Recognition of Genetic Conditions Encountered in Primary Care with Indications for Referral

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Objectives

• Review basic genetic principles
• Recognize clinical and historical findings encountered in primary care which may indicate a genetics based condition
• Accurately document history clinical findings consistent with a genetics based condition to make the genetics referral

Great Resources for Genetics

- Genetics Home Reference
- Gene Reviews
- Medical Genetics in Pediatric Practice
- Online Mendelian Inheritance in Man
- Unique Publications

Conflict of Interest Statement

The author has no conflict of interest nor financial interest regarding any content within this presentation.

This presentation is dedicated to
R. Stephen Amato, MD, PhD & Apostoles Psychogios, MD
...physicians, scientists, geneticists, professors, colleagues, veterans...
In appreciation for your support, confidence and teaching.
I am what I am because of you both!!

Genetics Home Reference
Genotype

• “...the genes in an organism”

• The dominant gene is expressed by a capital letter

• The recessive gene is expressed by a small letter


Phenotype

The observable characteristics of an organism.....

.....“what you see”

Karyotype

• “Organized profile of chromosomes”

• Normal Human Karyotype

46, XX or 46, XY

• 46, XY and 46, XX = “Euploid”

http://fig.cox.miami.edu/~cmallery/150/mendel/karyotype.htm

Chromosome – DNA – Gene - Base Pairs

Mode of Inheritance

• Autosomal Dominant

• Autosomal Recessive

• X-Linked Recessive

• X Linked Dominant

• Mitochondrial

• Multifactorial
Mode of Inheritance - Autosomal Dominant

Autosomal Dominant Conditions
- Marfan Syndrome
- Hypertrophic Cardiomyopathy

Mode of Inheritance – Autosomal Recessive

Autosomal Recessive Conditions
- PKU
- Sickle Cell
- Wilson Disease
- Galactosemia
- Familial Mediterranean Fever
- Hemochromotosis

Mode of Inheritance - X Linked Recessive

X Linked Recessive Disorders
- Hemophilia A
- Red green color blindness
- Duchenne Muscular Dystrophy
Mitochondrial Inheritance
- Mitochondrial DNA is circular
- Mitochondrial DNA contains 37 genes
- Mitochondria are exclusively maternally inherited
- Mitochondria are energy-producing; “power house” of the cell

Categories of Genetic Based Disorders
- Single Gene Disorders
- Aneuploid Conditions
- Deletion/Duplication Syndromes
- Mitochondrial Disorders
- Multifactorial Conditions

Single Gene Disorders
- A mutation affects one gene to cause the disorder
- Thousands of single gene disorders exist.....
- Examples
  - FBN1 - Marfan Syndrome
  - DOK 7 – Congenital Myasthenic Syndrome
  - FGFR3 – Achondroplasia
  - CFTR – Cystic Fibrosis
  - NF1 – Neurofibromatosis 1
  - TSC1 – Tuberous Sclerosis

Aneuploid Conditions
- Remember in humans – Normal karyotype is 46, XY or 46, XX - and therefore euploid
- So aneuploid conditions do not have 46 chromosomes.....
- Such as......
  - 45X – Turner Syndrome
  - Trisomy 21, Trisomy 13, Trisomy 18 – Trisomy conditions
  - 47, XXY – Klinefelter Syndrome
  - 47, XXX
  - 48, XXXX
  - Others

Aneuploid Conditions
-
Aneuploid Conditions

Turner Syndrome

Klinefelter Syndrome

https://pedclerk.bsd.uchicago.edu/page/turner-syndrome

https://andrologyaustralia.org/your-health/klinefelters-syndrome/

Deletion Syndromes

• Loss of a segment of DNA from a chromosome – generally involves numerous genes

  – DiGeorge Syndrome - 22q11.2 deletion
  – Cri-du-chat Syndrome – 5p deletion
  – Williams Syndrome – 7q11.23 deletion

