Genetic Polymorphism associated with Cancer

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Back Ground: Human diversity

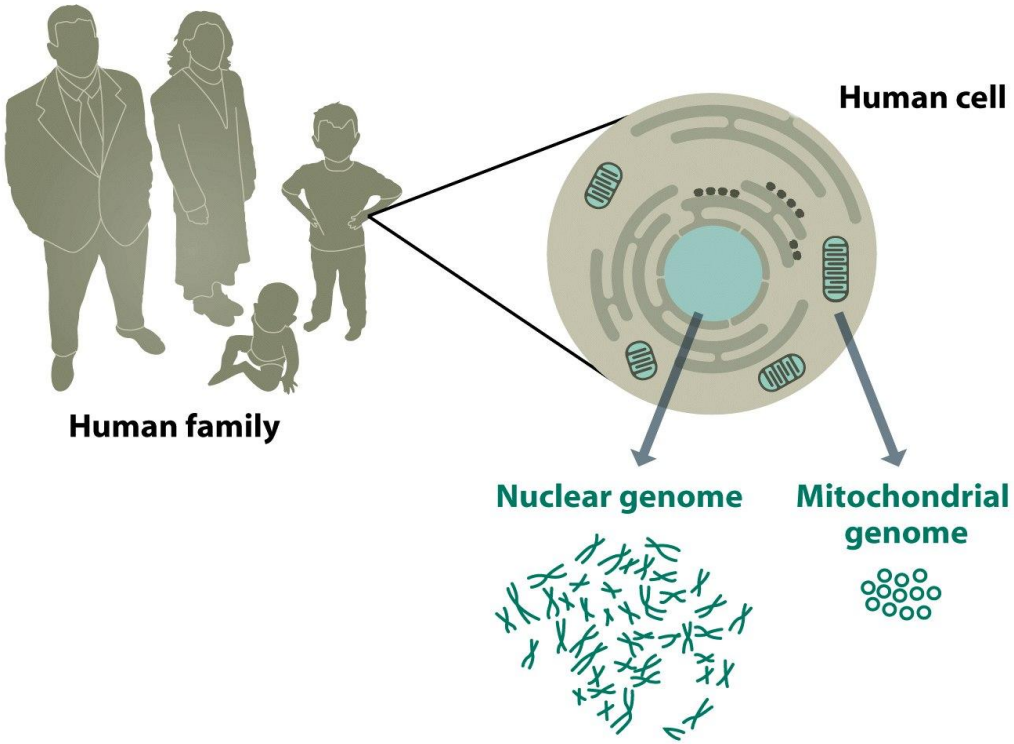
People of Indian sub-continent represent great diversity of morphological, genetic, cultural and linguistic features .

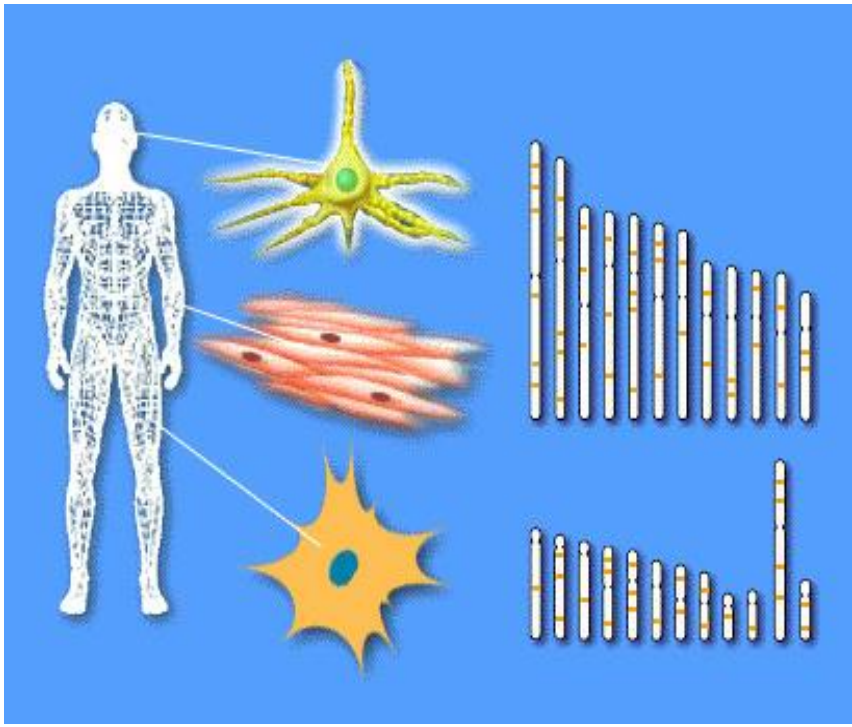
These differences have resulted from thousands of years of evolution.

