Advances in Perinatal Genetics

Common and Not-So-Common Genetic Conditions

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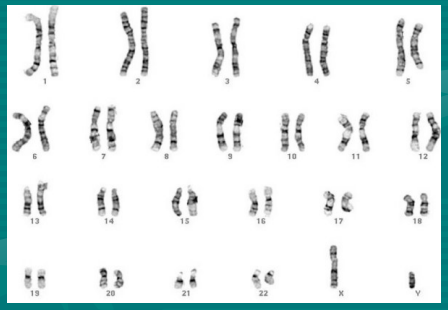
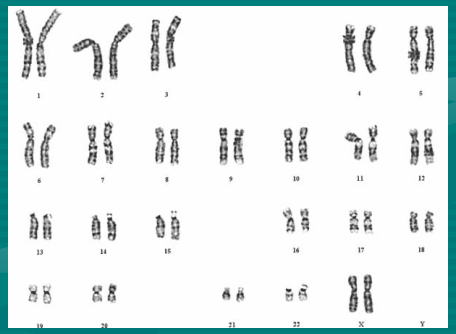
Top 5 reasons Genetics is Important:

- Everyone has 5 to 10 non-working genes
- Birth defects occur in 3-5% of all newborns
- About 30% of pediatric hospital admissions are due to genetic disorders
- About 50% of miscarriages have chromosome abnormalities
- Genetic conditions are treated by every pediatric subspecialty

