Unknown genetic predisposition in familial breast cancer can lie deep in family tree

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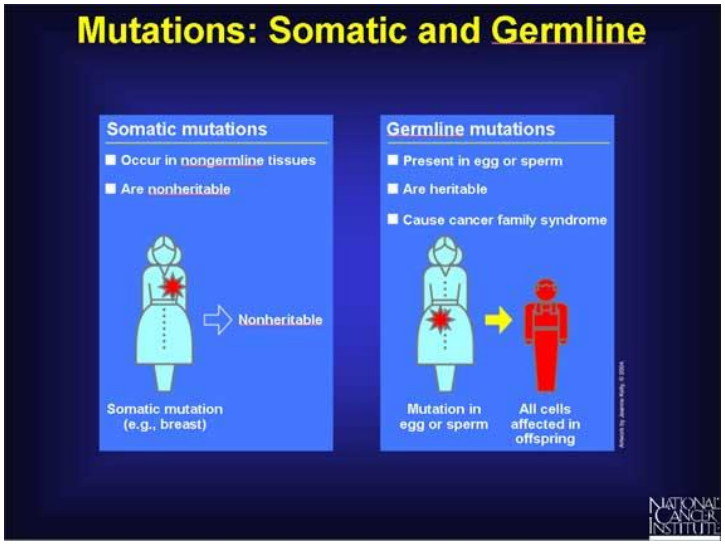
Genetically defined breast cancer

- Sporadic Breast Cancer caused by somatic mutation

  90% of breast cancer – “bad luck”

- Familial Breast Cancer caused by germline mutation

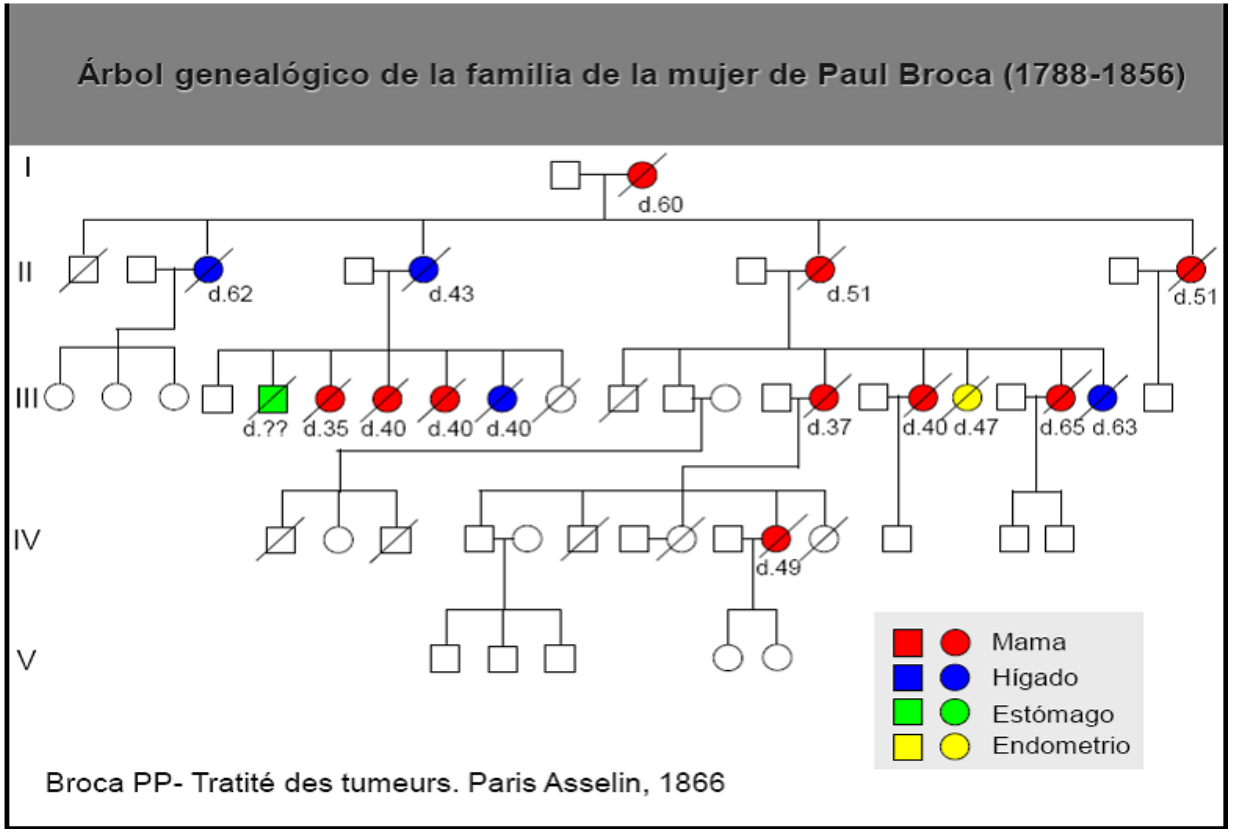
  10% of breast cancer - inherited



http://www.cancer.gov/types/breast

Familial Breast Cancer

In 1866, French physician Paul Broca reported 10 women over four generations in his wife's family died from breast cancer



