Basics concepts in genetic epidemiology

Mario Merialdi
merialdim@who.int
Office x 39
022 7913387

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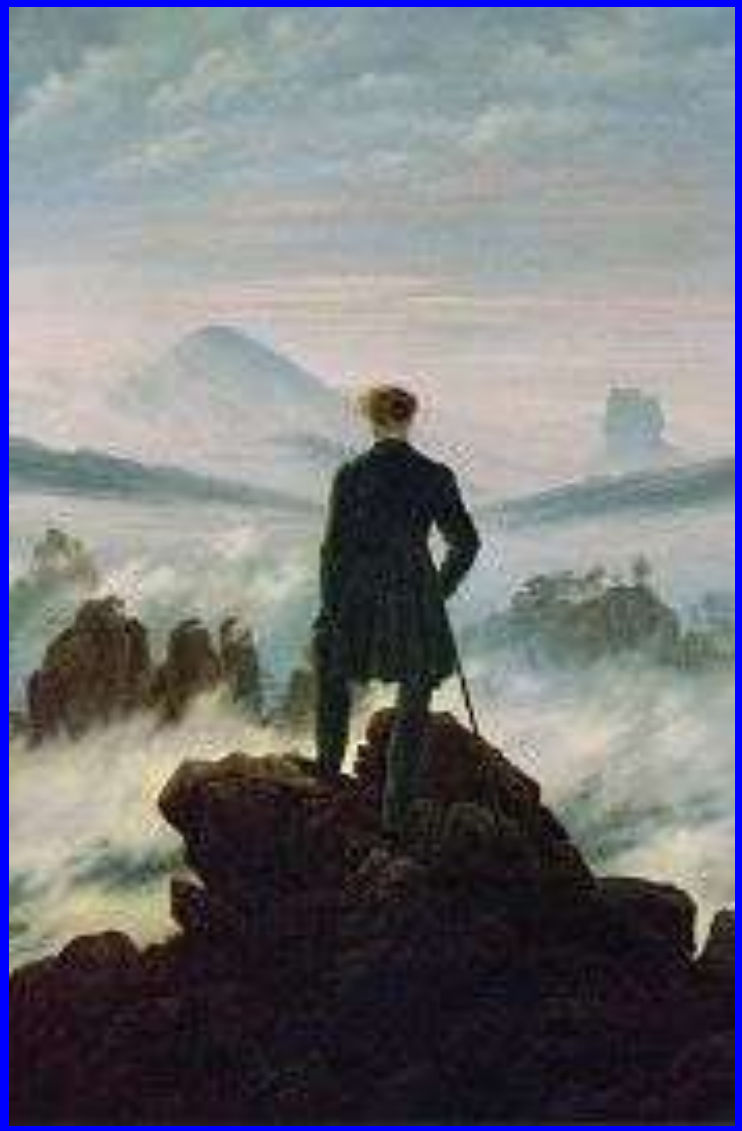
Looking at the future



How to find a gene?

