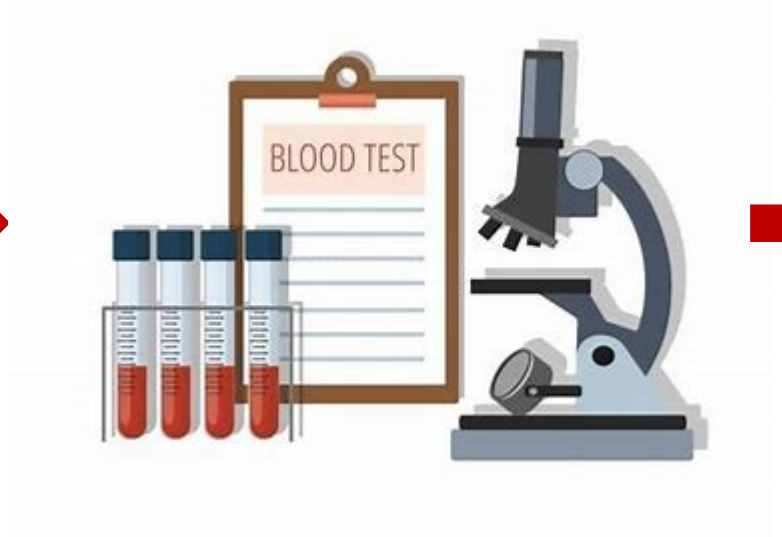
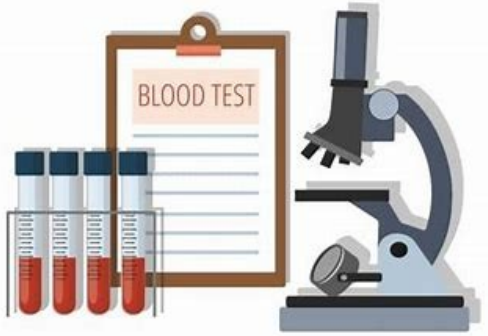
Does “Mendelian genetics” have any applications in the real world?

Imagine the future……..

It is the year 2050. You have set IIT as your goal for your undergraduate degree. You enroll in one of the numerous coaching classes that have an excellent success rate for cracking the JEE.

The first day you show up to the coaching class, you are asked to give a sample of your blood, which is given to a genetic testing lab to test your intelligence and ability to be an engineer. After 2 days, the results of your genetic test shows that you have a 90% probability of being an outstanding engineer. You are admitted into IIT Bombay immediately!





You have understood why we took your blood as the sample for the genetic test

You also came up with some other possible samples for the genetic test.

You also know that there are variations between individuals.

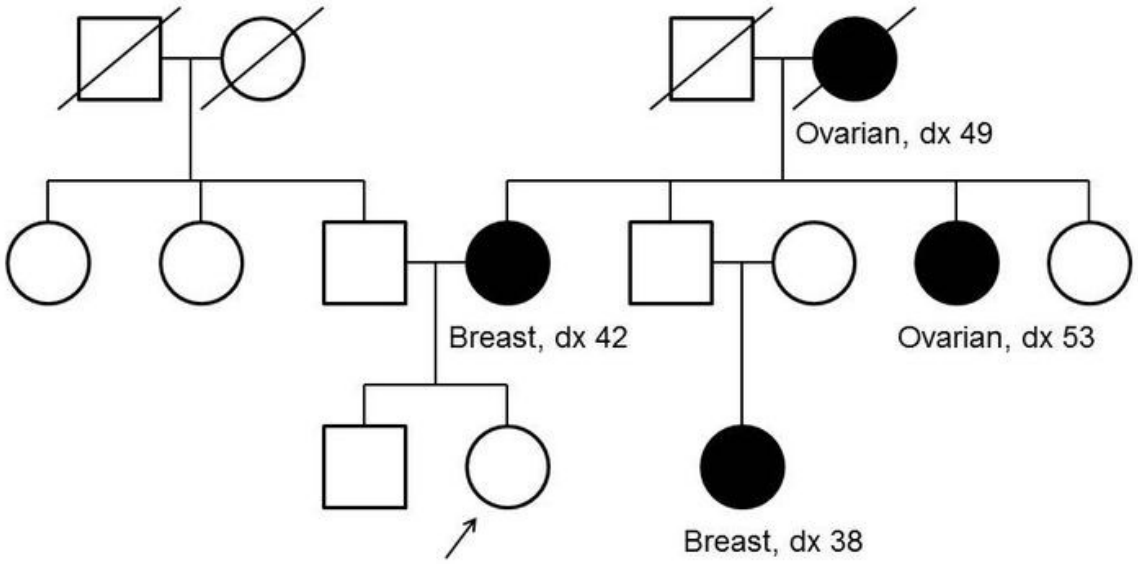
New question: how can these variations be used to find genes associated with phenotypes?