Genetic predisposition is the major factor for familial breast cancer

- Factors contributing to cancer include environment, life style, nutrition, infection, genetics etc.
- Genetic predisposition is considered as the major factor responsible for familial breast cancer
- Familial breast cancer is a genetic disease

BRCAx familial breast cancer

- Germline mutations in *BRCA1 and BRCA 2 genes* are known genetic predispositions for familial breast cancer
- Germline mutations in *BRCA1 and BRCA 2* genes are present in 10-20% of familial breast cancer
- Predispositions for 40-50% of FBC are known
- Predispositions for 50-60% of FBC remain unknown

Efforts made to identify the unknown predispositions

- linkage analysis, positional cloning, genomic arrays, targeted sequencing, GWAS, exome sequencing have been applied
- Large sample sizes of tenth of thousand cases per study are routinely used
- Newly identified predispositions are very limited

Newly identified predisposition are all rare

Predisposition	BC cases	BC cases with mutation	References
XRCC2	3,371	5	Park et al, 2012
XRCC2	3,548	0	Hilbers et al, 2012
FANCC	1,435	1	Tompson et al, 2012
BLM	1,435	4	Tompson et al, 2012
BRIP1/BACH1	357	2	Cao et al. 2010
PPM1D	6,634	21	Ruark et al.
Total	**16,789**	**33 (0.5%)**	

The rarity makes it indistinguishable between disease and normal population

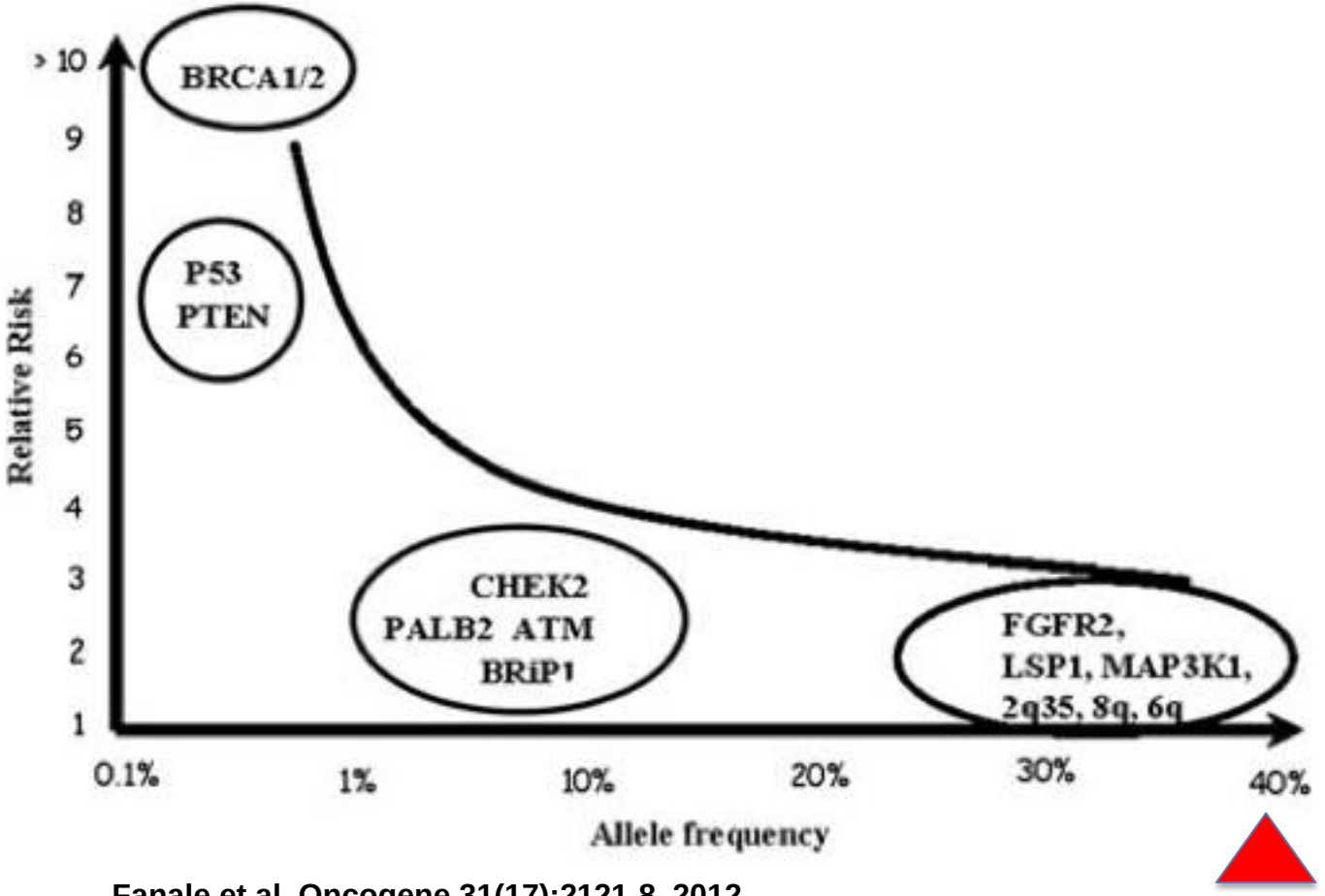
- Identified rare germline mutations in *XRCC2* in 5 out of 3,371 BRCA1/2-negative familial breast cancer cases. (Park, et al. Am J Hum Genet. (4):734-9, 2012)