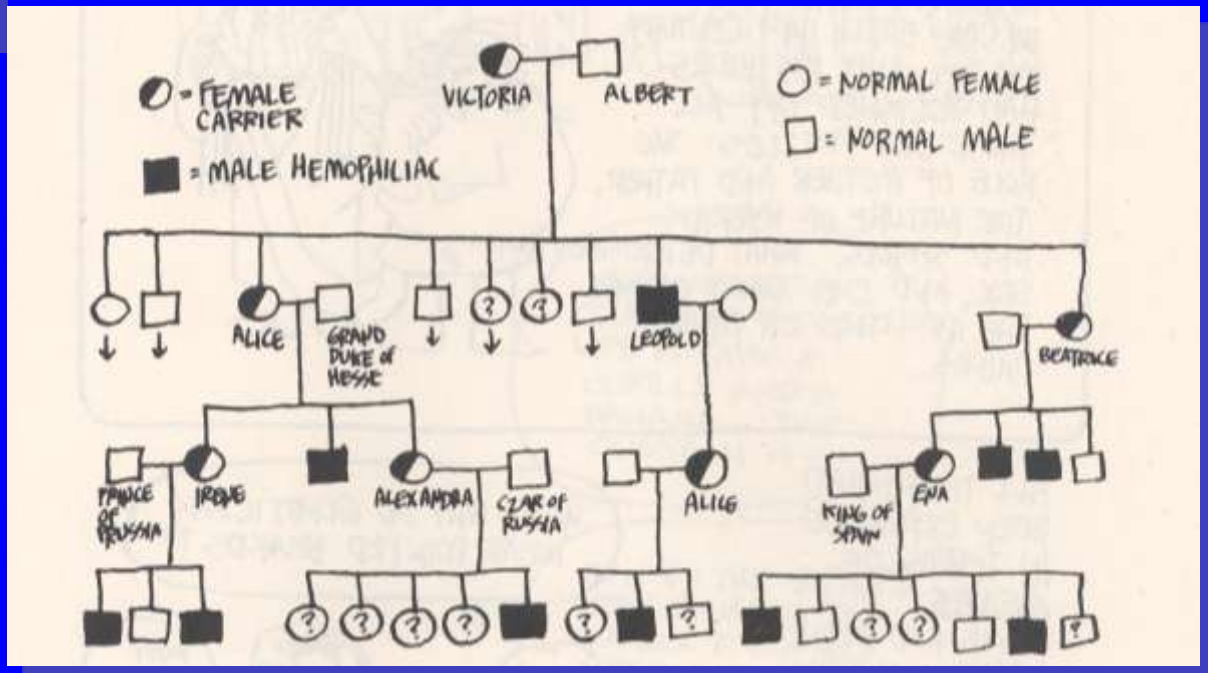
How do we know if susceptibility to a disease is genetic?

- Most diseases run in families
- Shared environment vs. common genes
- Compare concordance rates among monozygotic (MZ) and dizygotic (DZ) twins
- Concordance rates are high in both MZ and DZ: shared environment
- Concordance rates higher in MZ than in DZ: genetic influence

How susceptibility is inherited?

- Studies of familial segregation
- By examining how a disease is transmitted in the family we can determine if the disease depends on a single gene (Mendelian inheritance) or on several genes with possible influence of the environment (multifactorial inheritance)

Haemophilia and Queen Victoria




YOUR GRANDMOTHER IS A MUTANT!

Alleles and genetic variation

- An allele is one of several forms of a gene at a particular location (locus) on a chromosome (different alleles at the same locus produce different characteristics, e.g., the colour of the eyes)
- Alleles can be rare or frequent in a population
- When an allele is frequent (>1%), it is called polymorphism

How can we use genetic variation?

- Polymorphisms are genetic markers.
- In a family, genetic markers tend to be transmitted with the others genes located on the chromosome nearby them (linkage).
- If one of the genes near the markers is the gene causing the disease, all affected people in the family will receive both the marker and the gene causing the disease.

Linkage analysis: Map susceptibility genes

- By the analysis of DNA we know where specific markers are located (in which region of a chromosome).
- If we find that a marker is associated with the disease in a family we can have an idea of where the gene that causes the disease is located: we can map the susceptibility gene (even if we still do not know which is the gene that causes the disease).

Some confusion

- Linkage analysis is about following markers that are near to the gene of interest on a chromosome.
- Finding a linkage means that we have a reasonable likelihood of knowing where to look on a chromosome for the gene of interest.
- Finding linkage does not mean finding a gene.

