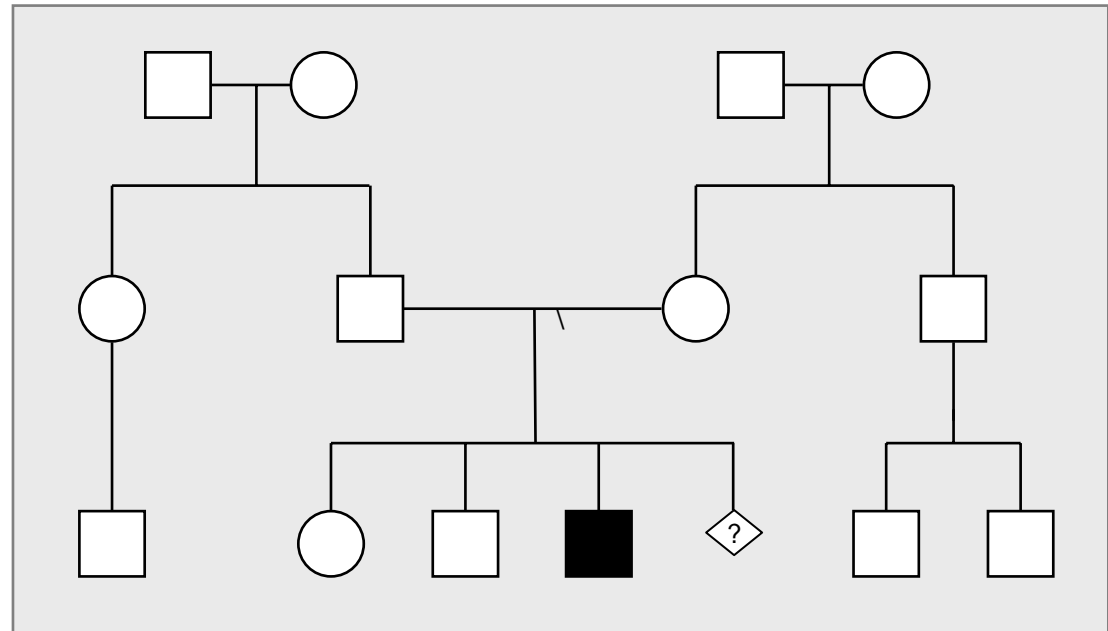
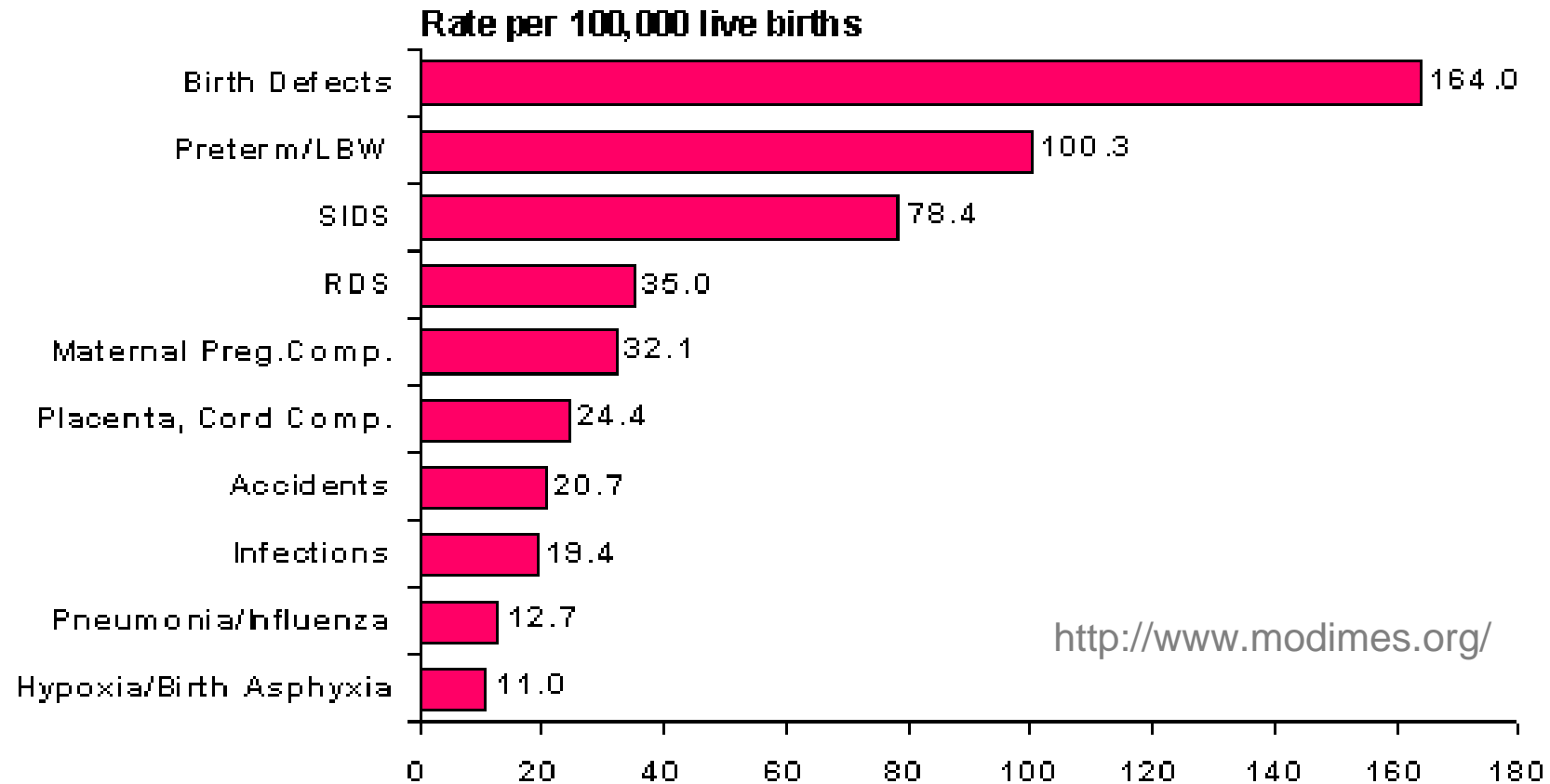


