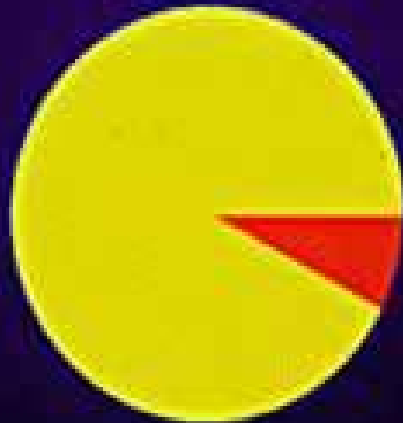


Basic Overview of Genetics and Genetic Epidemiology

Virtually All Diseases (Except Maybe Trauma) Have a Genetic Component



Cystic Fibrosis



Adult Onset
Diabetes



AIDS

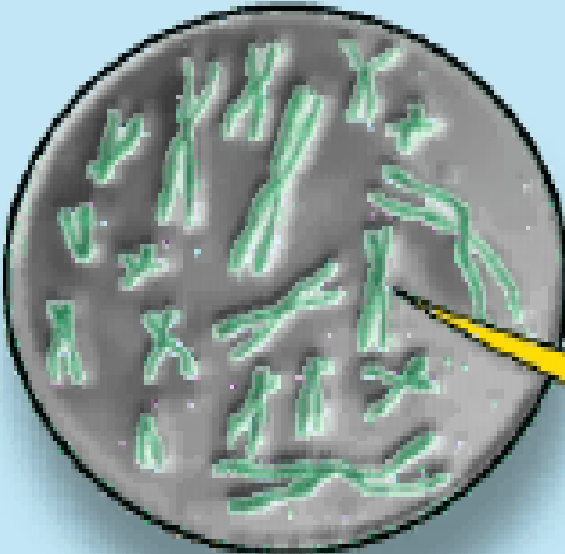
Genetic Component 

Environmental Component 

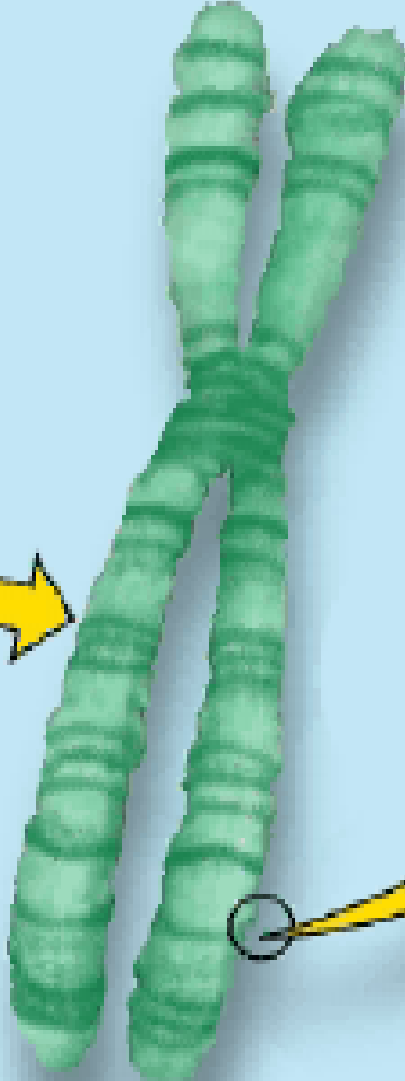


How are genes inherited?