Normal male chromosomes

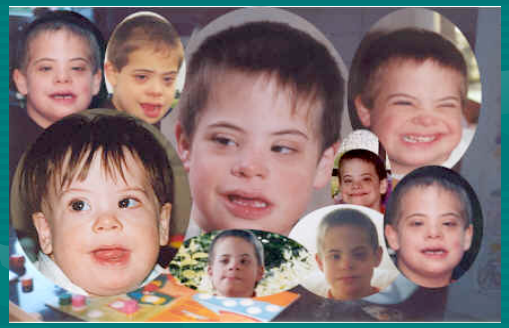


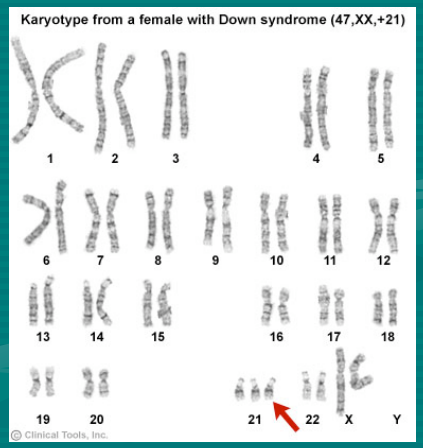
Normal female chromosomes



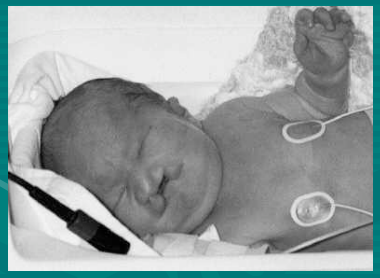
Single palmar crease

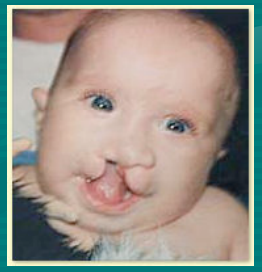
Down Syndrome



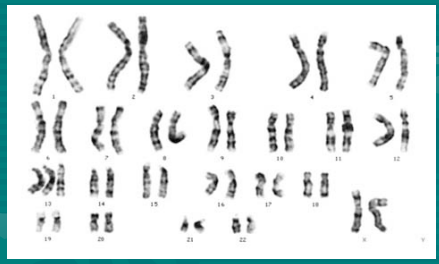


Trisomy 13

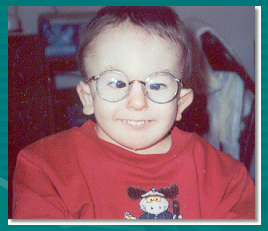




Trisomy 13

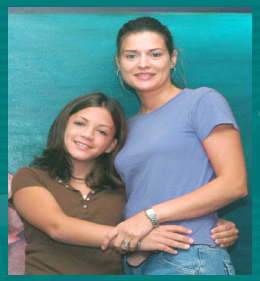


Trisomy 18

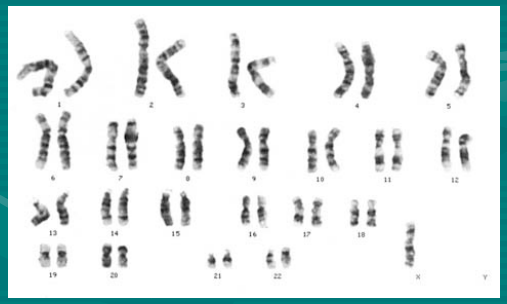


Trisomy 18

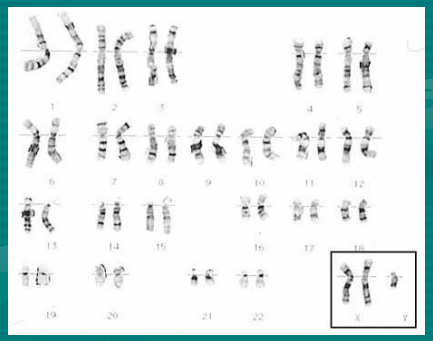
Turner Syndrome



45, X karyotype



47, XXY

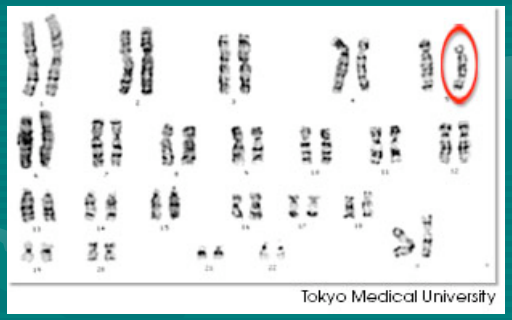


Klinefelter Syndrome

- Learning disabilities
- Usually normal intelligence
- Gynecomastia
- Low testosterone levels
- Decreased body hair
- Delayed puberty
- Infertility

Cri du chat syndrome

5p minus



Cornelia de Lange Syndrome

Cornelia de Lange Syndrome

De Lange Syndrome

- Usually sporadic, due to a particular genetic mutation in about half of cases
- Prenatal and postnatal growth retardation
- Limb abnormalities
- Often severe mental retardation
- Long, curly eyelashes
- Synophrys
- Hirsutism

It ain't all chromosomes….

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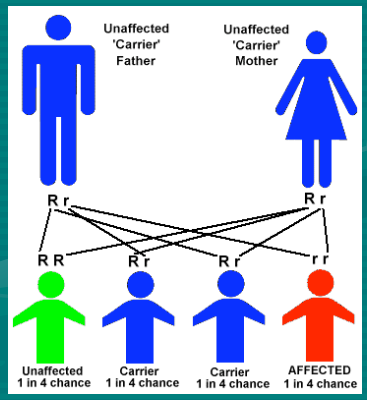
Modes of Inheritance

- Chromosomal
- Autosomal recessive
- Autosomal dominant
- X-linked
- Multifactorial
- Y-linked (rare)

Recessive inheritance

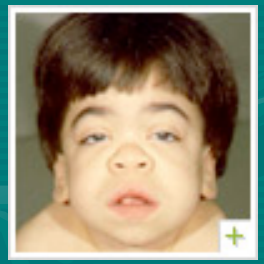


Recessive inheritance

- Both parents must be carriers to have an affected child
- Carrier parents have a 25% chance of having an affected child
- Males or females can be affected
- Usually the disease is fairly consistent within a family