# Case 1: Cleft Lip and Palate



[www.widesmiles.org](http://www.widesmiles.org)

# Birth Defects

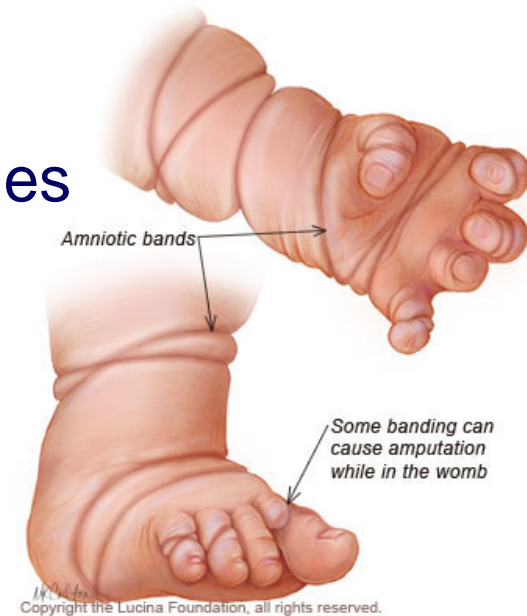


# Birth Defects Classification

- **deformations** - mechanical distortion
  - e.g. positional talipes, plagiocephaly



- **disruption** - destruction of normal tissues
  - e.g. amniotic bands



# Birth Defects Classification

- **malformation** - failure of embryonic processes
  - e.g. omphalocele, bladder extrophy



- **dysmorphism** - rare variants of development
  - e.g. upslanting palpebral fissures in caucasians



