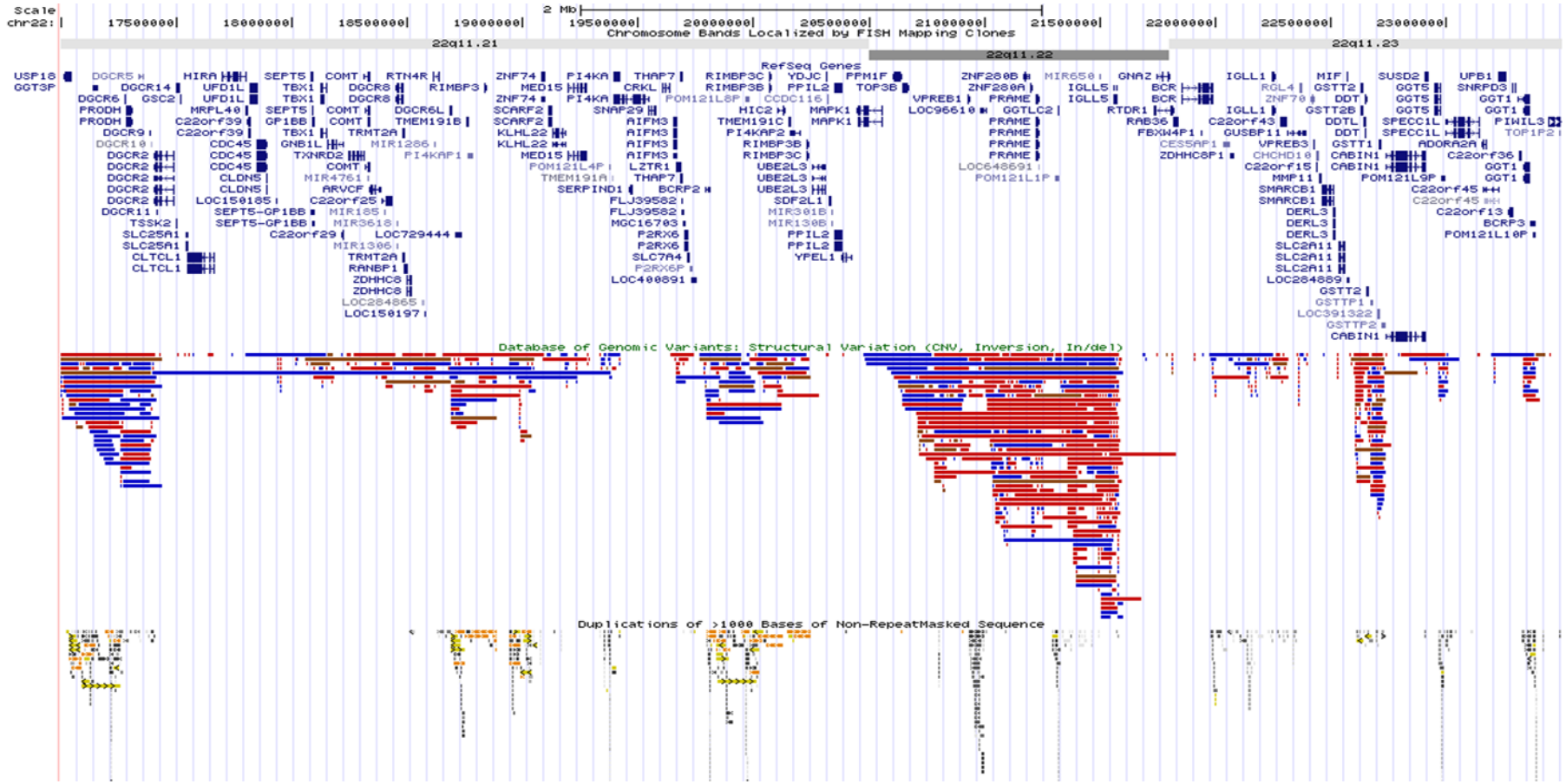


Girirajan S et al. Annu Rev Genet 2011;45:203-26

Benign CNVs

- A recent estimate of the proportion of the human genome that is structurally variant (i.e. benign CNVs) is in the order of ~5-10%