The present diversity of man is the results of development of genetically distinct population within a single species or sub-species through the process of micro-evolution (Hirszfeld and Hirszfeld, 1919).

During the process of evolution, new genes may be introduced by way of mutation or recombination and this variation is transmitted from one generation to the next.

Background: Cells and Chromosomes





The human body is made up of 100 trillion cells.

Each cell has at least one nucleus, which houses the chromosomes.

Each having 23 pairs of chromosomes- 44 Autosomes & Sex chromosome- XY

Sperm and eggs contain one of each sex chromosome.

Approximately 30,000 genes

Approximately 3 billions nucleotides.

How diversity exist?

The diversity of modern human DNA results from the accumulation of mutations as it passes down to us from our ancestors.

This diversity in the form of DNA polymorphisms, can be analyzed & used to investigate our genetic history & relatedness- a method of studying human evolution & variation.

So, 2 in 1000 bp genome sequence is different in any two individuals due to polymorphism.

Polymorphism

AGT CGG CTA **A**TCC

AGT CGG CTA **C**TC C

Frequency >.05% in population

Changes in function and structure not always

Mutation

CCT T**A**C TGA CTA A

CCT TG**C** TGA CTA A

Frequency <.05% in population

Mostly changes in structure and function

Some Facts

- In human beings, 99.9 percent of bases are the same.
- Remaining 0.1 percent makes a person unique.
  - Different attributes / characteristics / traits
    - how a person looks,
    - diseases he or she develops.
- - These variations can be:
  - Harmless (change in phenotype)
  - Harmful (diabetes, cancer, heart disease, hemophilia etc.)
  - Latent (variations found in coding and regulatory regions, are not harmful on their own, and the change in each gene only becomes apparent under certain conditions e.g. susceptibility to lung cancer)

One important use of DNA polymorphism knowledge

- **Association study**
- **To know risk of the disease by candidate gene approach**

i.e. **whether alleles of a locus or loci are associated with the risk of a disease**

What is Cancer?

- Generic name for a biological phenomenon
- Not a single disease but a wide spectrum of conditions.
  Biologically different
  Causation and carcinogenesis different.
- Only common feature
  Uncontrolled proliferation leading to death
  If not successfully treated

Difference between:

Normal Cells

- Cells are the building blocks of all living beings.
- Inherent capacity to multiply
- Growth is orderly, purposeful and subserves function
- Cells recognise and respect each other.
- Stop growing if they come in contact with another cell.

Cancer Cells

- Cancer Cell is an anarchist.
- Does not respect its neighbours.
- Has a law of its own.
- Multiplies regardless of neighbouring cells.
- Invades surrounding tissue.
- Behaves like an aggressive enemy
- Cellular regulating mechanism lost.
- Cells multiply without purpose, without limit, without function, at the expense of normal tissue.

This is cancer.