Sanfilippo syndrome

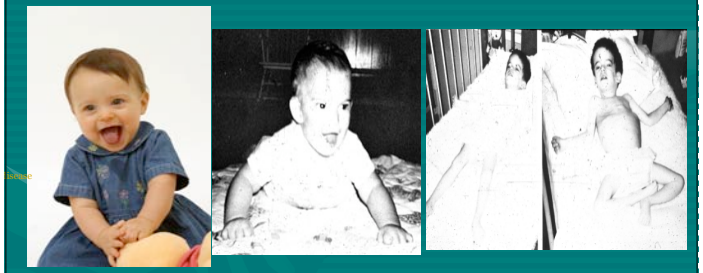
Mucopolysaccharidosis



MPS III

- MPS III or Sanfilippo syndrome is a rare recessive syndrome
- Caused by an enzyme deficiency that leads to the build-up of heparin sulfate
- Coarse facial features
- Regression of development
- Progressive and ultimately fatal

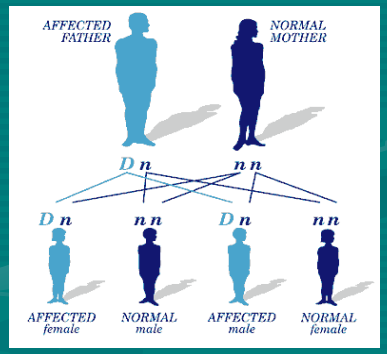
Tay Sachs disease



Other recessive conditions

- Cystic fibrosis (1 in 25 Caucasians are carriers)
- Sickle cell trait (1 in 10 to 1 in 20 African Americans are carriers)
- Thalassemia trait (more common in the Mediterranean and Asian communities)
- Most inborn errors of metabolism

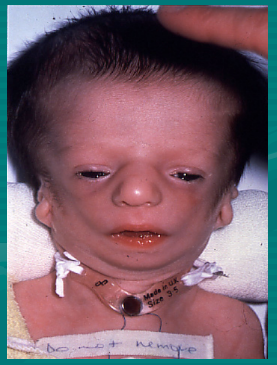
Autosomal Dominant Inheritance



Dominant inheritance

- Direct parent to child transmission
- 50% recurrence risk for each child
- Males or females may be affected
- Dominant traits are notoriously variable, even within a family

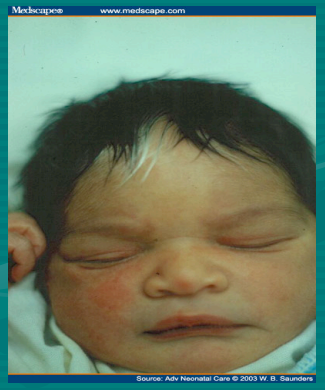
Treacher Collins



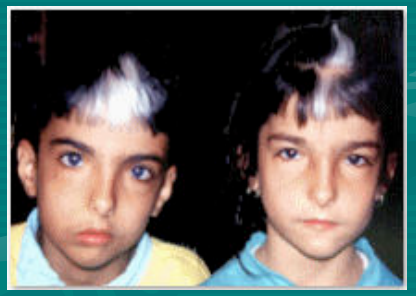
Treacher Collins

- Characterized by eyelid abnormalities
- Small chin (malar/mandibular hypoplasia)
- Cleft palate
- Ear anomalies
- Rumor has it that Sylvester Stallone has an affected son – check out Sly's eyes the next time you are watching "Rocky"!

Name that syndrome….