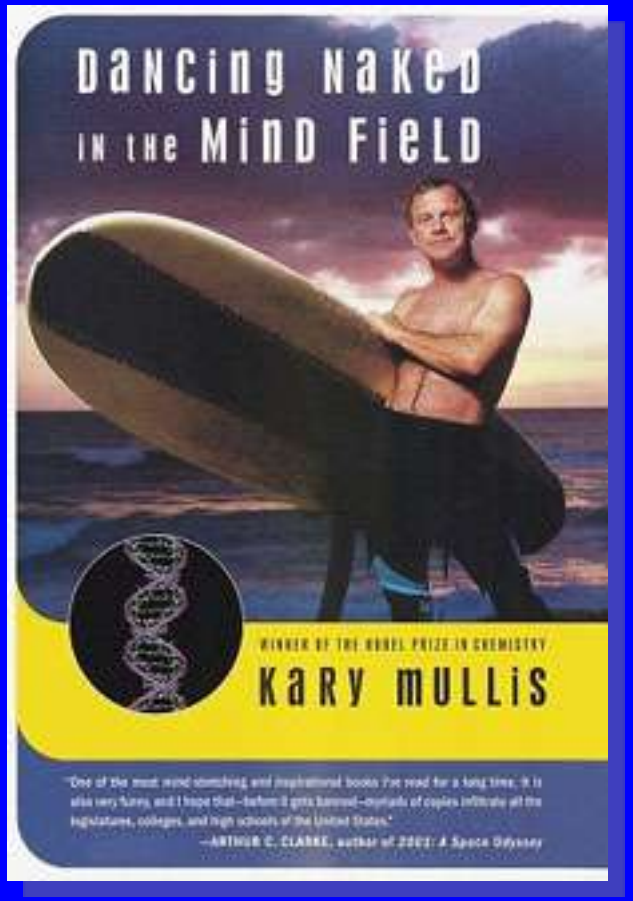
Narrow down the candidate region on the chromosome

- We can perform case-control association studies.
- We want to determine if in a population a specific allele (gene variant) is more frequent in cases than in controls.
- Which gene to look for?
  - Gene located in a chromosomal region previously found significant in a linkage study (indirect)
  - We know that a polymorphisms is potentially functional (direct)