Risk of Carcinogenic Hazard

- Depends on potency of carcinogen
- Most chemical carcinogens are
  Organ and species specific
- Carcinogenicity: direct or thro metabolites
- Organ and species specific

Chemicals as part of life style

Tobacco use: Chewing, smoking, snuffing & dipping

40% of cancers in men 12% of cancers in women	Tobacco related

Mouth, pharynx, larynx, lung & lip

Environmental exposure to Tobacco	Indoor & outdoor (Passive smoking) Increases mortality of lung cancer by 20-30%

Intensity of Smoking & Lung Cancer

- One pack cigarettes per day 10 times risk
- Two packs cigarettes per day 20 times risk
- Smoking enhances risk of lung cancer in asbestos workers
- Alcohol enhances smokers risk to cancer

Tobacco habit and Cancer

Tobacco Chewing		:	Buccal Cancer (cheek)
Tobacco smoking		:	
Type	Beedi	:	Oral commisure
	Cheroot	:	Palate
	Cigarette	:	Epipharynx, Pharynx, Lung, Bladder
	Cigar & Pipe	:	No association

World pattern : High and Low incidence

Site	High incidence	Low incidence
Oral (Mouth)	India, Srilanka, Brazil	Europe & Japan
Stomach	Japan, Finland	US White
Colon	USA	India & Japan
Lung	UK, USA, Europe	India
Skin	Australia, Southern USA	India (colored races)
Breast	UK, USA, Europe	S.E.Asia, India(Int) Japan(Lowest)
Cervix	India, S.E.Asia, US(spanish), Brazil	Europe, Japan(Int) Isreal
Gall Bladder (Female)	India (North)	Finland

- **Polymorphism and cancer sensitivity**

  - **Polymorphisms in drug-metabolizing enzymes: GSTs, CYP genes**

  - **Polymorphism in p53 gene**

HIGH and LOW risk Genes responsible for Cancer

High risk/penetrant genes (p53, APC etc):

Mutation/DNA sequence change increase the risk of disease 60-80%.

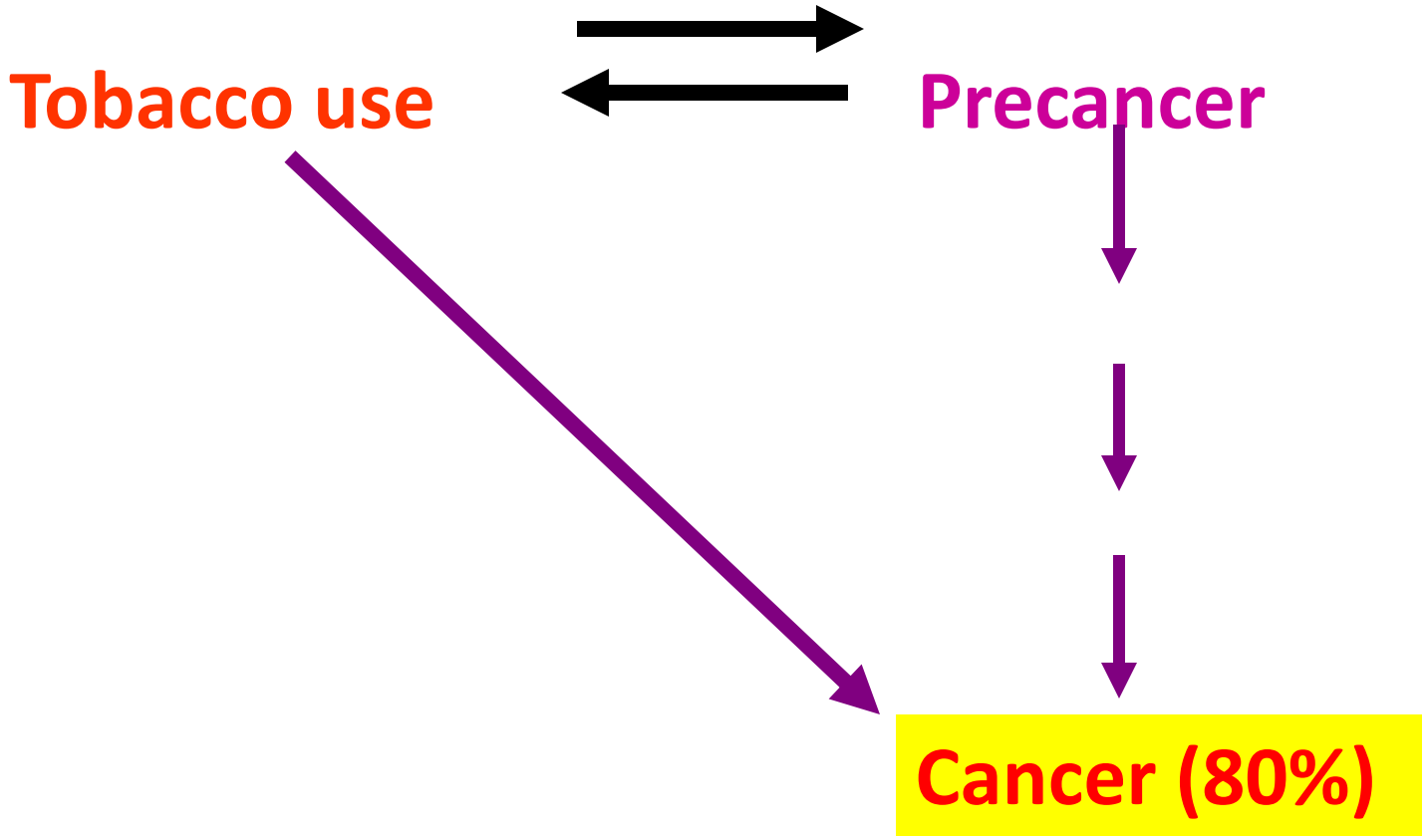
Even mutation/variation in one high risk gene is not sufficient to explain carcinogenesis but variation in high risk genes are rare in population