# Causes of Birth Defects

- genetic

  - monogenic

  - chromosomal

- environmental

  - maternal infections

  - maternal illness

  - medications

  - substances

- unknown

# Cleft Lip: Clinical Features



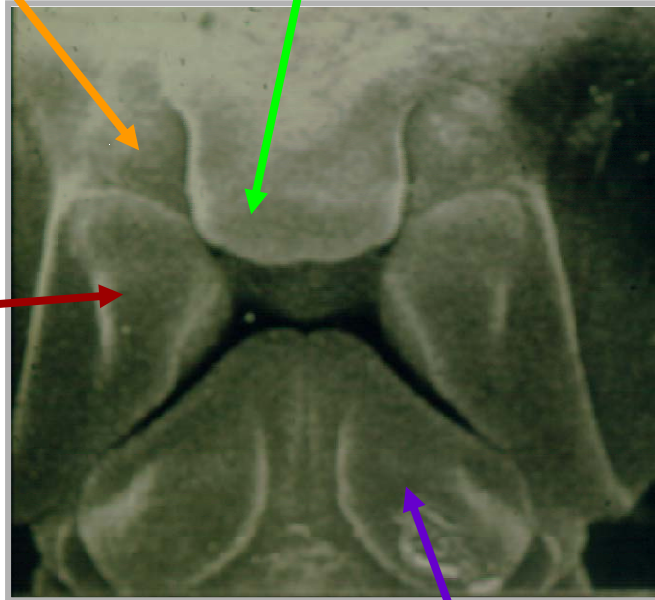
- 1:1000 live births
- male > female
- left > right
- 1/3 bilateral
- 2/3 cleft palate
- 1/4 other birth defects

# frontonasal mass

lateral nasal process

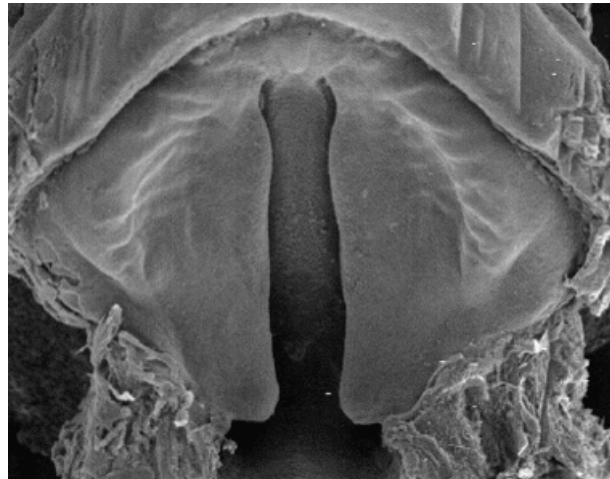
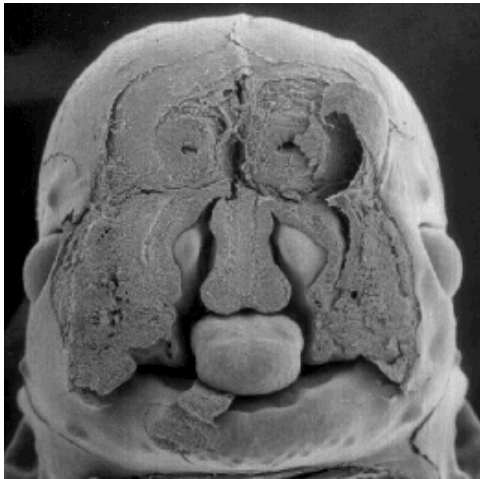
medial nasal process