Eukaryotic chromosome

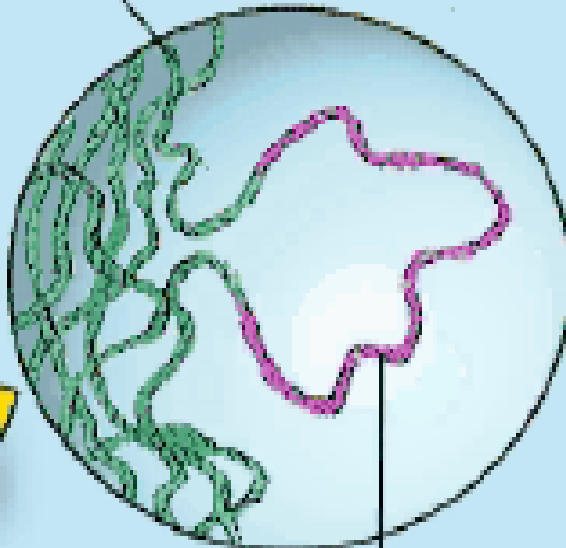


A eukaryotic chromosome set



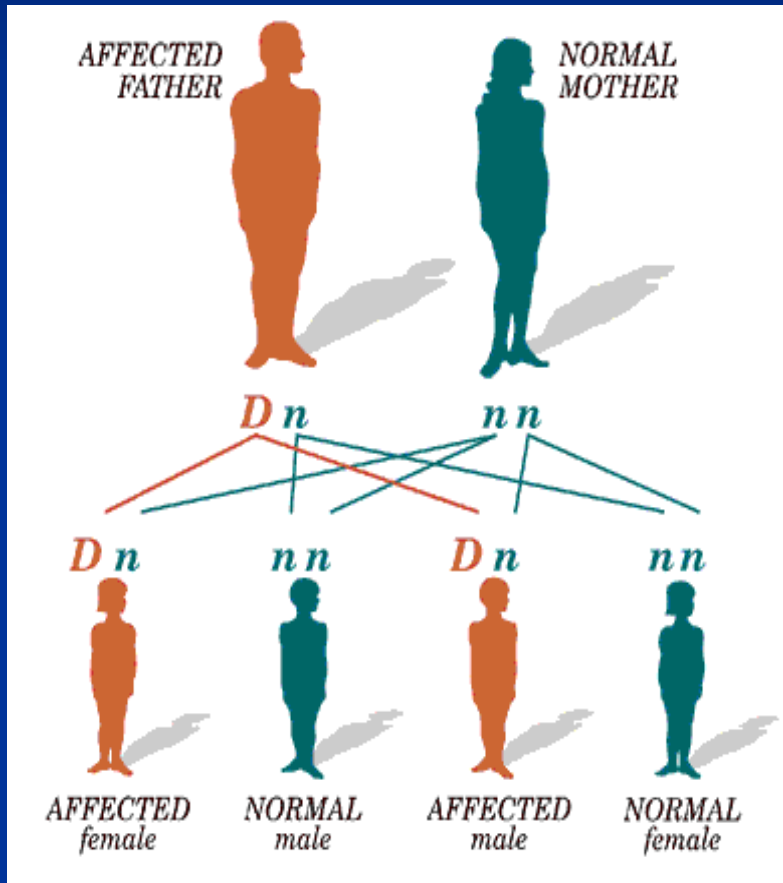
Chromosome

DNA