- The same mutation failed to be detected in another 3,548 BRCA1/2-negative familial breast cancer cases but in 1 of 1,435 normal control (Hilbers et al. J Med Genet. 49(10):618-20, 2012)

Current theory to explain germline predispositions in familial breast cancer

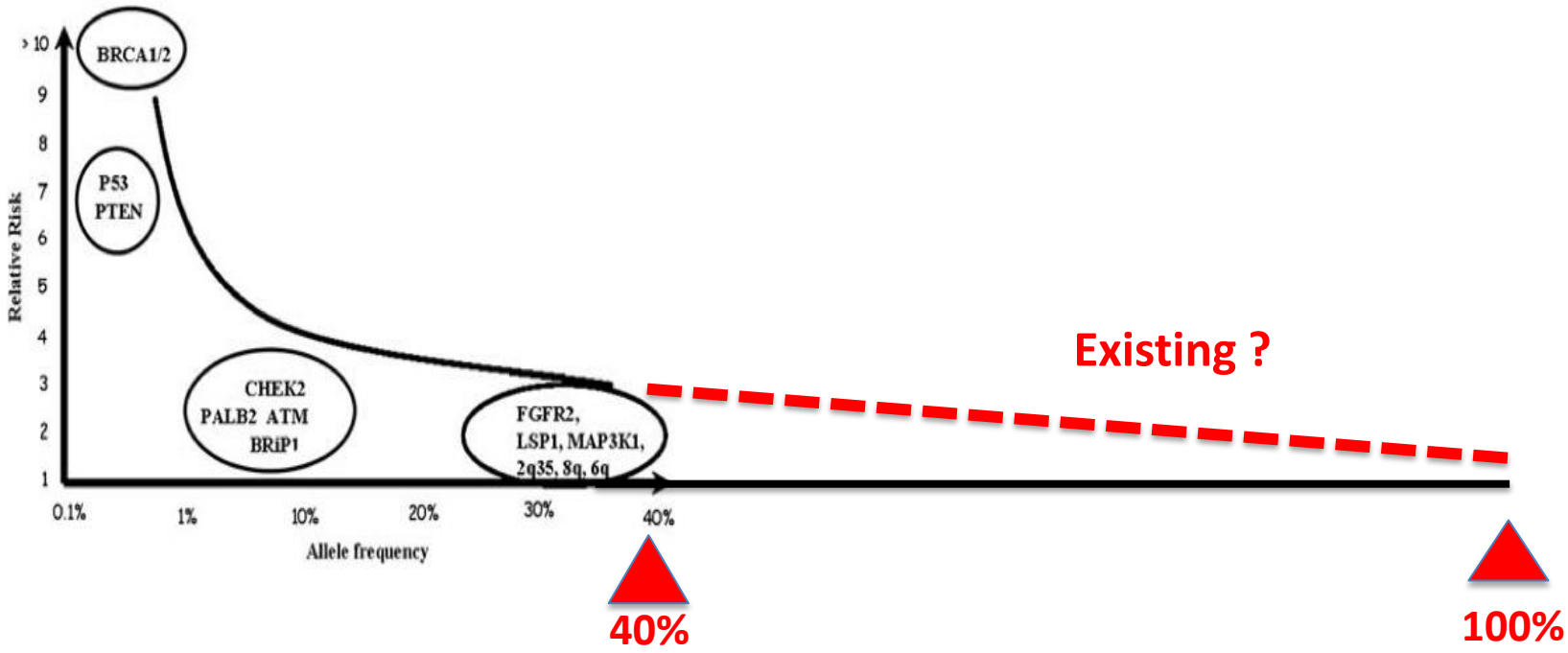
- High-risk genes: rare mutations convey high-risk, such as *BRCA1*;
- Intermediate-risk genes: rare mutations convey intermediate risk, such as *CHEK2*;
- Modest risk genetic variants: common genetic variants such as the SNPs detected by GWAS population studies