Technological developments

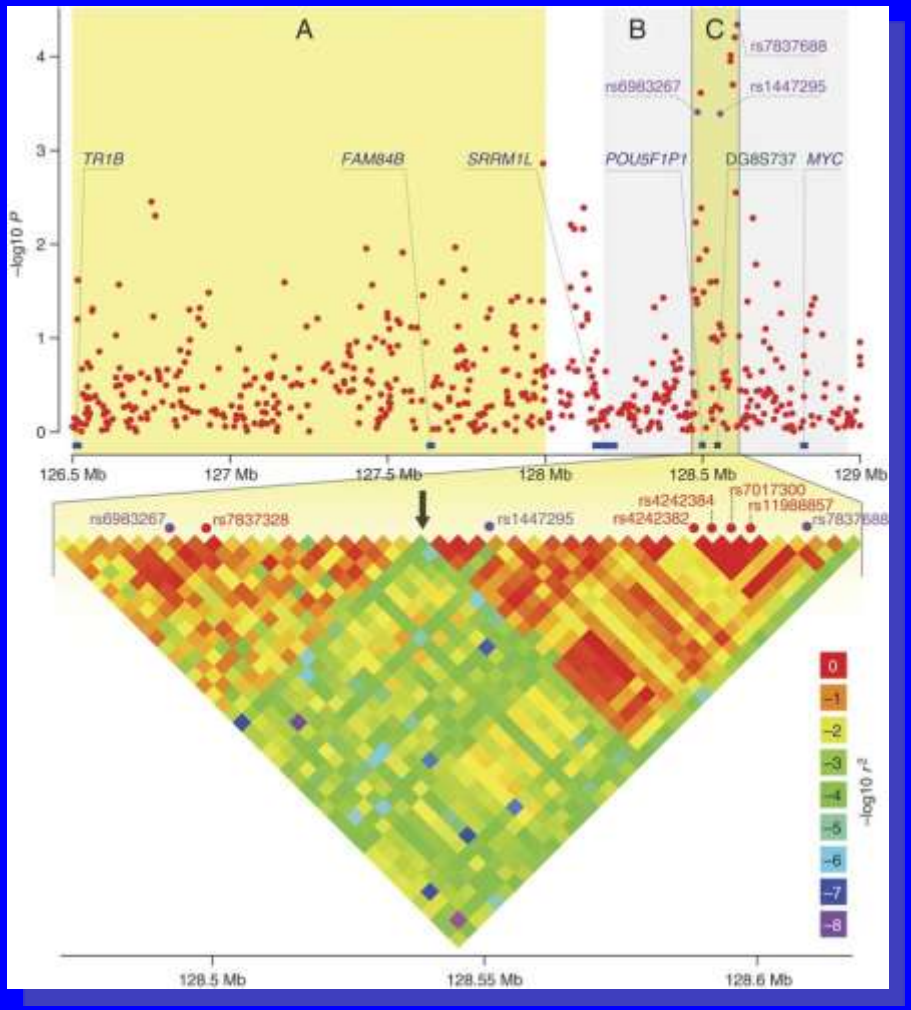
PCR

- Polymerase chain reaction
- How to make copies of a strand of DNA you are interested in?
- LSD, Aliens, HIV and OJ Simpson (and a Nobel prize in 1993)



GWAS

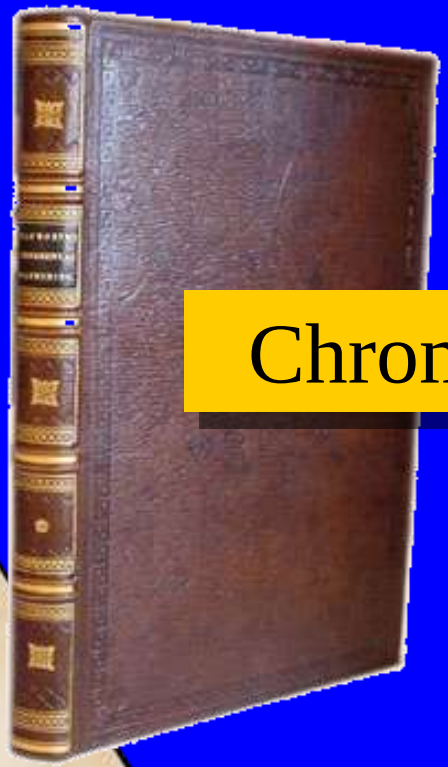
- Genome-wide association studies



The final step

- To identify the gene variants which predispose to the disease and determine their biological function.

Genome



Chromosome

Chromosome region

Gene

…..this is a gene variation……

….this is a gene variation….

The story of the breast cancer genes

- In the '80s a segregation analysis in 1500 families suggested that 4-5% of breast cancers can be due to inherited factors.
- In the '90s, linkage analysis showed that two susceptibility genes were likely to be located in regions on chromosomes 17 and 13.
- In 1994 and 1995 the two specific genes were identified.

What is the function of the breast cancer genes?

- The two genes act as tumour suppressors.
- The inherited mutations cause loss of the function.

What are the public health implications?