Finding genes associated with phenotypes in humans: example of breast cancer genes BRCA1 and BRCA2

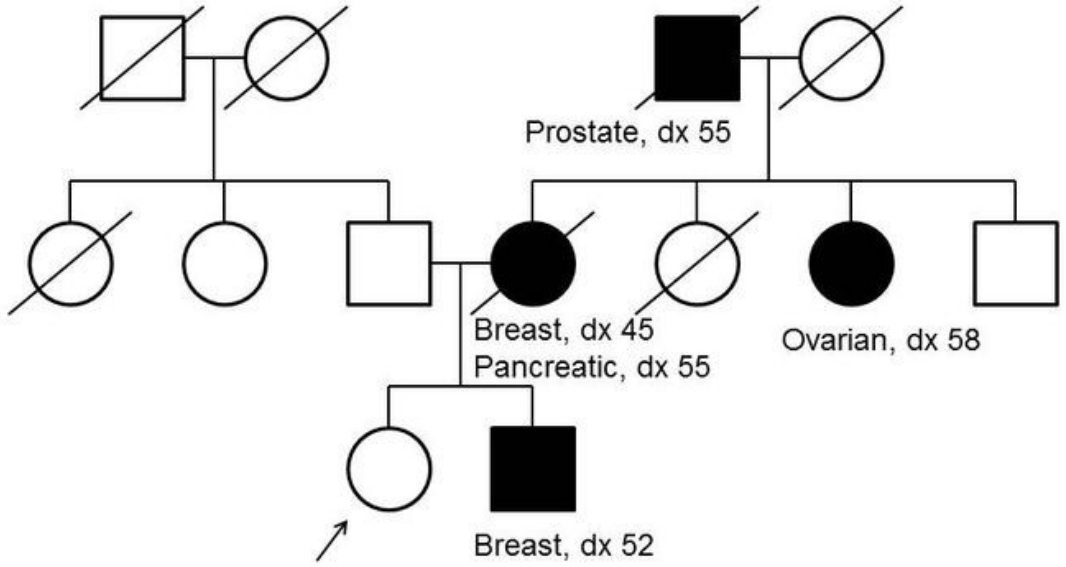
First step: breast cancer runs in families, affects both males and females

Recruit many such families in your research study and isolate DNA from their blood

Classic *BRCA1* Pedigree



Classic *BRCA2* Pedigree



Female, unaffected Male, unaffected Female, affected Male, affected Deceased

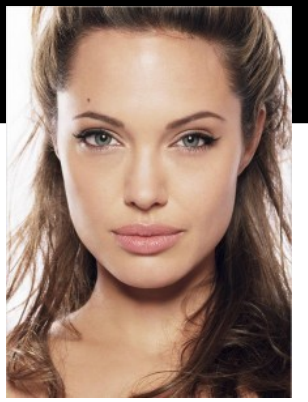
Look for variations in the DNA that associate with the disease

Carry out experiments for SNPs and/or variable repeat regions

Find out which variations show a correlation with the disease

Search in the genome around the region of these variations for genes

A modern example of genetic analysis



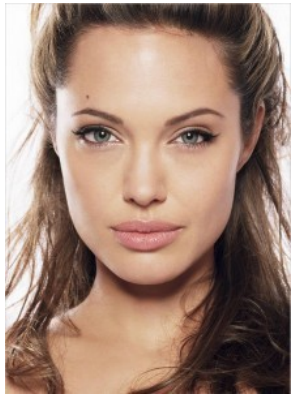
- Women with a family history of breast and ovarian cancer and mutations in the BRCA1 gene are given a risk assessment of their own chances of getting the disease
- As there is no ‘cure’ for breast cancer once it appears, some women assess their risk and decide to undergo a mastectomy to reduce their risk of getting breast cancer