Distribution of known genetic predispositions



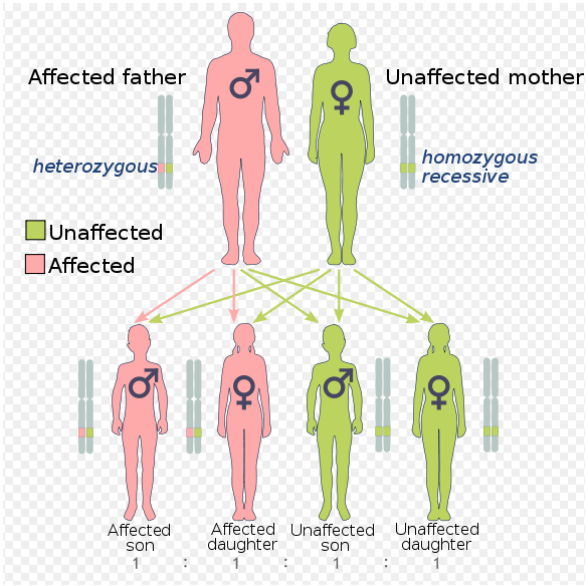
Fanale et al. Oncogene 31(17):2121-8, 2012

Question: frequency of unknown predispositions

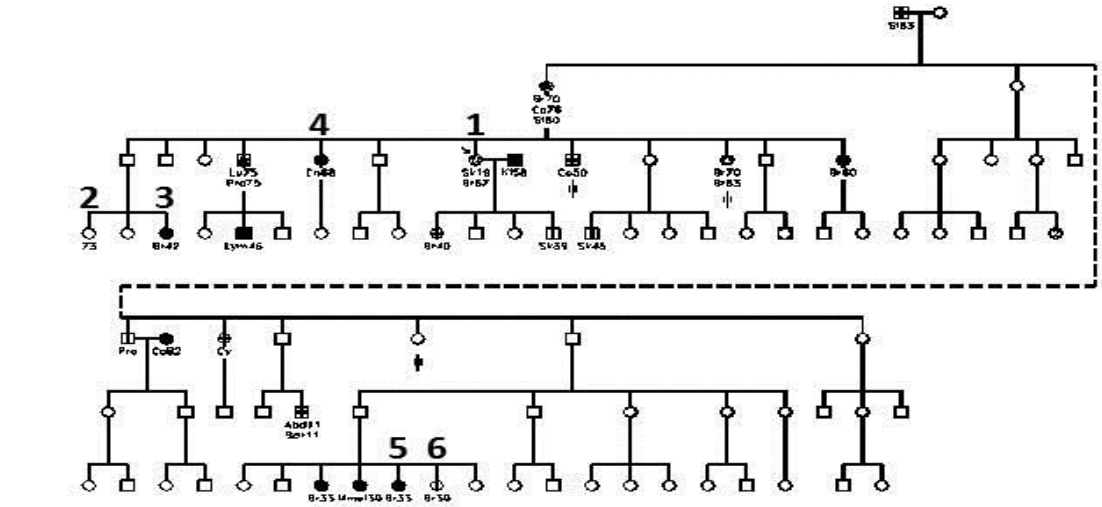


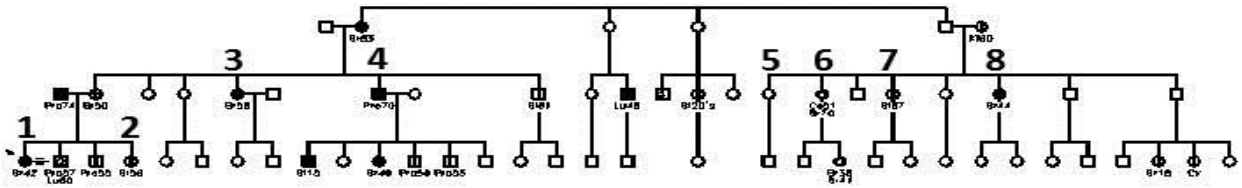
Hypothesis:
Unknown predisposition can be family-specific

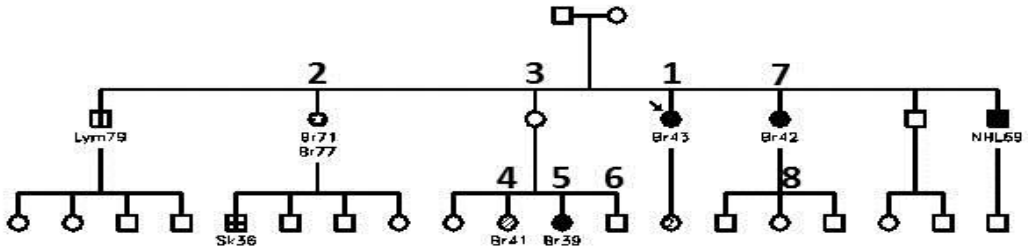
- FBC is an autosomal dominant disease
- Each family is enriched with the predisposition
- Focus on family may have higher chance to identify the unknown predisposition than population screening (diluted)