maxillary process



mandibular process

Chick ~5.5GD, Mouse ~11GD, Human ~29GD



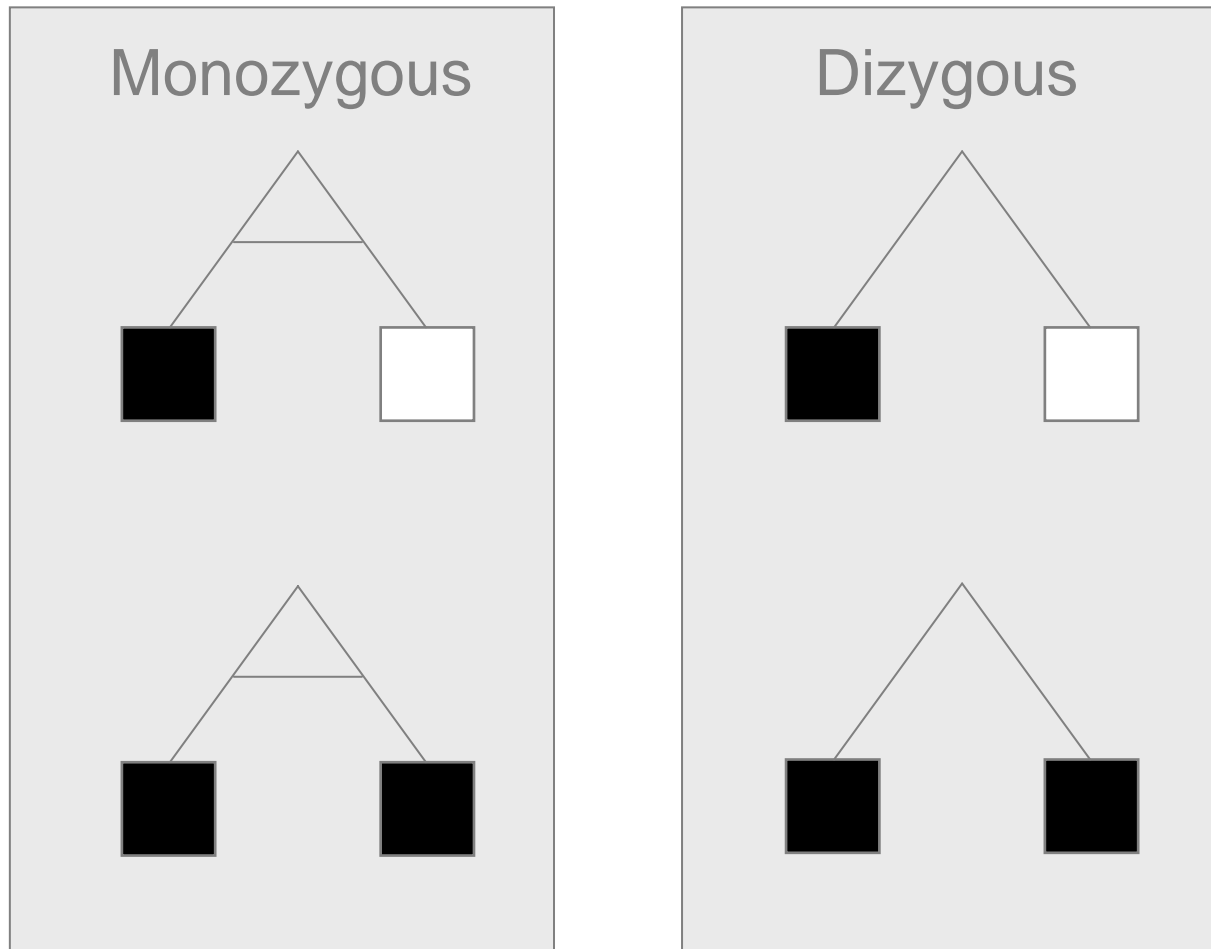
- **initiation and vertical growth** of palatal primordia (mouse 12GD, human 44GD)
- **elevation of palatal shelves** (mouse 14GD, human 54GD)
- **formation of midline epithelial seam** (mouse 14.5GD, human 56.5GD)
- **establishing mesenchymal continuity** between shelves (mouse 15GD, human 58GD)