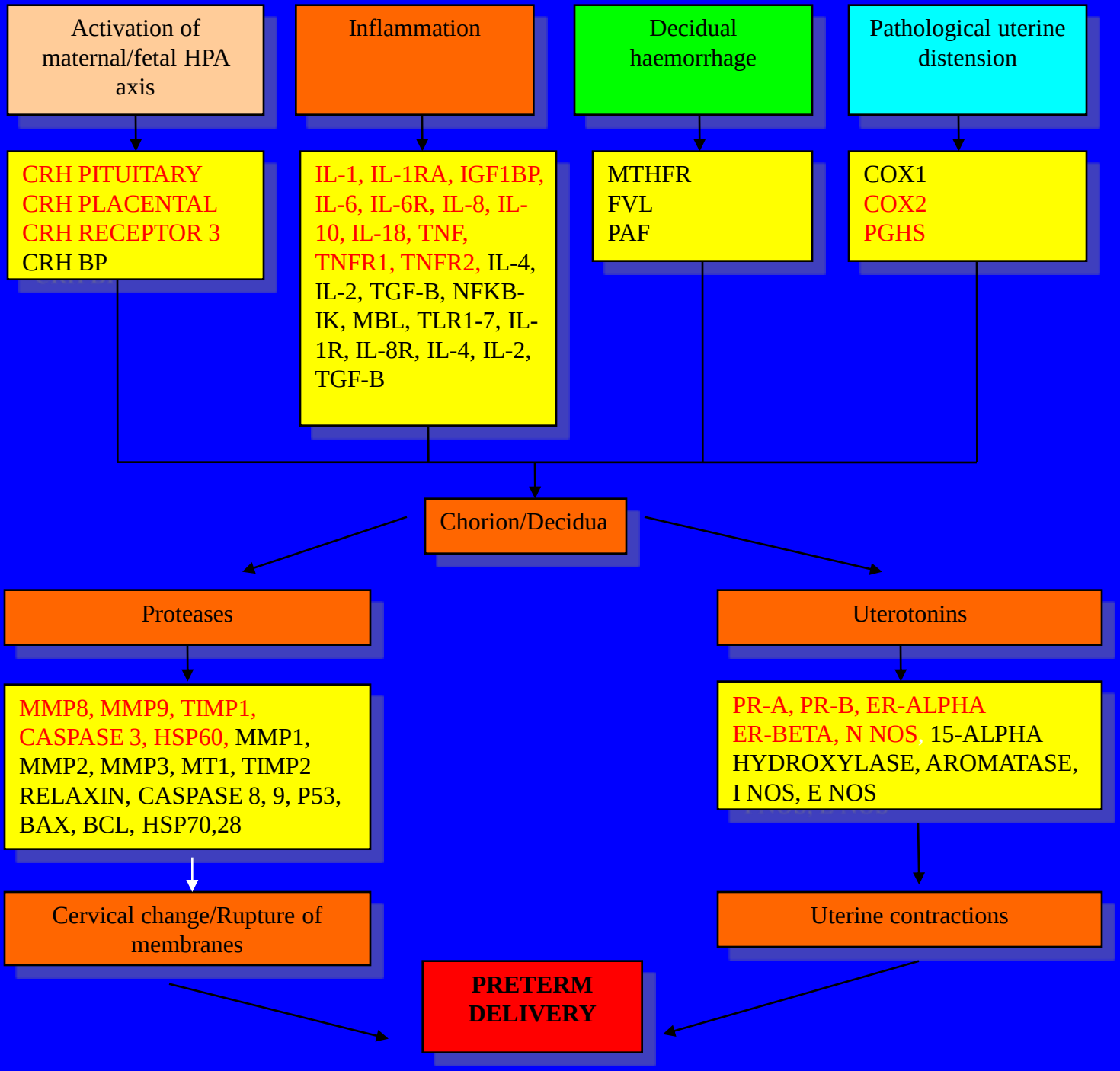
- Inherited mutation in the breast cancer genes are responsible for the development of the tumour in 4-5% of the general population.
- Most cases of cancer are not related to the genes.
- Initial estimates indicated that the risk associated with carrying the genes was 85-90%.
- Later estimates in the general population indicate that the risk is probably 36%.

What we do after we have identified a susceptibility gene?

- We have a better understanding of the patho-physiology of the disease
- This should lead to the development of better treatment options
- Screening tests could be developed
  - Feasibility
  - Cost
  - Ethical issues

Genetics and preterm delivery

- There is evidence that the risk of having a preterm delivery may be increased in women with genetic predisposition (Porter et al The risk of preterm birth across generations. Obstet Gynecol 1997)
- From the identification of potentially causal genes, screening tests could be developed and more knowledge on the presently unknown causes of preterm delivery could be derived. This would allow for developing those preventive/treatment strategies that are now not available.