- **On the next slide, you will see how genetic analysis is applied to the scenario of “risk of breast cancer”**

    - By the way, breast cancer genetics are not this simple but it is a good example of the real world consequences of genes

A modern example of genetic analysis

BRCA1 variations are dominant i.e. their presence can give rise to breast cancer and we know the following about Angelina Jolie:



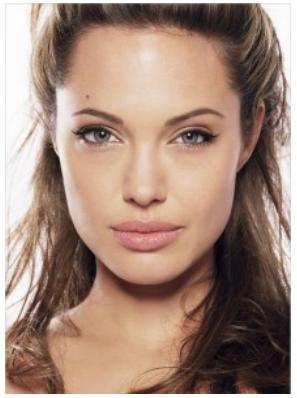
- Her mother died of ovarian cancer and maternal aunt died of breast cancer
- She has the variations in BRCA1 that predispose to breast cancer
- **Assuming Angelina Jolie is heterozygous for BRCA1 variations and Brad Pitt has no BRCA1 variations, draw a Punnett square showing the genotypes and phenotypes for breast cancer of their children**

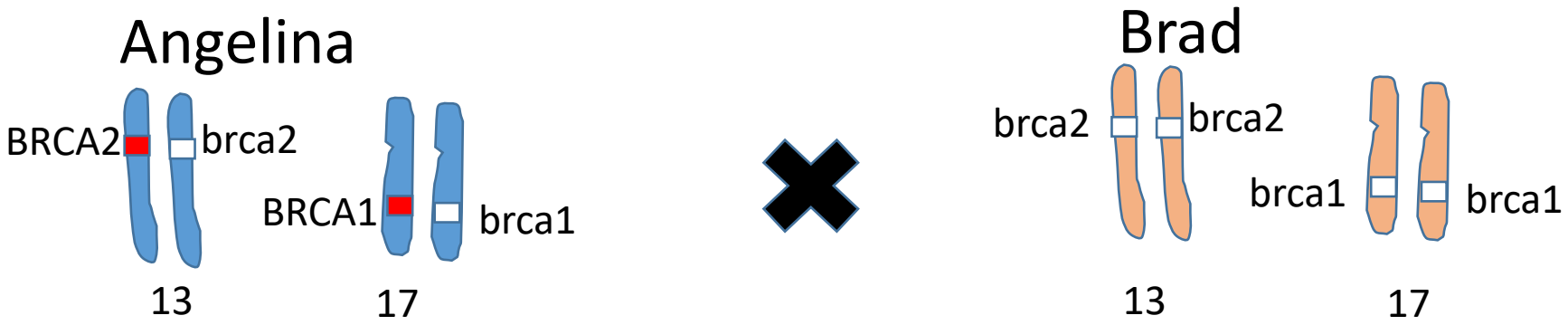
Brad Pitt / Angelina Jolie	brca1	brca1
BRCA1	BRCA1/brca1	BRCA1/brca1
brca1	brca1/brca1	brca1/brca1

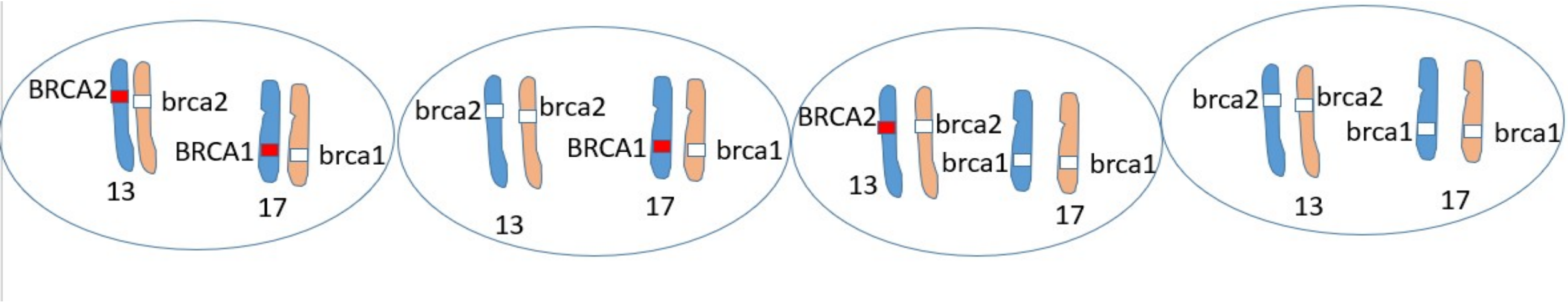
Children have 50% chance of getting BRCA1