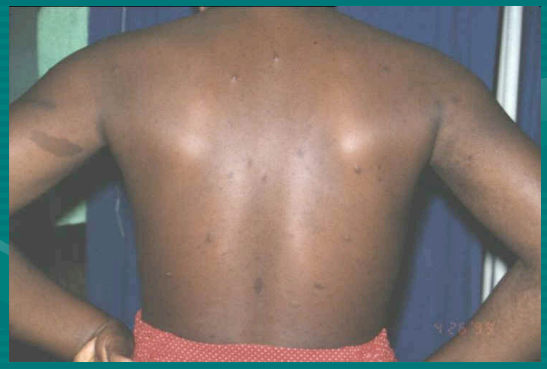
Waardenburg Syndrome



Waardenburg Syndrome

- Characterized by pigmentary differences, particularly the often striking white forelock
- Light blue eyes or one blue and one green eye
- Sensorineural deafness
- Narrow nose with slightly broader tip
- Hypertelorism

Name that syndrome, too….



Neurofibromatosis

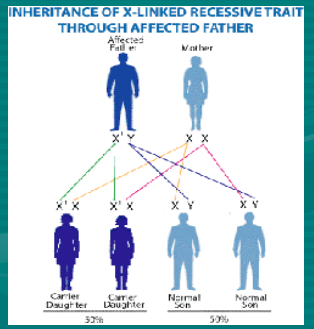
Neurofibromatosis

- One of the most common genetic disorders
- Multiple café-au-lait spots
- Axillary freckling
- Lisch nodules in the eyes
- Neurofibromas can grow anywhere, both externally and internally
- Highly variable

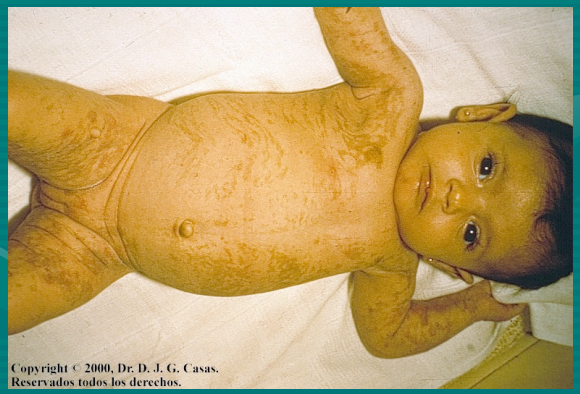
X-linked Inheritance

- Transmitted from carrier females to their sons
- Females can also be affected, but symptoms are usually milder
- Conditions range from fairly common to extremely rare: hemophilia to incontinentia pigmenti

X-linked inheritance



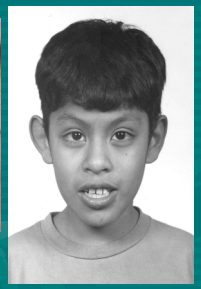
Incontinentia pigmenti



Incontinentia Pigmenti

- Usually identified in the newborn phase by punctate rash
- Rash evolves into unusual swirled pattern in skin
- X-inactivation in individual cells determines the pattern
- Apparently lethal in males; only females survive

Fragile X


Fragile X

- Caused by a mutation of a small region on the bottom of the X chromosome
- One of the first "multiple repeat" syndromes to be identified, the disorder is due to many repetitions of CGG base pairs within the DNA
- Normal individuals have about 30 CGG repeats
- Affected individuals can have hundreds of CGG repeats
- Carriers have more than 200 repeats

Fragile X

- Considered to be one of the most common causes of mental retardation in males; females may also have symptoms
- Characteristic facial features – long, narrow face, flattened cheekbones, prominent chin, prominent ears
- Autistic like behavior
- Language difficulty, particularly echolalia

Multifactorial Inheritance

- Where genes and environment collide OR
- Nature vs. Nurture

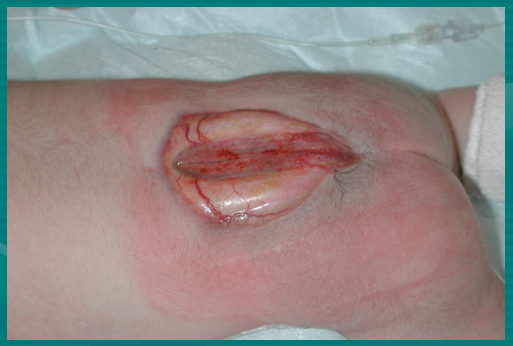
Multifactorial inheritance

- Genes and unknown environmental influences can interact to cause a specific birth defect
- Many hereditary conditions are thought to be multifactorial in nature as well