Studies in *BRCAx* families

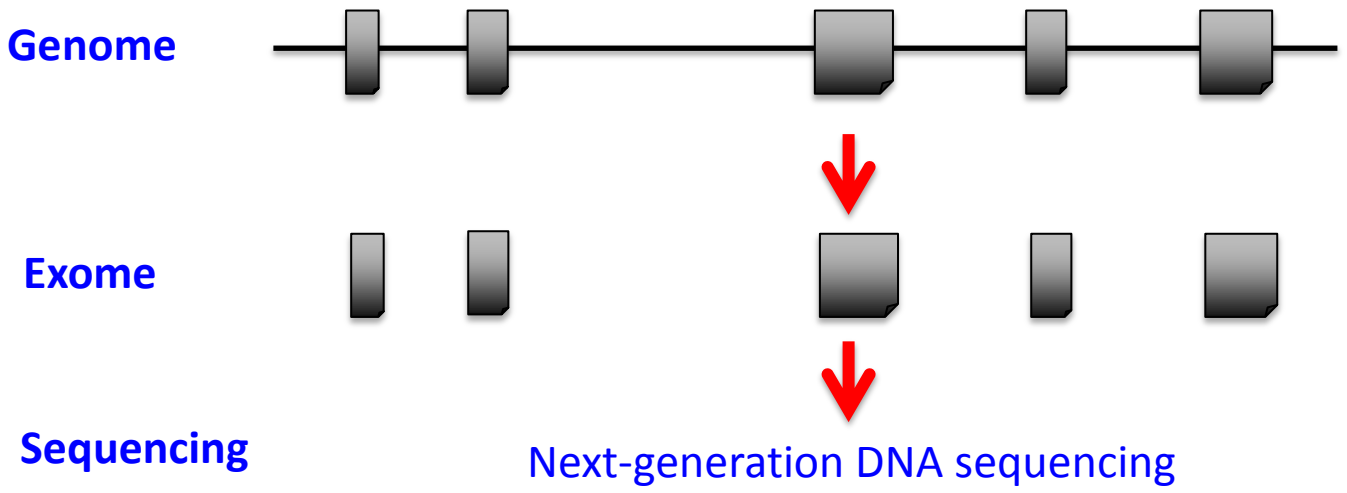




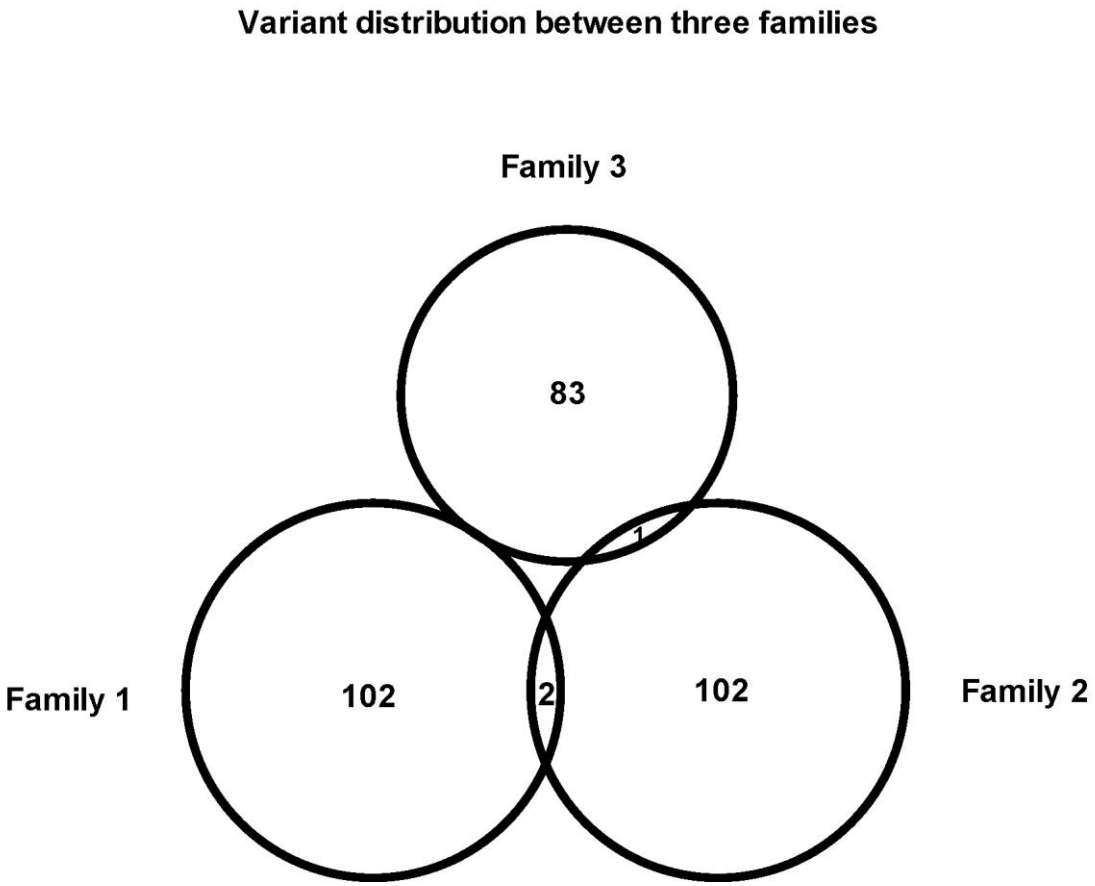


Exome sequencing

- Next-generation sequencing-based
- >180,000 exons from around 20,000 genes in the human genome
- 1/100 genome DNA content
- 1/5 cost of sequencing whole genome ($1,000)
- 85% of known genetic diseases are caused by mutation in exon !



Germline mutations in three *BRCAx* families are highly family-specific

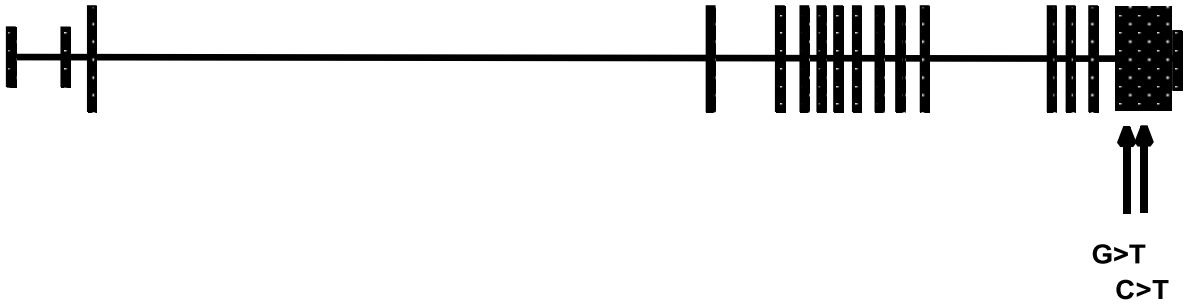


Putative genetic predisposition in each *BRCAx* family