Activation of maternal/fetal HPA axis
Inflammation
Decidual haemorrhage
Pathological uterine distension
CRH PITUITARY
CRH PLACENTAL
CRH RECEPTOR 3
CRH BP
IL-1, IL-1RA, IGF1BP, IL-6, IL-6R, IL-8, IL-10, IL-18, TNF, TNFR1, TNFR2, IL-4, IL-2, TGF-B, NFKB-IK, MBL, TLR1-7, IL-1R, IL-8R, IL-4, IL-2, TGF-B
MTHFR
FVL
PAF
COX1
COX2
PGHS
Chorion/Decidua
Proteases
Uterotonins
MMP8, MMP9, TIMP1, CASPASE 3, HSP60, MMP1, MMP2, MMP3, MT1, TIMP2 RELAXIN, CASPASE 8, 9, P53, BAX, BCL, HSP70,28
PR-A, PR-B, ER-ALPHA ER-BETA, N NOS, 15-ALPHA HYDROXYLASE, AROMATASE, I NOS, E NOS
Cervical change/Rupture of membranes
Uterine contractions
PRETERM DELIVERY

Positive conjuncture

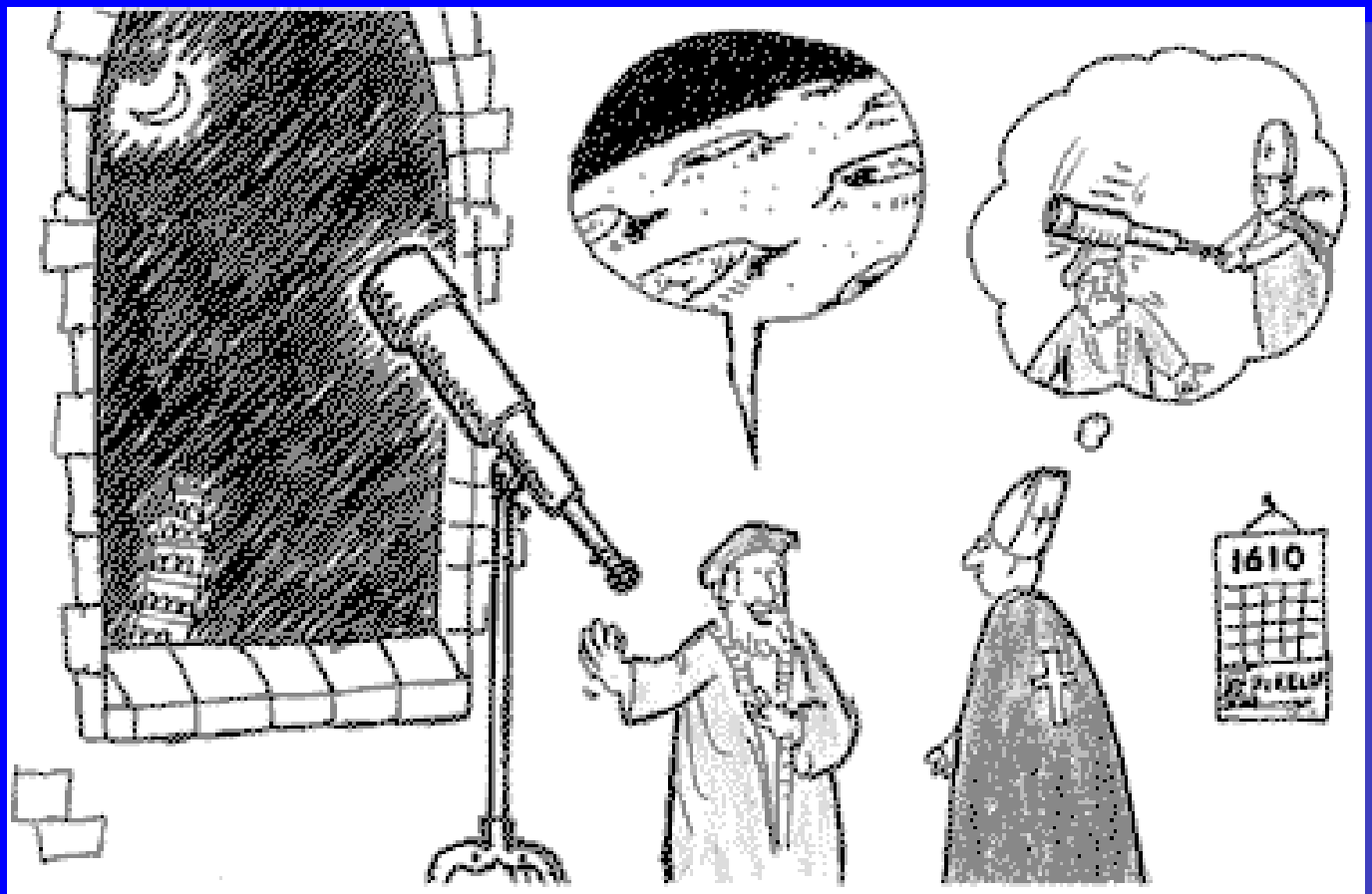
- This is an area of science in constant and rapid development
- Focus of research in medicine is shifting from biochemical mechanisms to genes
- Strong interest from researchers both in developed and developing countries
- Large multinational studies of gene-disease association are feasible
- Discovery