EXAMPLES

- Spina bifida and anencephaly
- Diabetes
- Heart disease

Spina bifida



Genetic Counseling

- Helps the family understand the diagnosis
- Explains the inheritance, prognosis and recurrence risk
- Aids the family in navigating the medical system
- Helps parents, grandparents and siblings cope with their emotions
- Advocates for families and children

Genetic Counselors and Others

- The genetic counselors is often the go-between for families and other health care providers
- We enlist the help of caregivers, doctors, nurses, social workers, insurance companies, psychologists and other counselors to help a family or a patient
- Sometimes we are the first person from genetics to see a newborn patient – we obtain information from the medical record, from the baby's nurse and from the family to provide to the geneticist

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Applying this to the patient

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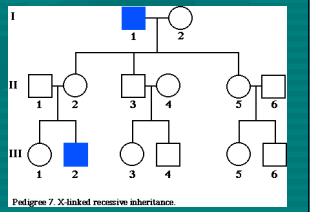
- DYSMORPHOLOGY IS THE BRANCH OF CLINICAL GENETICS in which clinicians and researchers study and attempt to interpret the patterns of human growth and structural defects.

Why search for a diagnosis ?

- Improved medical/educational management
- Psychological burden of disability
- Genetic Counseling

How does one approach a diagnosis in dysmorphology?

- Family history-3 generations
- Pregnancy history
- Exposures history
- Delivery history
- Developmental history
- Medical records

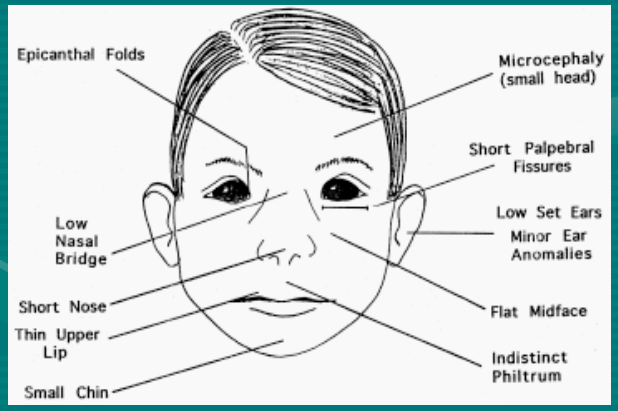


Pedigree 7. X-linked recessive inheritance.

Table 1: A list of some minor anomalies that are used in syndrome delineation

Craniofacial	Other body areas	Skin
• Sagittal fontannelle	• Bifid xiphoid	• Hypopigmented patches
• Upslanting palpebrae	• Unusual umbilical position	• Aplasia cutis congenita
• Short palpebrae	• 5th finger clinodactyly	• Various nevi
• Anteverted nares	• Excess nuchal skin	• Hairy patch on lower spine
• Natal teeth	• Supernumerary nipple	• Sebaceous nevus
• Malar underdevelopment	• Deep sacral dimple	• Mild skin syndactyly
• Bifid uvula	• Prominent heels	• Café au lait spots
• Posteriorly rotated ears	• Pectus excavatum	• Pigment streaking
• Open metopic suture	• Umbilical hernia	
• Brushfield spots	• Single palmar crease	
• Ocular heterochromia	• Single umbilical artery	
• Flat philtrum	• Shawl scrotum	
• Hypoplasia anguli oris		
• Single central inscisor		
• Micrognathia		
• Preauricular pits or tags		
• Multiple hair whorls		
• Epicanthic folds		
• Wide/close-spaced eyes		
• Low nasal bridge		
• Hypodontia		
• Missing lip frenulum		
• Ear helix anomalies		