A modern example of genetic analysis

BRCA1 is on chromosome 17 and BRCA2 is on chromosome 13. Draw the alleles on the chromosomes for Angelina Jolie, Brad Pitt and their children if she is heterozygous for BRCA2 variations (dominant) as well as BRCA1 variations. Brad has no BRCA2 variations.

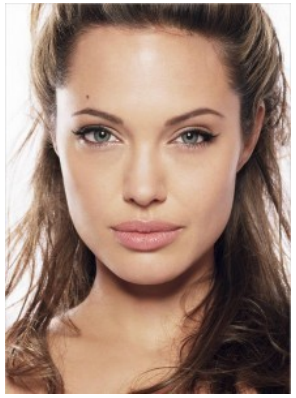






A modern example of genetic analysis

BRCA1 is on chromosome 17 and BRCA2 is on chromosome 13. Draw a Punnett square for Angelina Jolie, Brad Pitt and their children if she is heterozygous for BRCA2 variations (dominant) as well as BRCA1 variations. Brad has no BRCA2 variations.



Angelina \ Brad	brca1/brca2	brca1/brca2	brca1/brca2	brca1/brca2
BRCA1/BRCA2	B1b1 and B2b2	B1b1 and B2b2	B1b1 and B2b2	B1b1 and B2b2
BRCA1/brca2	B1b1 and b2b2	B1b1 and b2b2	B1b1 and b2b2	B1b1 and b2b2
brca1/BRCA2	b1b1 and B2b2	b1b1 and B2b2	b1b1 and B2b2	b1b1 and B2b2
brca1/brca2	b1b1 and b2b2	b1b1 and b2b2	b1b1 and b2b2	b1b1 and b2b2

Assuming that either BRCA1 and BRCA2 can give rise to cancer if heterozygous (dominant), children have 75% chance of getting cancer. We can find out the sequence of the BRCA1 and BRCA2 genes (B1 or b1? B2 or b2?) in the children, and therefore we can predict their cancer risk more accurately.

Can the breast cancer example be extrapolated to the entrance exam for IIT Bombay based on genetic tests?

Not yet! “Intelligence” is a complex trait that has many genes. Getting into IITB is even more complex.

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Association of *COMT* and *PRODH* gene variants with intelligence quotient (IQ) and executive functions in 22q11.2DS subjects☆

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Proteins that play roles in your brain cells

ARTICLE INFO

Article history:
Received 27 January 2014
Received in revised form
23 April 2014
Accepted 24 April 2014

Keywords:
22q11.2DS
Intelligence quotient (IQ)
Executive function (EF)
COMT

ABSTRACT

The 22q11.2 deletion syndrome (22q11.2DS) carries the highest genetic risk factor for the development of schizophrenia. We investigated the association of genetic variants in two schizophrenia candidate genes with executive function (EF) and IQ in 22q11.2DS individuals.

Ninety two individuals with 22q11.2 deletion were studied for the genetic association between *COMT* and *PRODH* variants and EF and IQ. Subjects were divided into children (under 12 years old), adolescents (between 12 and 18 years old) and adults (older than 18 years), and genotyped for the *COMT* Val158Met (rs4680) and *PRODH* Arg185Trp (rs4819756) polymorphisms. The participants underwent psychiatric evaluation and EF assessment. Our main finding is a significant influence of the *COMT* Val158Met polymorphism on both IQ and EF performance. Specifically, 22q11.2DS subjects with Met allele displayed higher IQ scores in all age groups compared to Val carriers, reaching significance in both adolescents and adults. The Met allele carriers performed better than Val carriers in EF tasks, being statistically significant in the adult group. *PRODH* Arg185Trp variant did not affect IQ or EF in our 22q11.2DS cohort. In conclusion, functional *COMT* variant, but not *PRODH*, affects IQ and EF in 22q11.2DS subjects during neurodevelopment with a maximal effect at adulthood. Future studies should monitor the cognitive performance of the same individuals from childhood to old age.