Low risk/penetrant genes:

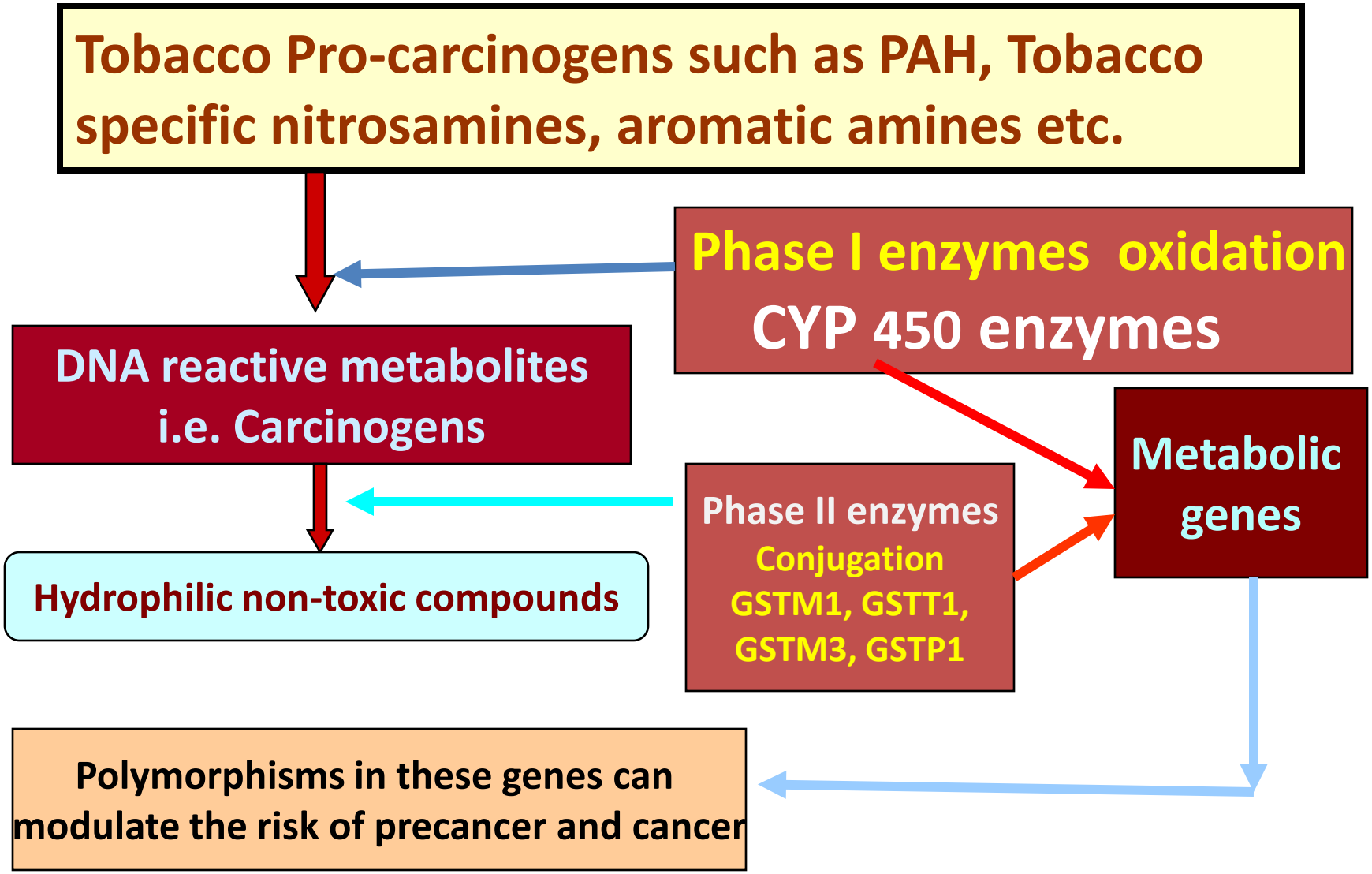
(GSTs, NAT2, CYP2E1, XRCC1):

Polymorphism/DNA sequence variation increase the risk of disease by 10-20%. But variation in low risk genes are common in population

- It is known that Tobacco use increases the risk of oral cavity precancer (such as leukoplakia) and cancer



Activation & Inactivation of Pro-carcinogens



FOCUS OF OUR STUDY

1. Low penetrant genes are usually polymorphic that confer low individual risk to cancer but collectively confer a high risk