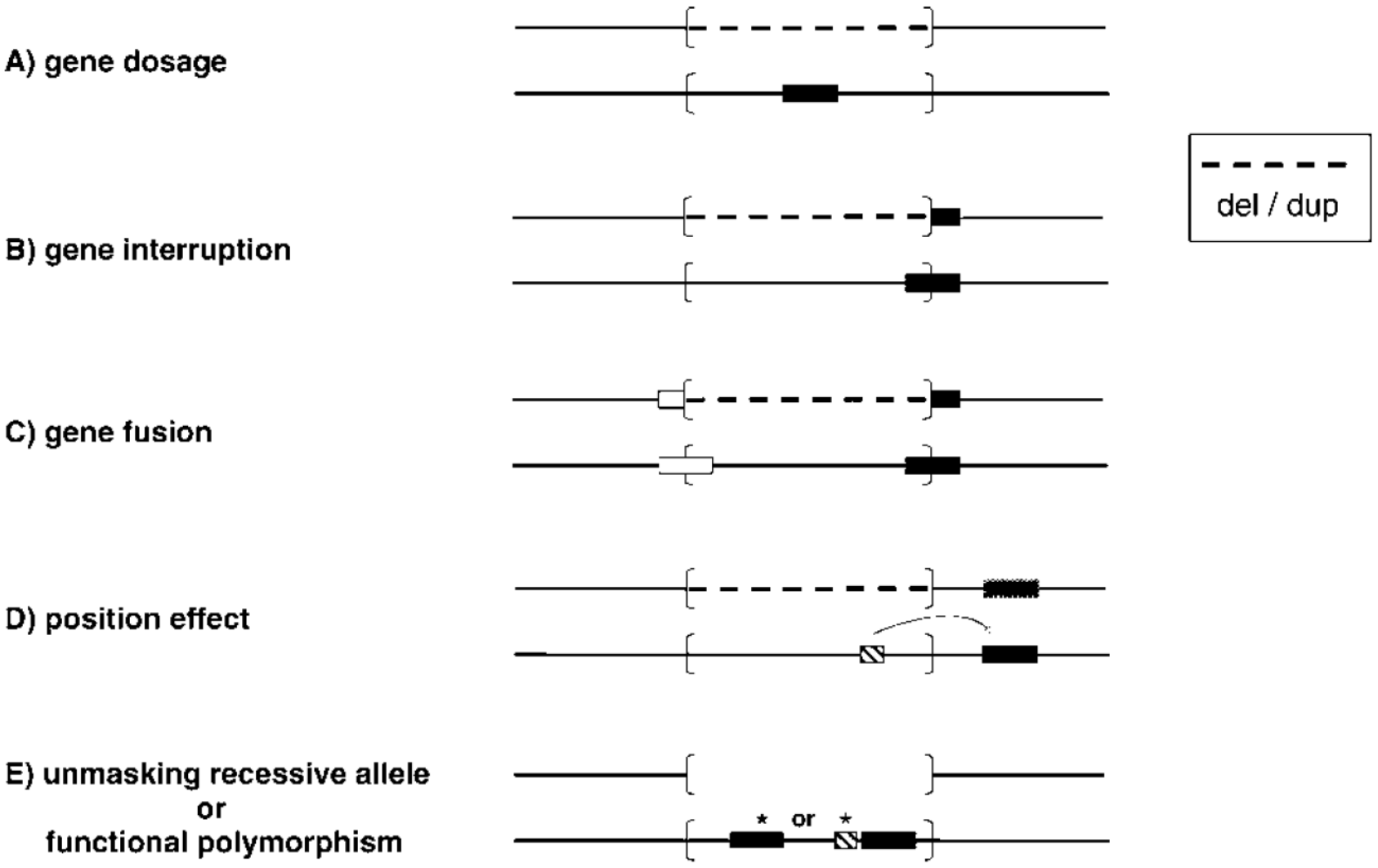
- The majority (>95%) of benign CNVs in humans are <100 kb in size



