How to be a clinical geneticist

March of Dimes 2013

Ana Bircher, MD
ABMG Certified Clinical Geneticist

Medical Genetics

• Genetics is playing an increasingly important role in the practice of medicine.

• In the past it was confined to very rare conditions seen by few specialists

• It is now the main component of understanding most major medical conditions like heart disease, diabetes, cancers, psychiatric disorders

Clinical Genetics

• Clinical genetics is a very complex medical field

• It is the most difficult and challenging specialty of all medical specialties

• In 2010 there were 850,085 physicians in US holding an active medical license

• There are 1419 Board Certified Clinical Geneticists in USA (ABMG website)

• Why is this ? Because it is almost impossible to be a good geneticist, you need to be brilliant, smarter than the smartest...

• We use words that are difficult to pronounce like Beckwith-Wiedemann,  spondyloepiphyseal dysplasia...
It is easy!!

What do you need?
1. A good pair of eyes
2. A good pair of ears
3. A computer with internet access
4. TIME!

Few concepts

• Hundreds of thousands of babies are born everyday
• Every baby is unique
• Every baby comes with a blueprint for life

This blueprint is called DNA
- The DNA is a chemical compound with double helix structure
- It resembles a right handed spiral staircase
- The two sides of the ladder are composed by a sugar and a phosphate
- Projecting from each side there are the steps
- They are composed by four bases
  - Adenine
  - Guanine
  - Thymine
  - Cytosine

- Adenine always pairs with Thymine
- Cytosine always pairs with Guanine
- These are called BASE PAIRS

The DNA of every two people is 99.9% identical.
Only one tenth of one percent is different.
And this is what makes us unique.
**DNA functions**

The DNA carries chemical information that allows the exact transmission of genetic information from a cell to a daughter cell.

And from one generation to the next.

**DNA structure**

- The base pairs contained in one loop is what is called GENE.
- GENES are units of genetic information.
- They instruct the cell how to perform specific functions or create cell structures.
- Half of our chromosomes and genes come from a maternal egg – half from the sperm.
- All these 46 chromosomes contain all the information needed to create a whole baby.
- As the cells divide, the DNA is copied over and over into each new cell.
In each cell the DNA is packed as chromatin. Chromatin is a relatively homogeneous nuclear structure under the microscope. Just before the cells undergo division, the chromatin condenses to form cone-shaped structures called chromosomes. Chromosomes represent the most compact form of DNA.

**Chromosome structure**

- The smallest chromosome (#21) has 50 million base pairs.
- The longest chromosome (number#1) has 250 million base pairs.
- If we could stretch the DNA in a single cell it would measure 2 meters.

**Chromosome structure**

- 3,000,000,000 The whole genome contains around 3 billion base pairs.
- A person can have thousands (even millions) of base pairs deleted or duplicated and be normal.
- Change in ONE base pair could lead to a lethal condition.
Chromosome structure

- A normal patient with a large deletion/duplication may have multiple pregnancy losses and/or children with multiple malformations and severe mental retardation caused by the SAME chromosome abnormality.

Errors in embryogenesis

- The creation of a baby is a very complex and amazing mechanism.
- There are so many things that can go wrong:
  - Some cells can die or be killed.
  - There can be errors in the copying process.

And yet the embryo can recover.

Which branch of medicine studies this?

Genetics

Specialty that deals with the diagnosis, management, and treatment of hereditary disorders.
It is focused on the patient and the entire family.
Clinical genetics

- Prenatal
- Adult
- Pediatrics

Family History

- 32 week preemie
- Hypotonia - breathing difficulties
- Joint contractures
- Normal NBS
- Normal chromosomes
- Normal methylation PWS

Family History

- Hundreds of conditions
- Neuro-muscular disorders (SMA, myastenia gravis, myastenic syndromes, neurotransmitter disorders…)
- Muscle problems (congenital muscular dystrophies, dystrophinopathies – Duchenne…)
- Inborn errors of metabolism (CDG, lysosomal disorders – Gaucher syndrome…)
- Single gene disorders (arthrogryposis syndromes, DNA abnormal repair syndromes – Cockayne syndrome, Bloom syndrome, COFS syndrome…)
Family History

- First child of the couple
- Mother had multiple medical consults in the past due to arm numbness, sharp pain and weakness.
- May drop things when trying to grab them
- EMG “all normal”
- Physical exam: trouble with grip hand release
- MYOTONIA

Myotonic dystrophy

- Muscle weakness
- Myotonia (sustained muscle contraction)
- Continuum of manifestations from Mild (adult) – Classic – Congenital
- Triple repeat expansion
- Anticipation occurs with maternal transmission

Congenital anomalies

- Occur in approximately 1 in 200 live born infants
- 2-3 of neonates have a congenital disease
- Account for 20-25% of deaths in neonatal intensive care units
Medical genetics

• Chromosome disorders
  – Microscopic
  – Sub-microscopic
• Single gene disorders
• Multi-factorial disorders
  • Genetic component associated with environmental factors
• Teratogens

Multi-factorial disorder

• More than 50% of human developmental abnormalities are caused by a combination of genetic and environmental factors

Thrombocytopenia-absent radius syndrome

• Absence of radii with presence or both thumbs
• Thrombocytopenia congenital or develop within first few weeks
• Other skeletal anomalies
• Deletion of 200kb region on chromosome 1q21.1
• Multiple genes
Chromosome vs. single gene

- Chromosome disorders
  - Microscopic
  - Sub-microscopic
- Single gene disorders