2. Such common polymorphisms exhibit high genotype environment interactions

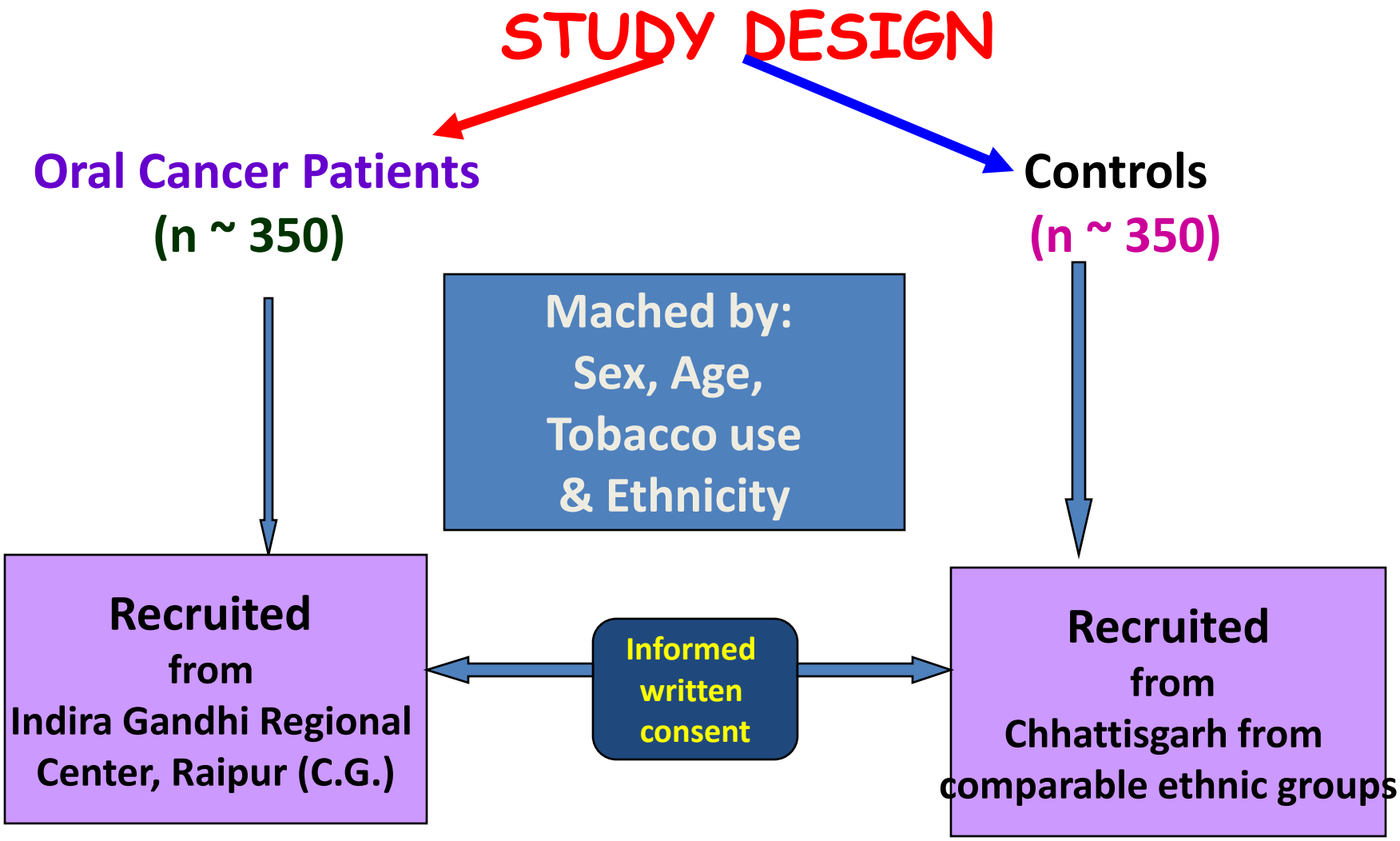
3. Association studies are method of choice

OBJECTIVES

To estimate:

- Relative risk of oral squamous cell carcinoma in relation to polymorphisms at GSTM1, GSTT1, GSTM3 & GSTP1 and CYP2 loci among Tobacco users in *Chhattisgarh* population.

- Risk of the disease due to gene-gene and gene-tobacco dose interaction.


STUDY DESIGN
Oral Cancer Patients
(n ~ 350)
Controls
(n ~ 350)
Mached by:
Sex, Age,
Tobacco use
& Ethnicity
Recruited
from
Indira Gandhi Regional
Center, Raipur (C.G.)
Informed
written
consent
Recruited
from
Chhattisgarh from
comparable ethnic groups

Subjects and blood collection for DNA:

Hospital based case-control study:

Patients:

Unrelated, both male and female, no cancer in the family and first degree relatives, should have tobacco smoking or chewing habit at least for 5 yr., primary cancer or leukoplakia in oral cavity (diagnosed histopathologically)

Controls:

Unrelated, both male and female, no lesion in oral cavity, should have tobacco habit for at least 5 yrs., no cancer in family and first degree relatives