- Search for hidden anomalies
  - imaging studies such as renal ultrasound
- Multi-system (gestalt) approach
  - review of growth parameters
  - past medical history

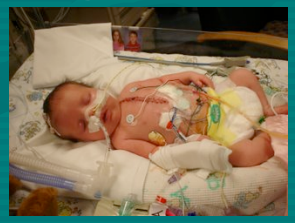


The Face and the Heart

- The heart forms during the third week of embryonic life when the nutritional requirements of the embryo can no longer be supplied by diffusion.
- Positioning and structure of the heart depends on the brain growth with cephalic folding of the embryo.

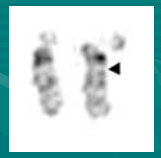
Velo-Cardio-Facial Syndrome

- Deletion of 22q11 (85%)
- Learning disabilities (40%)
- Psychiatric disorders (10%)
- Cleft palate (50%)
- Cardiac defects (85%)

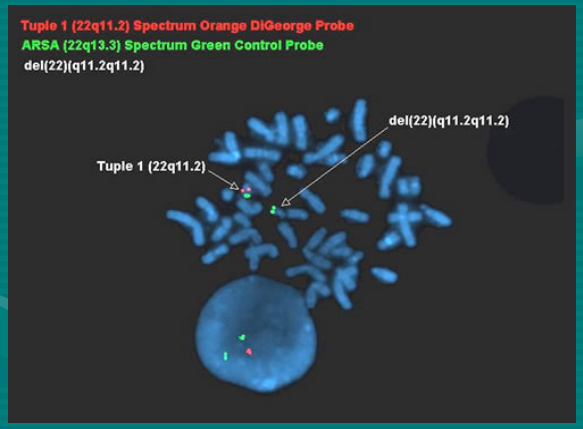


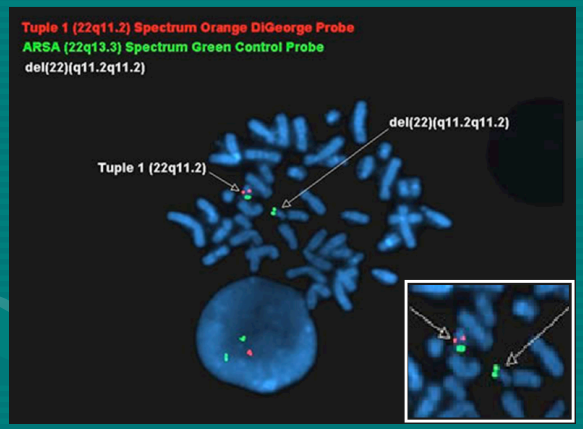
Velo-Cardio-Facial Syndrome

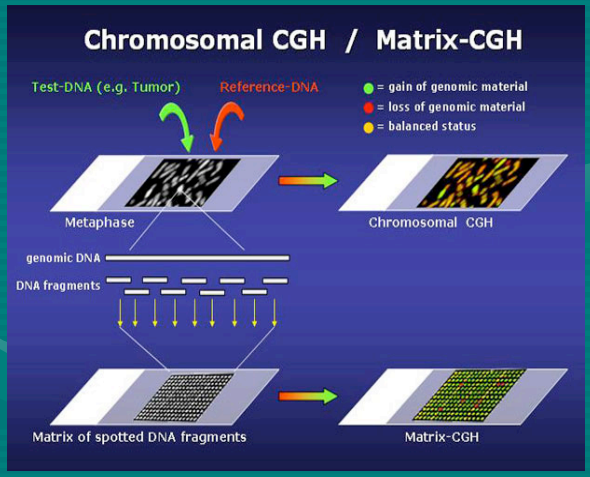
- Incidence 1 in 4000
- 8% of children with cleft palate
- 25% of children with Tetralogy of Fallot