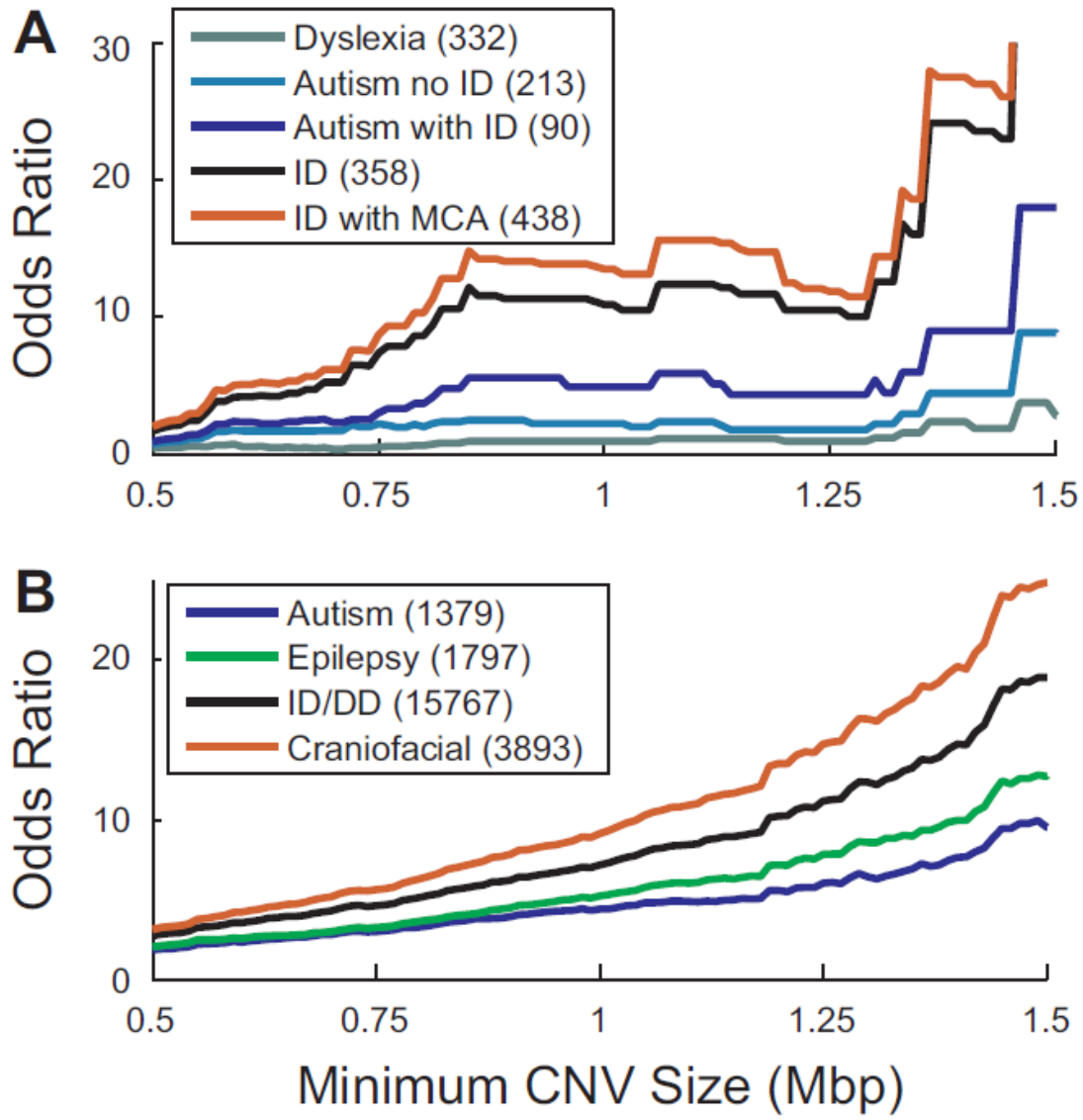
Can CNVs cause disease?

- Most CNVs are benign variants that will not directly cause disease.
- CNVs that affect critical developmental genes can cause disease.
- Recent reviews have listed 17 conditions of the nervous system alone – including Parkinson's Disease and Alzheimer's Disease – that can result from copy number variation.
- Genes that are involved in the immune system and in brain development and activity – two functions that have evolved rapidly in humans – tend to be enriched in CNVs.

Molecular mechanisms by which CNVs can convey phenotypes



CNV burden across various neurodevelopmental phenotypes



Coe BP et al. Am J Med Genet C Semin Med Genet 2012;160C:118-29