HUMAN GENOMICS LAB

Oral Cancer

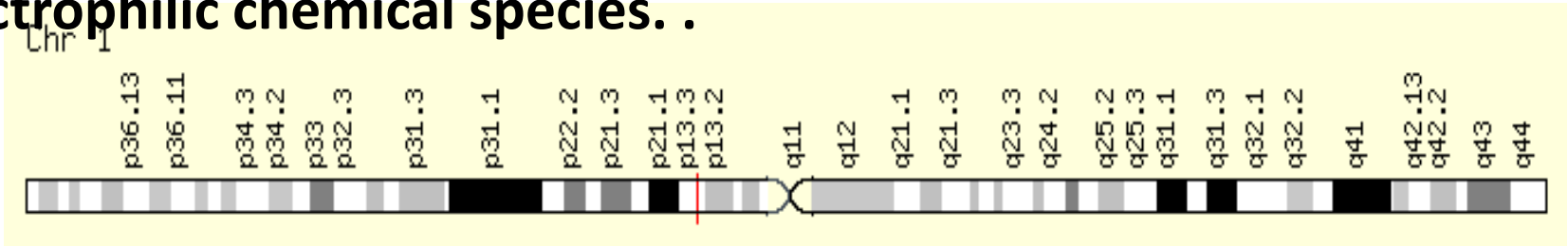
- An individual's genotype could be-
- GSTM1(W/W) or GSTM1(W/N) or GSTM1(N/N)

- GSTM1(W/W)---- Normal enzyme synthesis
- GSTM1(W/N) -----Normal enzyme synthesis
- GSTM1 (N/N) ----- No enzyme synthesis

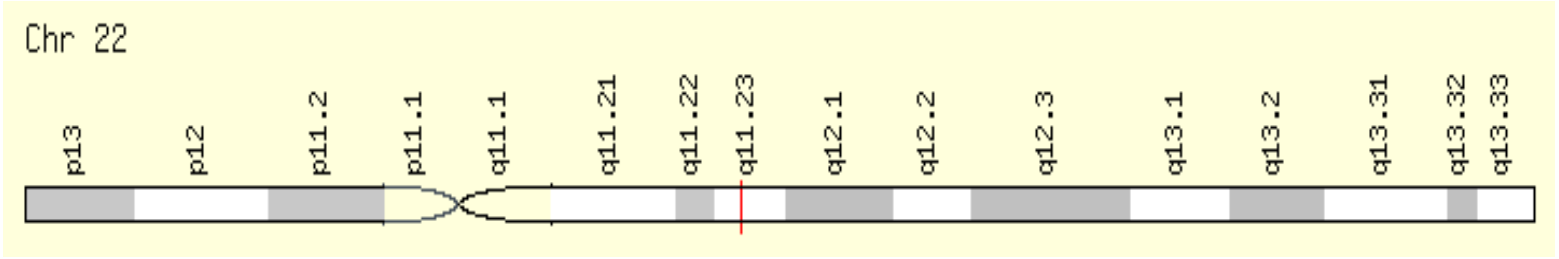
- An individual with GSTM1(N/N) will detoxify less toxic materials

Drug metabolizing gene - GST glutathione- S transferase

Glutathione S-transferases (GSTs) are a super family of dimeric phase II metabolic enzymes. The multi-gene family consists of four major genes, GSTA (alpha), GSTT1 (theta), GSTM1 (mu), and GSTP1 (pi), and they play an active role in the detoxification and elimination of carcinogens. GST enzymes provides defence against electrophilic chemical species. .



Location of GSTM1gene in human chromosome 1



Location of GSTT1gene in human chromosome 22

:Inference:

More than 90% of the diseases are due to the effects of environments.

The environments initially react with our common metabolic enzymes or receptors.

An individual may become susceptible to the environment due to presence of polymorphic alleles of genes.

Since the prevalence of polymorphic alleles vary in different population, so sensitivity to environment is different.

Knowledge of prevalence of polymorphic allele in a population could be used for counseling to avoid a environment responsible for a disease.