Potential criticisms

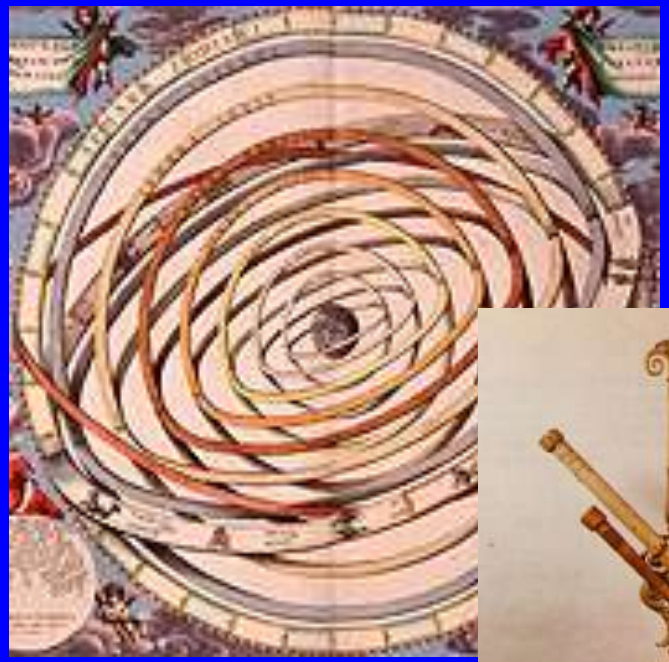
- Not unexpected, considering the novel approach
- Research: which genes to study?
- Public Health implications: how feasible is it to implement the results?