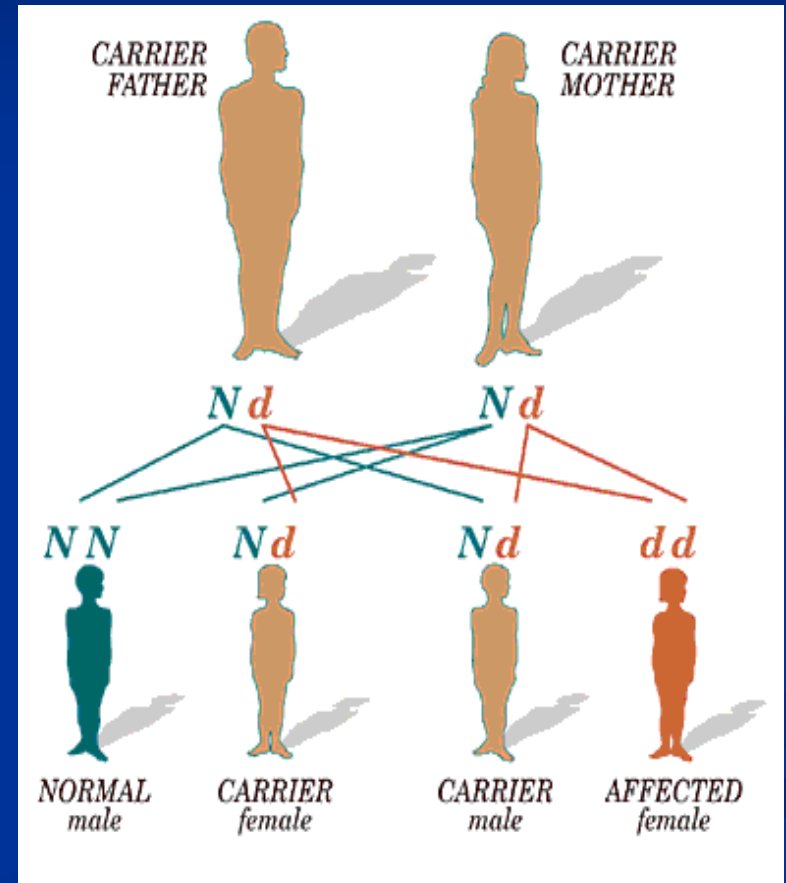


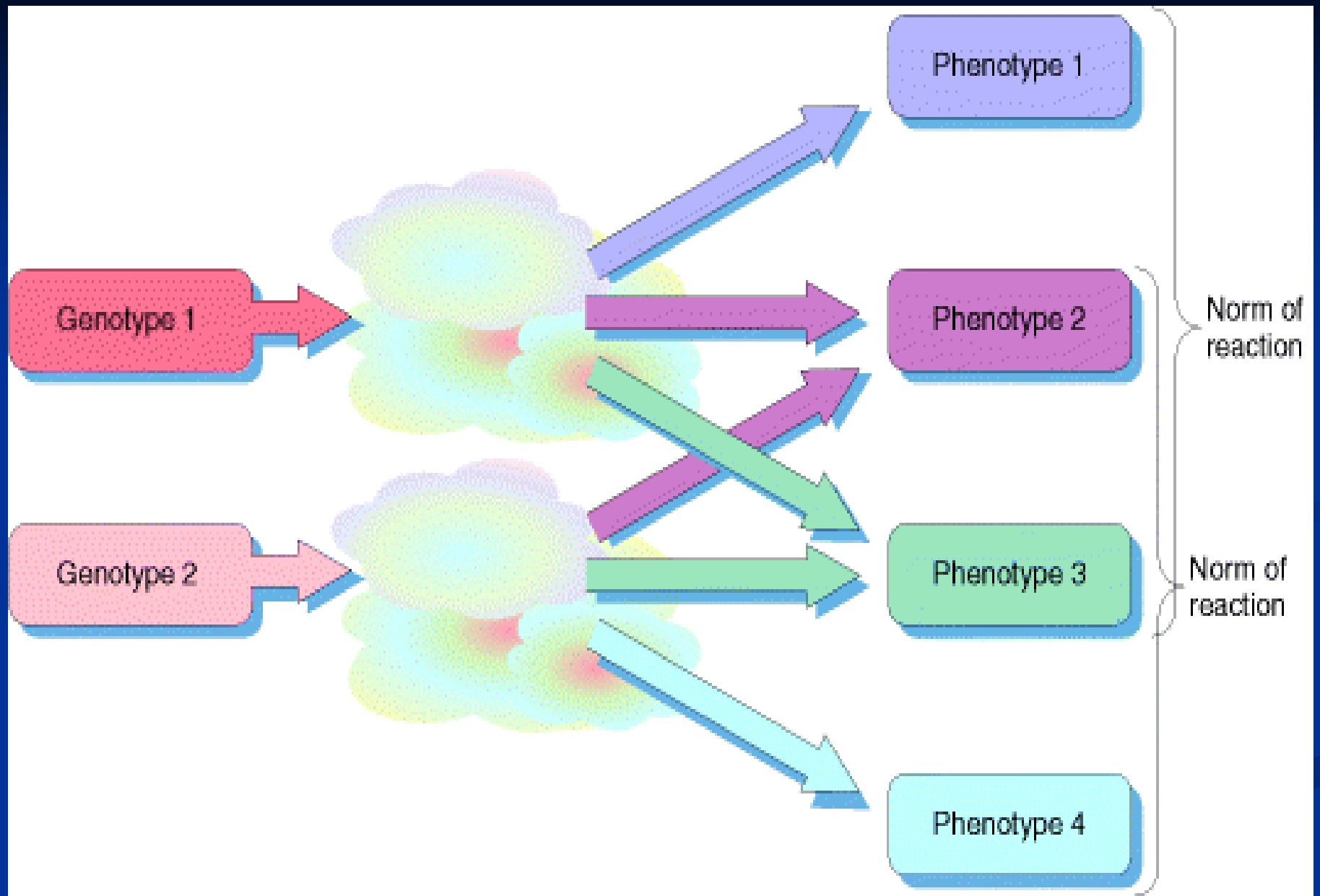
Gene locus

Dominant inheritance pattern



Recessive inheritance pattern



