Standards and Guidelines for the Interpretation of Sequence Variants

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Standards and Guidelines for the Interpretation of Sequence Variants

- To describe variants identified in **Mendelian disorders**
- **American College of Medical Genetics and Genomics (ACMG)**[1]
- ENIGMA BRCA1/2 Gene Variant Classification Criteria
- International Agency for Research on Cancer (IARC)

Why is BRCA1/2 special?

- High prevalence in population
- Frequent benign variant

What about hereditary breast and ovarian cancer syndrome (HBOCS)

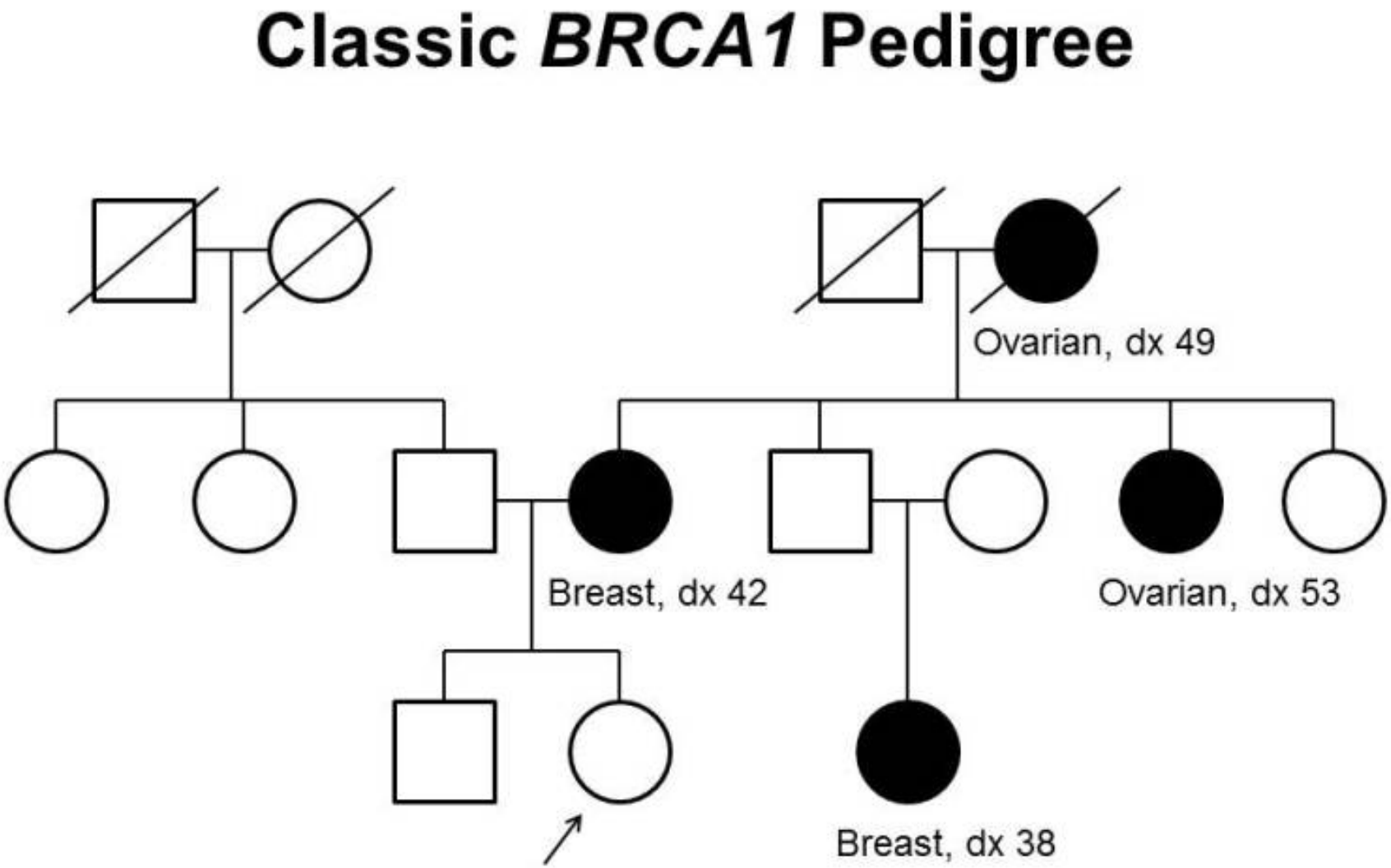
- BRCA1/2 and other genes
- Breast, ovarian cancer and other cancers
- Prevalence (between 1 in 200 to 1 in 800 people)
- Penetration rate (40-90%)

Categories of interpretation of variants

- Pathogenic
- Likely-pathogenic
- Uncertain (VUS)
- Likely-benign
- Benign

Let's guess the evidences

Famly pedigree



Segregation data (BS1, PP1)

- Caveat: linkage disequilibrium
- Penetration rate
- Difficult statistical evaluation

Population data

2016 Medical and Population Genetics Primer

ExAC: mutational constraint and de novo mutations

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Population data

- To high minor allele frequency (MAF)
- 5%: benign stand alone (BA1)
- 1% ?? (Think about prevalence of HBOCS) (BS1)
- Wow! The first time observed variant! (Absent in population DB, PM2)

Null variant

- Frameshift, Nonsense, canonical +-1 or 2 splicing site, initiation codon
- Caveat: LOF variants at the extreme 3 end of a gene
- Caveat: presence of multiple transcripts

Computational (in silico) data

- PolyPhen2, SIFT, MutationTaster, etc
- Mutational hot spot and/or critical and wellestablished (PM1)
- Protein length changes due to in-frame deletions/insertions and stop losses functional domain (PM4 BP3)
- Novel missense at the same position (PM5)

Other evidence

- de novo variants (PS2 PM6)
- functional studies (PS3 BS3)
- Computational (in silico) data
- Allelic data (BP2 PM3)
- Phenotype to support variant claims

Evidences of interpretation

- Population data
- Computational data
- Functional data
- Segregation data
- De novo data
- Allele data
- Other databases
- Other data