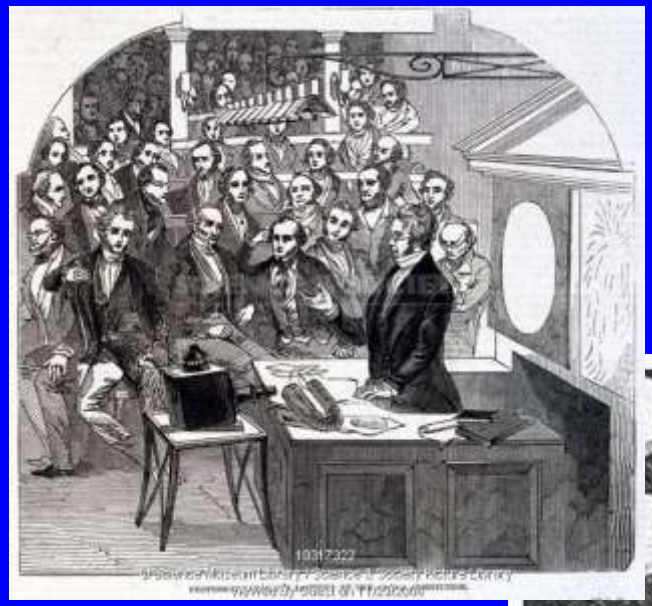
A critical time

- Innovations in technology can contribute to progress in science

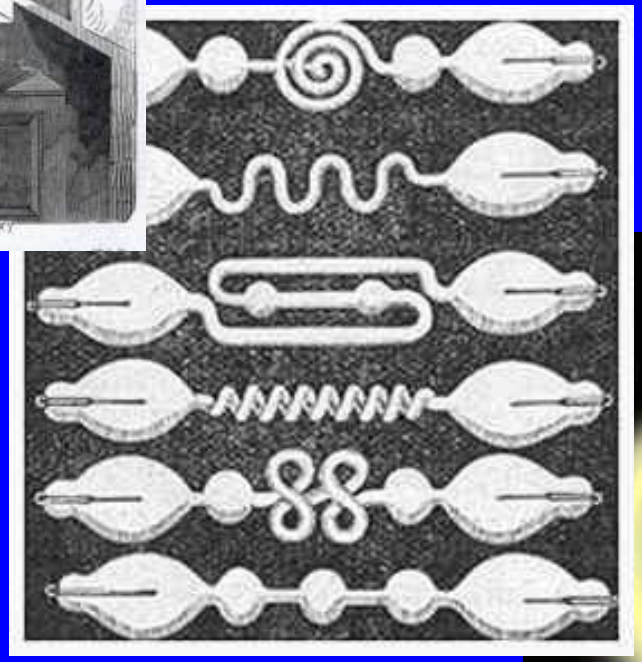


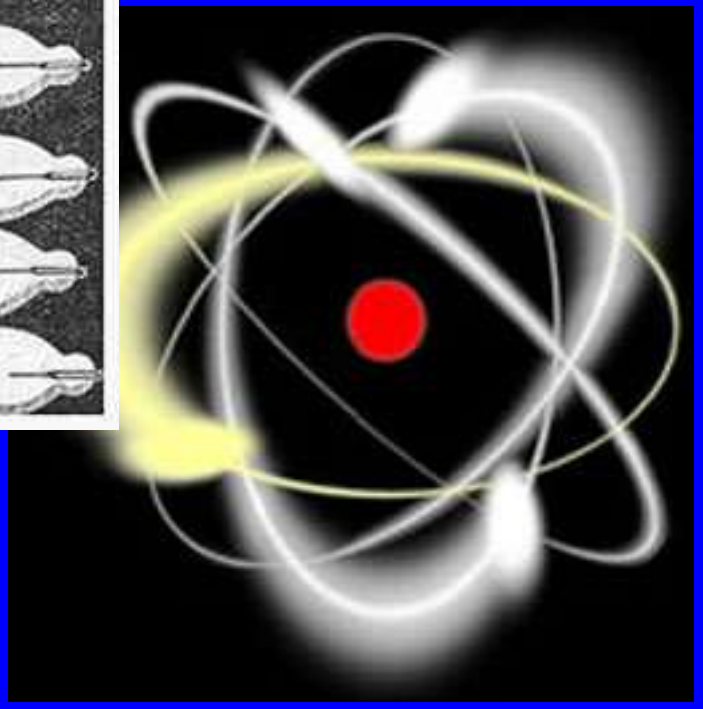
Galileo discusses his discoveries with the church.





1880s





Grameen Phone, Bangladesh's leading cell phone operator, is offering a special low-priced package to so-called 'phone ladies' in small villages, where fixed telephone lines are non-existent. The phone ladies share their cell phones with other villagers at a few taka a call, raking in monthly earnings that could top USD 170: a serious income in a nation where the average annual per capita income is USD 368. Internet access over wireless phones is next. (Source: Reuters.)

Future efforts

- Develop international collaborations
- Need to increase public awareness
- Need to influence and convince the scientific community and donors
- Assure that research results are translated into equitable and ethically correct health care practices