# Cleft Lip: Genetic Features

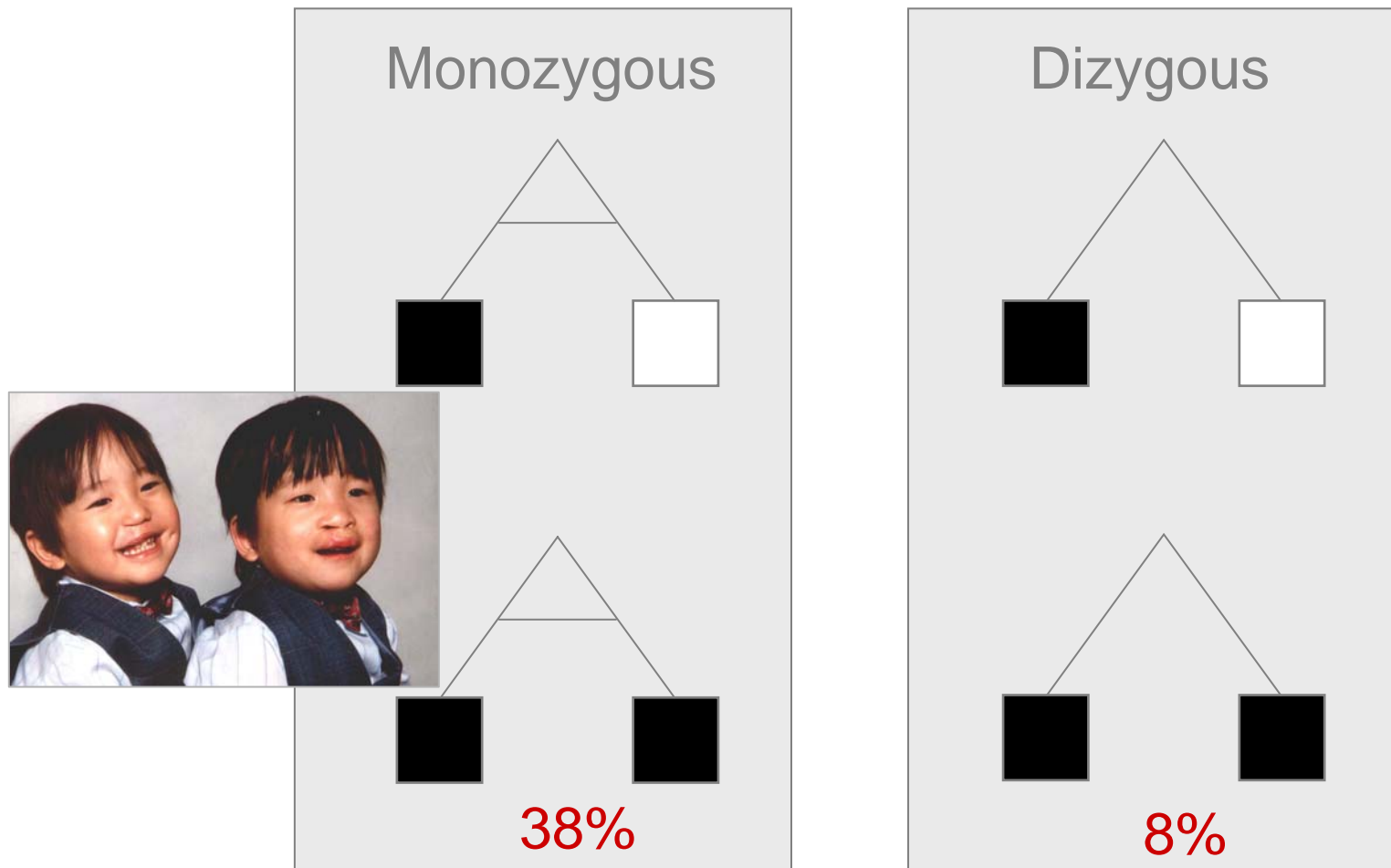


- sibling RR 2-4% ( $\uparrow \sim 30X$ )
- offspring RR same
- RR $\uparrow$  if proband female
- RR $\uparrow$  if severe defect in proband