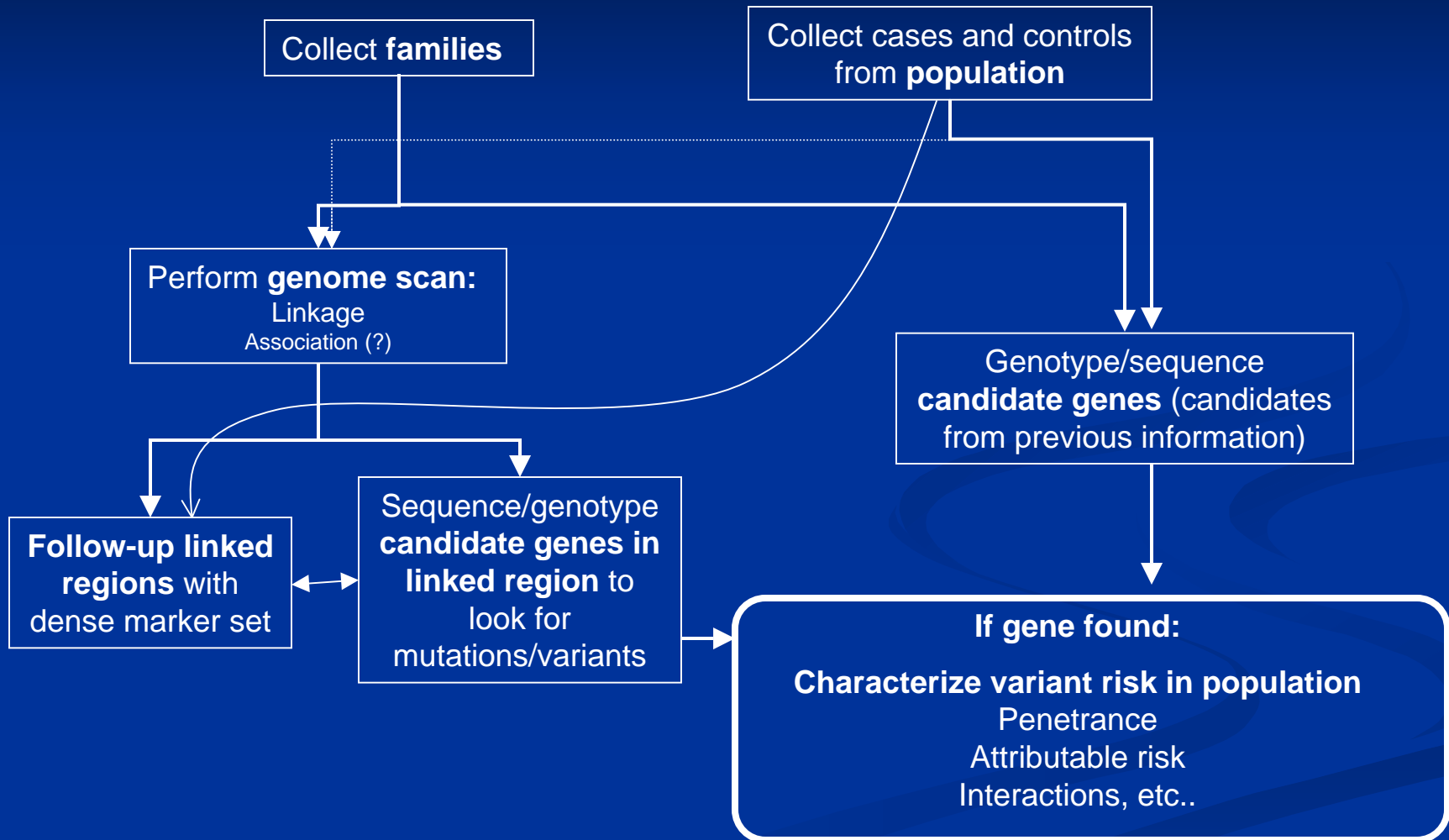


Genetic Epidemiologic Study Designs

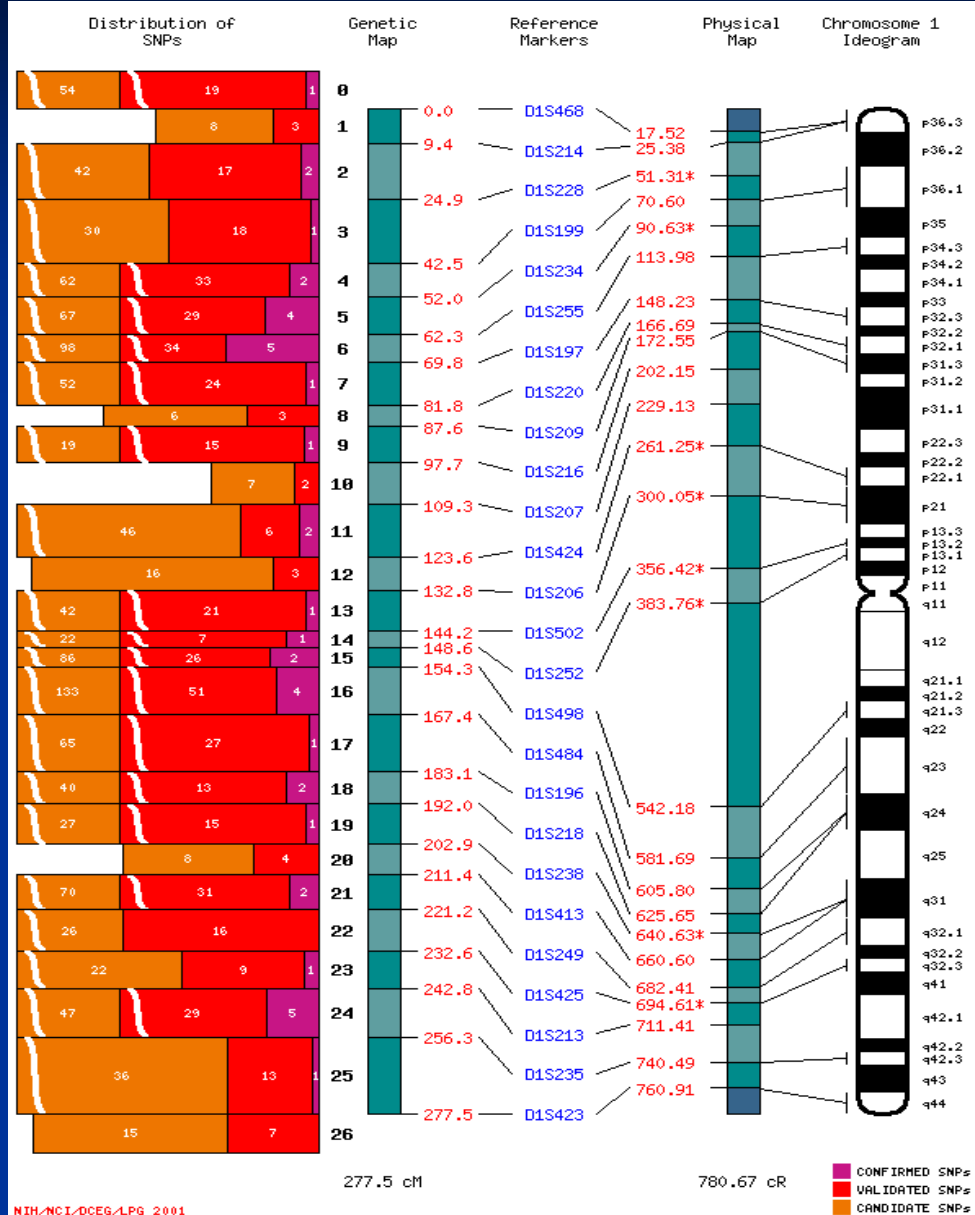
- **Family based (Linkage)**
 - Extended families
 - Sib pairs
 - **Population based (Association)**
 - Case-control
 - Cohort
 - Trios
 - **Model organisms**
 - Intercross
 - Backcross
- Human populations**
-