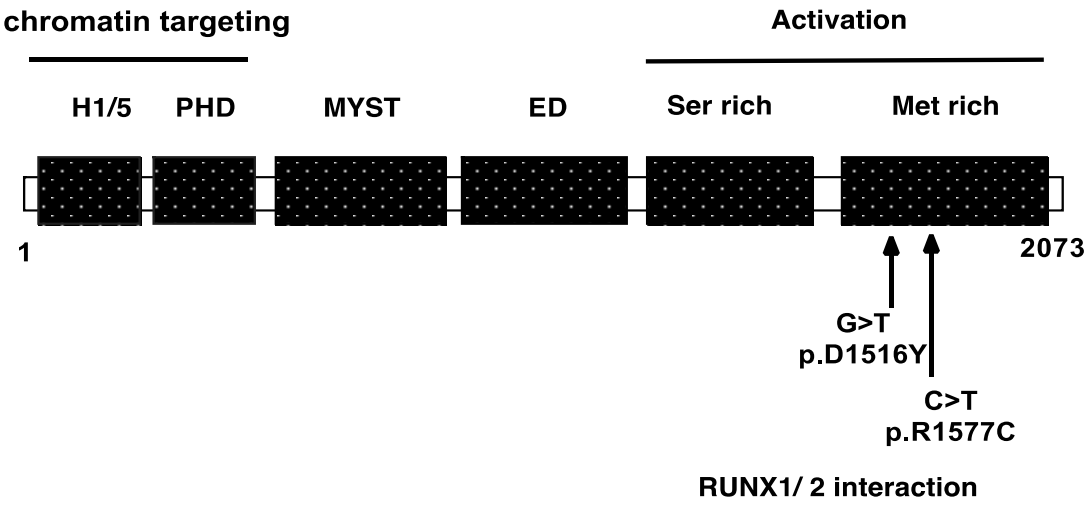
Gene	Position	Change	Distribution					
Family 1								
PINK1	chr1:20972051	-2A>G	-	+	+	-	-	-
USP28	chr11:113683049	A>G	-	+	+	-	-	-
TIGD2	chr4:90034310	C>T	-	-	-	-	+	+
Family 2								
KAT6B	chr10:76789128	G>T	+	+	+	+	+	+
KAT6B	chr10:76789311	C>T	+	+	+	+	+	+
NOTCH2	chr1:120459167	C>T	+	-	-	-	-	+
Family 3								
ADCY9	chr16:4016224	G>A	+	-	+	-	-	
PHKB	chr16:47628126	+1G>T	+	-	-	+	-	
NANP	chr20:25596725	A>G	-	+	+	-	-	
PPP6R2	chr22:50857867	C>A	-	-	-	+	+	