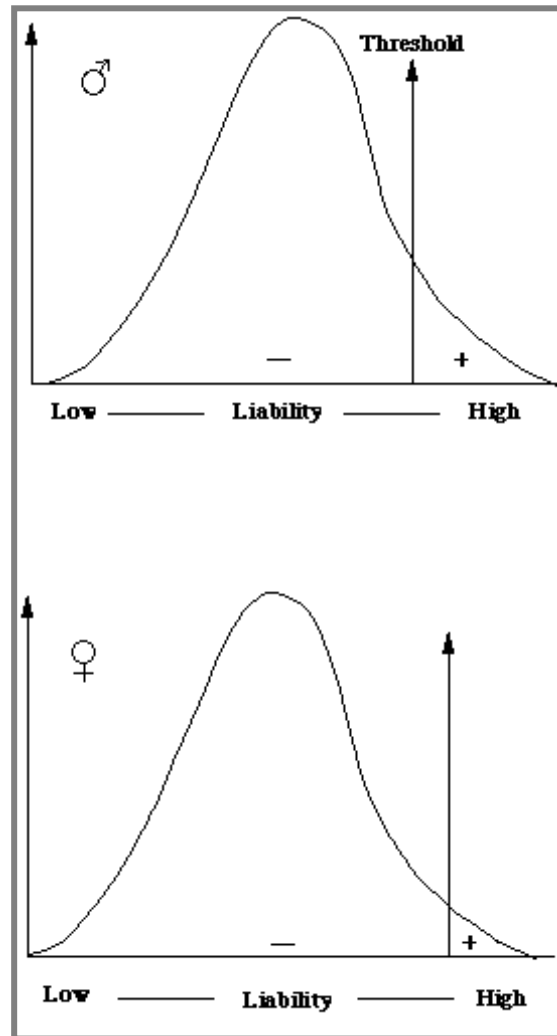
# Twin Studies



# Twin Studies

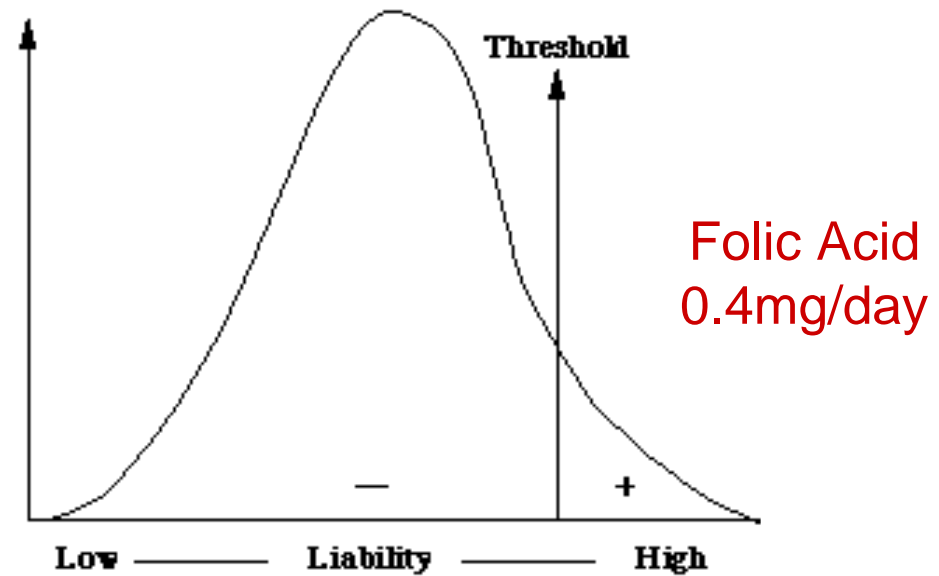


# Cleft Lip: Genetic Features



Birth Defects Lecture 2009  
David FitzPatrick

# Primary Prevention



# syndromal forms of clefts

van der Woude syndrome

IRF6 gene

Stickler Syndrome

COL2A1 gene

CO11A1 gene

CO11A2 gene

# Suspect a Syndrome if...

- birth defect associated with:
  - family history
  - craniofacial dysmorphisms
  - behavioral phenotype
  - growth disorder
  - learning disability

# computer-aided diagnosis

- >2000 disorders
  - eponyms
  - acronyms
- computerised catalogue
  - photo library
  - clinical abstracts
  - reference list

# genetic of common disease

(complex genetic disease)

- non-mendelian familial clustering
- gene-environment interaction common
- recurrence risks usually empirical
- rare mendelian forms usually exist
- simple interpretation of genetic tests not appropriate

# severe eye malformations

- eye development
  - outgrowth of forebrain
  - optic cup formation
  - optic fissure closure
  - retinal formation and growth
  - lens induction and growth

# SOX2 Anophthalmia Syndrome

- structural eye defects
  - severe, bilateral
    - anophthalmia
    - microphthalmia
    - sclerocornea
    - aphakia
    - coloboma
- growth failure
  - postnatal
- other malformations
  - male genital tract
  - pituitary hypoplasia
- learning disability
  - variable
- brain malformations
- seizures
- motor deficits
  - bradykinesia, dyspraxia, myopathy
- genetic features
  - null mutations
  - mostly *de novo* mutations
  - pseudo-recessive family
    - parental mosaicism (rr 5%)