Reference: Approaches to Gene Mapping in Complex Human Diseases (1998). Editors: J.L. Haines, M.A. Pericak-Vance. Wiley Liss, Inc [ISBN: 0-471-17195-6]

Strategies for Human Genetic Epidemiology Studies



Genome Scan



- A genome scan consists of approximately 5,860 SNP markers spread across all 23 human chromosomes. These markers are like a dragnet, enabling us to pinpoint the location of disease genes.
- Shown on the left is a map of human chromosome 1 with different type of markers (Single nucleotide polymorphisms and microsatellites) overlaid on the map.

Big Picture

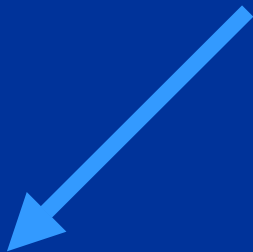
Disease with genetic component



Map the disease gene



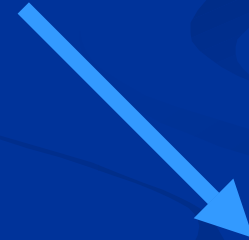
Clone the disease gene



Diagnostics



Gene therapy



**Drug or
Interventional
therapy**

Some previous studies involving the genetics of FECD

Familial Clustering

- Rosenblum et. al. in 1980 described a study of 102 individuals from 25 families in which at least one member was known to have FECD.
- They used slit-lamp examination, corneal pachymetry, and specular microscopy, in conjunction with examination of pathology records.
- Record review of 79 cases of PKPs done solely for phakic FECD between 1940 and 1978 demonstrated a marked predominance of females.
- In contrast, the clinical study demonstrated a more even sex distribution in the families with evidence for an autosomal-dominant mode of inheritance, a high degree of penetrance, and variable expressivity, with generally increased severity among females.

More Recent Work

- Biswas et al (2001) found mutations in the COL8A2 gene on chromosome 1 in young onset patients.
- This gene encodes α -2 chain of type VIII collagen part of Descemet's membrane, suggesting a role of type VIII collagen in influencing terminal differentiation of the corneal endothelium
- Confirmed by Gottsch et. al.
- Not confirmed by Kobayashi et. al. nor Vellore et. al.
- We also conducted a pilot study and sequenced 40 cases with FECD.

Hopfer et. al.

- Hopfer et. al. made knockout mice for the COL8A1 and COL8A2 genes.
- Saw anterior segment abnormalities in the eye.
- Therefore, COL8A1 and COL8A2 do have an important role in the disease.