Chromosome abnormalities

Chromosome study

- Limitations

It detects chromosome abnormalities of approx. 5-10 Mb

5,000,000 bases
Limitations of chromosome analysis

- Karyotype only depicts deletions or duplications of 5 to 10Mb
- Five to ten million of base pairs
- It depends on how stretched the chromosomes are
- 450-900 bands
- Karyotype does not depict smaller chromosome abnormalities
- Karyotype does not depict single gene mutations

Diagnosis of chromosome abnormalities

Courtesy Genetics Associates INC
Chromosome disorders

- Down syndrome
- Duplications
- Deletions
- Sex chromosome
- Rings
- Other aneuploidies
- Smaller chromosome abnormalities
FISH

FISH can detect deletions/duplications of 30-40 Kb
30,000 bases

DNA arrays

Copy number changes down to 1Kb
1,000 bases

Single gene disorders

- Other genetic conditions are caused by a mutation or “misspelling” in only one gene
- This “typo” can cause the gene not to function well or even not to work at all
- Misspell in ONE letter of the 3,000,000,000 letters of our genome can cause a severe genetic condition and even death
- We have about 30,000 genes
- Some other mutations do not cause any disease
Single gene disorders

- You need to “read” the recipe
  - Sequence the gene
- You need to have an idea of which gene to sequence
- Few laboratories in USA do specific sequencing

- Testing is NOT available for all known conditions
  - Some conditions are diagnosed by strict clinical criteria (tuberous sclerosis, NF, Beckwith-Wiedemann…)
  - Some conditions don’t even have criteria set yet

Single-gene disorders

Look at the baby
- Does he/she have major malformations?
- Does he/she have minor malformations or unusual features

Carefully read the medical records
- Listen to what specialists say
- Test results?

Grab the computer and type the following:
Google.com
OMIM
Online Mendelian Inheritance in Man

OMIM only contains single-gene syndromes and small chromosome abnormalities. It does not contain chromosome disorders.

Case#1

Term baby
-Tetralogy of Fallot
-Hypotonia
-Feeding difficulties
-Hypocalcemia
Di-George syndrome

- Congenital heart disease 75%
- Abnormalities in the palate 70%
- Immune deficiency 77%
- Hypocalcemia 50%
- Characteristic facies
- Learning difficulties
- Hearing loss, short stature, feeding problems, renal abnormalities, autoimmune disorders, seizures
- Micro-deletion syndrome

Case#2
Case#2

Chromosome: Normal 46,XY male
Campomelic dysplasia

Case#3

8 months-old infant
Macrocephaly
History of polydactyly
MRI: Hemi-megalencephaly
Brain dysgenesis
Normal chromosomes
### MEGALENCEPHALY-CAPILLARY MALFORMATION POLYMICROGYRIA SYNDROME (MCP)

#### Clinical Features

- Hypotonia
- Seizures
- Developmental delay
- Brain asymmetry

### Clinical Course

A newborn boy (2) was found to be a slow walker, and at the age of 6 months, he was noted to have hypotonia and severe seizures. At the age of 1 year, he was noted to have developmental delay.
Case#3

- Chromosome analysis
- Lactic acid, ammonia, plasma amino acids, acylcarnitines, urine organic acids
- VLCFA (Zellweger syndrome?)
- Considering sequencing of GLI3 gene (Pallister-Hall syndrome) brain MRI?

- Chromosomes: 47,XY + 21

Down syndrome
Case#4

- 1-day old neonate
- Dysmorphic features
- Abnormal skull shape
- Breathing difficulties
- X-Ray: elbow ankylosis
- Normal chromosomes
Case #5

3 weeks-old neonate
Severe Microcephaly
Severe growth restriction
Cerebellar hypoplasia
Optic nerve hypoplasia
Severe hearing loss
Nom 5 years old
Marked developmental delay
"Primordial dwarfism"

• Chromosome analysis
• Metabolic testing
• 7-dehydrocholesterol (SLO)
• Transferrin electrophoresis (CDG)
• Gene sequencing (no-charge) for CDG
• DNA oligosarray
• Chromosome breakage analysis (Fanconi anemia)
• Asked help from Ophthalmologists, ENT, radiologists…
• Asked for second-opinion with other Geneticists
• Called metabolic geneticists, cytogeneticists, molecular geneticists
• Talked about her with geneticists in an ACMG meeting
• Research protocol in London for types of primordial dwarfism
• Multiple gene sequencing
• Whole exome sequencing
• Whole DNA sequencing

Don't feel frustrated if we can't identify the problem

Case #6

3 weeks-old neonate
Severe Microcephaly
Severe growth restriction
Cerebellar hypoplasia
Optic nerve hypoplasia
Severe hearing loss
Nom 5 years old
Marked developmental delay
"Primordial dwarfism"

• Chromosome analysis
• Metabolic testing
• 7-dehydrocholesterol (SLO)
• Transferrin electrophoresis (CDG)
• Gene sequencing (no-charge) for CDG
• DNA oligosarray
• Chromosome breakage analysis (Fanconi anemia)
• Asked help from Ophthalmologists, ENT, radiologists…
• Asked for second-opinion with other Geneticists
• Called metabolic geneticists, cytogeneticists, molecular geneticists
• Talked about her with geneticists in an ACMG meeting
• Research protocol in London for types of primordial dwarfism
• Multiple gene sequencing
• Whole exome sequencing
• Whole DNA sequencing

Don't feel frustrated if we can't identify the problem