KAT6B

***KAT6B* gene structure**



***KAT6B* protein domains**



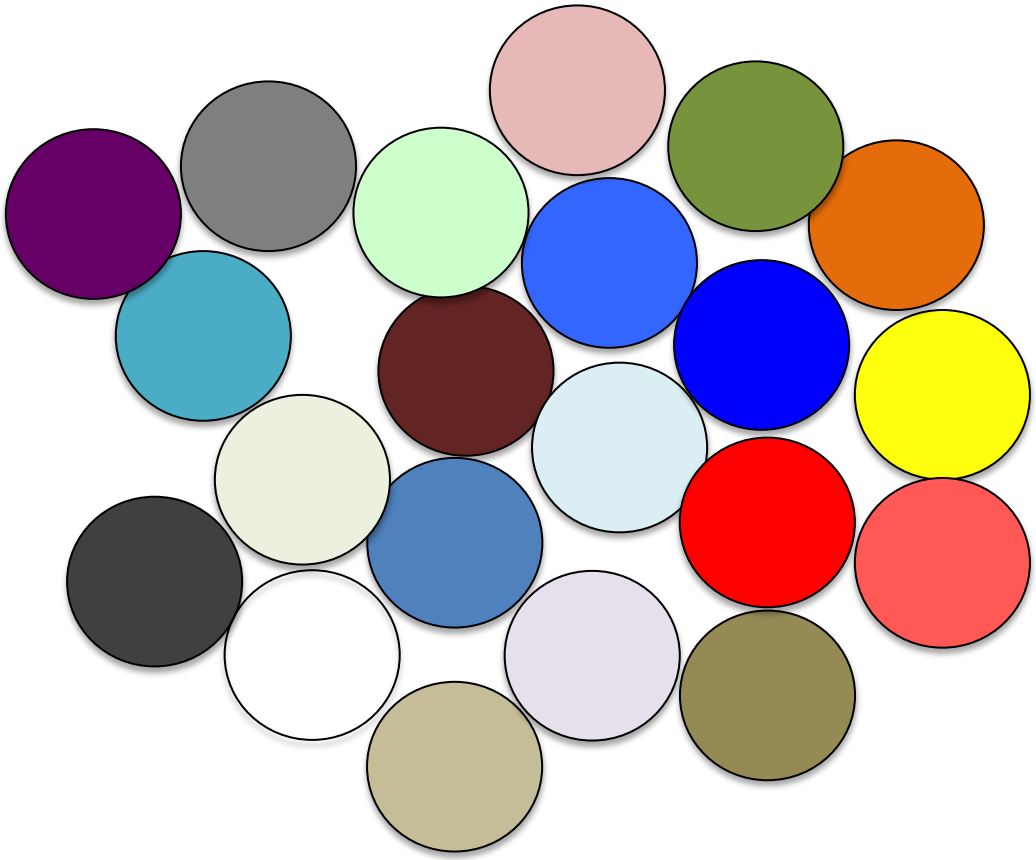
KAT6B

- A histone acetyl-transferase
- Its N-terminal is involved in transcriptional repression while its C-terminal is involved in transcriptional activation
- Interacts with important transcriptional regulators RUNX1 and RUNX2.
- A component of the MOZ/MORF complex involved in DNA replication, transcriptional regulation, and epigenetic modification of chromatin structure
- Mutations cause several neural genetic disease
- Not known involved in familial breast cancer