Y.J. Li et.al.

Y.J. Li et.al. performed the first genome wide linkage scan using SNP markers on FECD families (2005).

- 5 regions were identified with positive linkage signals from all analyses on chromosomes 1, 7, 15, 17, and X.
- Chromosome 17q (~107 to 126cM region) contained the most overall significant results with LOD scores greater than 2 using both two-point and multi-point analyses.
- A peak chromosome at the 1p region result (LOD >2) is located near the COL8A2 gene. The authors suggested that a subset of families may have mutations in this gene warranting mutation screening of the COL8A2 gene.

FECD Pilot Study

The Goals of the Pilot Study

- To test the multi-center paradigm of data collection for Fuchs' Dystrophy.
- To test, modify and validate the Krachmer grading scale.
- To examine older onset FECD cases for mutations in the COL8A2 gene and determine if the gene has an important role in FECD.

Questions posed in the pilot study

- How common are mutations in COL8A2 in the US population?
- If there are mutations in COL8A2, are the mutations the same in each family?

Methods used in the Pilot Study

- Participants were recruited from 3 sites:
 - UH Cleveland, Michigan, Albany
- Index cases and affected relatives were collected (mostly bothers and sisters).
- The entire COL8A2 gene was sequenced to look for mutations.

Summary of Results from Pilot Study

- We were unable to find any mutations in the COL8A2 gene in 40 probands with FECD
- Note: These probands were in general older than the patients in the Biswas et al and Gottsch et al studies

Conclusions from Pilot Study

- Highly penetrant mutations in COL8A2 may be present in a proportion of cases with young-onset disease
- These mutations are not present (or at least not frequent) in older-onset disease cases
- Caveat: This does not mean that the COL8A2 gene can be excluded from playing a role in older-onset FECD

**Initiation of the full scale
FECD Genetics Multi-Center Study**

First Aim of the Study

- Identify cases with advanced FECD and characterize the extent of familial clustering using a clinical measure of severity as a semi-quantitative trait.
- This will be done by:
 - Collecting Family history, clinical, and other demographic information.
 - Obtaining Histopathologic Confirmation of advanced index cases.
 - Collecting Blood samples for molecular genetic analyses.
 - Using a web-based database to facilitate multi-site data collection.

Second Aim of Study

- Conduct a genome-wide scan utilizing DNA collected from the index cases and families ($N = 500$ families; estimated $N \geq 500$ sib pairs).
- Model-free linkage analysis will be conducted using the DNA marker data in conjunction with the clinical data on FECD to identify linkage signals.
- To confirm evidence of linkage and to narrow the initial interval, additional markers will be typed in regions that demonstrate moderate to significant evidence of linkage ($p \leq 0.05$; LOD score ~ 0.8).

Third Aim of Study

- Identify candidate genes using previous investigations of a limited number of families (e.g. COL8A2) and scanning these genes for mutations.
- We will investigate the importance of these genes on a more global basis by characterizing their role in a larger sample.

End Goal

- We anticipate this study will lead to novel insights into the etiology of FECD and the biology of the corneal endothelium.

How will we achieve this goal

- Leadership (PIs, Steering Committee, External Advisory Committee, Site Investigators)
- Organization
- Coordination
- Training (why we are here)
- Monitoring Progress/ Reporting
- Quality Control
- Sophisticated Analyses

Leadership

- Principal Investigator: Sudha Iyengar, PhD
 - Co-PI: Jonathan Lass, MD
- Steering Committee:
 - Sudha Iyengar, PhD
 - Jonathan H. Lass, MD
 - David S. Bardenstein, MD
 - Michael Belin, MD
 - Katrina Goddard, PhD
 - Mark Mannis, MD
 - Julia Richards, PhD
 - Alan Sugar, MD
 - Richard Yee, MD
- External Advisory Committee:
 - Curtis Margo, M.D., MPH.
 - Rohit Varma, M.D., M.P.H.
 - Genetic epidemiologist to be named

Organization