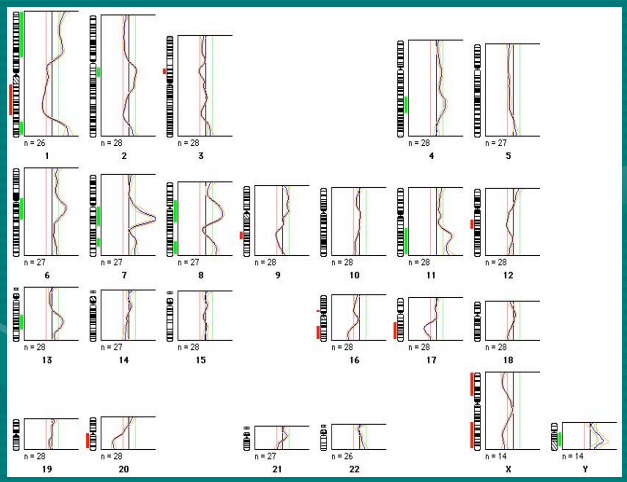


FISHin' for clues









Molecular Genetic syndromes

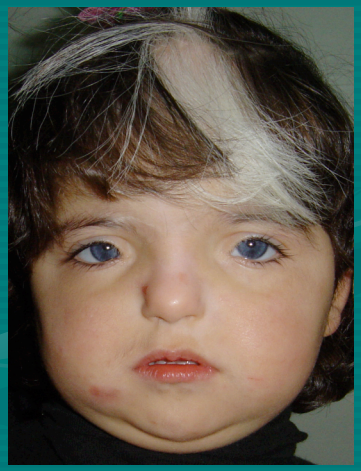
- Developmental genes
- Multi-system involvement

Current patient

- 31 week infant in NICU with decreased bowel motility
- Further evaluation showed Hirschsprung disease and malrotation

Review of the family history

- Multiple miscarriages in maternal grandmother and mother
- Deafness in maternal aunt with chronic constipation
- Two maternal cousins with IBS, chronic constipation and 'long colon'
- Maternal great uncle with white forelock
- Sibling with a de-pigmented hair since birth



Waardenburg syndrome

- Originally described by Petrus Johannes Waardenburg in 1951
- Main features cited:
  - White forelock
  - Broad nasal root
  - Lateral displacement of medial canthi
  - Hypertrichosis of medial part of eyebrows
  - Heterochromia irides
  - Deaf mutism

Waardenburg-Shah syndrome

- In 1981, Krishnakumar Shah described Waardenburg variant with long segment Hirschsprung's disease
- Waardenburg-Shah syndrome has greater than 50 published cases
- Two modes of inheritance identified:
  - Autosomal recessive inheritance with mutations in the endothelin-B receptor (EDNRB) or endothelin-3 (EDN3) genes
  - Autosomal dominant with mutations in the SOX10 gene

- During embryonic development, neural cells originate in a strip along the back (called the neural crest) and migrate from there to the rest of the body
- Pigment cells are a subset of these neural crest cells. Additional neural cells that do this migration include ones that innervate the colon and neural cells that go into the inner ear

Bowel Involvement Is Characteristic

- There is absence of the myenteric (Auerbach) plexus and the submucous (Meissner) plexus with hyperganglionosis and ectopic ganglia in the lamina propria of the long segment.
  - This leads to chronic constipation, intestinal obstruction, and failure to thrive, which usually begins during the time of weaning.

A precise genetic diagnosis:

- makes available all the accumulated knowledge and experience of that condition
- provides a better estimate of the risk of recurrence
- informs prognosis
- permits interventions that may prevent, anticipate or more successfully treat complications
- facilitates getting support, such as financial and educational aid
- allows families to interact with specific support groups
- is key to research into the identification of causative genes, interventions and treatments.