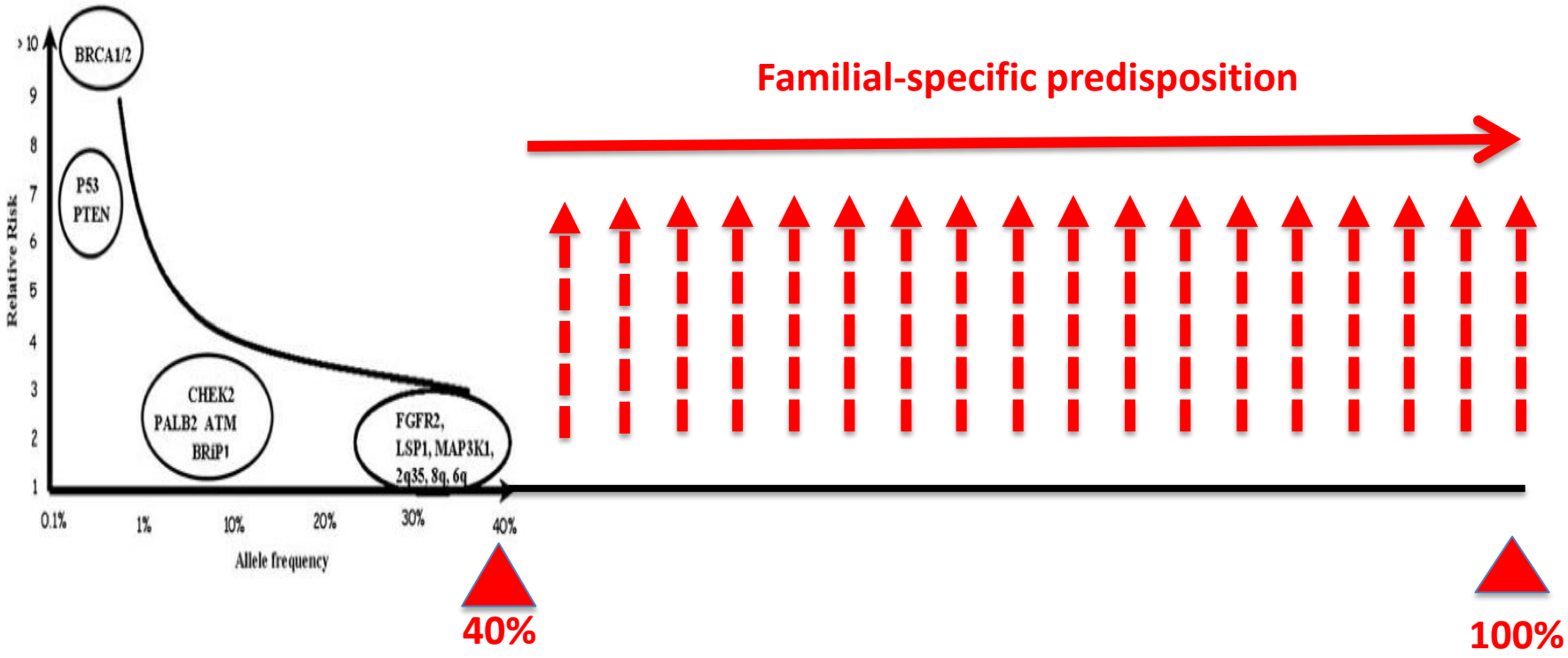
Are the same germline mutations in KAT6B also present in other *BRCAx* families?

- 42 additional cancers from 26 *BRCAx* families were tested
- None of the mutations are present in these families
- Sequencing entire *KAT6B* gene see no mutations

Distribution of germline mutations in 26 *BRCAx* families

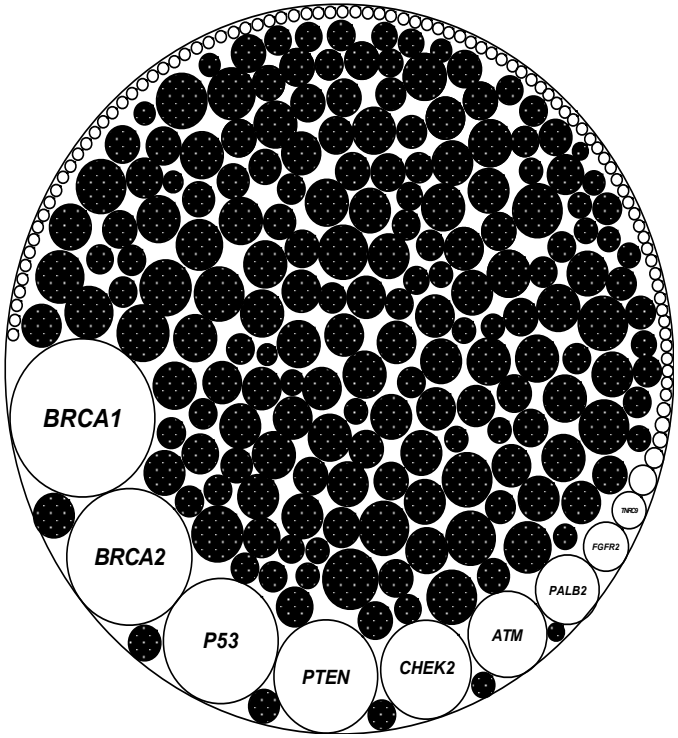


Each *BRCAx* breast cancer family may have its own genetic cause



Genetic predispositions in familial breast cancer: Same Disease, Different Causes

- Common predispositions only exist in a portion of familial breast cancer
- Family-specific predispositions are responsible for many familial breast cancer
- Family-based approach can identify the unknown predispositions
- Precision medicine, personalized medicine, familial medicine….



Wen et al. BMC Cancer. 2014 ;14:470

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