Refer to Genetics

• Disorders of Development
  – Global Developmental Delay - Significant delay in ≥ 2 areas
    • Gross or fine motor
    • Speech and language
    • Cognition
    • Social/personal
    • ASD
  – Autism Spectrum Disorders
  – Short stature (significant, especially with dev delay or with unusual phenotypical findings)
  – Somatic overgrowth (Hemihyper trophy, etc)
  – Excessive growth velocity

• Structural or Morphological Variations
  – Major Anomaly

• Minor Anomaly
  – Numerous – see following slides (Moeschler, 2013)

Disorders of Development - Definitions

• Global Developmental Delay - Significant delay in ≥ 2 areas (Children ≤ 5 yo)
  • Gross or fine motor
  • Speech and language
  • Cognition
  • Social/personal
  • ASD

• Intellectual Disability – Applies to older children when IQ testing is utilized with reliable and valid results.
  (Moeschler, 2013)

Autism Spectrum Disorder (ASD)

• AAP recommends screening all children at 18 – 24 months of age.
  – MCHAT - R (Modified Checklist for Autism in Toddlers - Revised)
  – Screen between at 16 and 30 months
  – Released December 2013, improved specificity
  – Remember MCHAT follow-up questions

• ASD –
  – Social impairment
  – Communication difficulties
  – Loss of social-emotional reciprocity
  – Repetitive and stereotyped behaviors

ASD – Diagnostic Criteria

DSM-5 Diagnostic Descriptors: ASD

Most meet the following criteria:

- Persistent deficit in social communication/social interaction across multiple contexts
- Difficulties in nonverbal communication, deficits in initiating, maintaining, and understanding relationships, deficits in social-emotional reciprocity
- Restricted, repetitive patterns of behavior, interests, activities manifested by at least two specific examples
- Be, stereotyped/repetitive movements, speech, rituals or circuits, restrictive interests
- HYPO- or hyperactivity to ensure input
- Symptoms must be present in early developmental period
- Symptoms impair and impact everyday functioning
- Symptoms are not explained by intellectual disability

Severity is based upon:
- Social communication impairments and restrictions, repetitive patterns of behavior
Minor vs Major Anomaly

- **Minor Anomaly**
  - ...structural finding in <5% of population, but no significant cosmetic/functional significance.
  - Mostly seen in head/face,
  - hands/feet
  - Not always obvious!!!
  - Examples
    - Single palmar crease
    - Low set ears
    - Sandal gap toes
    - Pes planus

- **Major Anomaly**
  - ...structural finding in <5% of population, with significant cosmetic/functional impairment.
  - Always obvious!!!
  - Examples
    - Omphalocele
    - Cleft lip
    - Cleft palate
    - Spina bifida

(Adapted from Whelan, et al. 2004)

Genetic Red Flags

**“F-GENES”**

- **F** – Family history ...
  - Multiple affected family members in multiple generations
- **G** – Groups of congenital anomalies...
  - ≥ 2 anomalies
- **E** - Extreme exceptional presentation ....
  - Early onset of disease, severe reaction to metabolic stress/illness
- **N** – Neurodevelopmental delay or regression
- **E** – Extreme or exceptional pathology...
  - Rare or multiple primary tumors
- **S** – Surprising lab values ....
  - Extreme values or abnormal in supposedly healthy individuals

(Adapted from Whelan, et al. 2004)

Unusual Phenotypical Findings

**Minor Anomalies**

Clinical Examples

- Smooth Philtrum

- Protruding Tongue/Macroglossia

- High Arched Palate
Eye Placement

Hypertelorism

Hypotelorism

Brushfield Spots

Ptosis

Palpebral Fissures

Upslanted vs Downslanted

Upslanted Palpebral Fissures

Prominent Epicanthal Folds
Overfolded Ears

Low Set Ears

Pre-Auricular Pit/Tag

Hand Findings

Camptodactyly

Clinodactyly
Tapered Fingers

Syndactyly

Polydactyly

Long Fingers/Arachnodactyly

Fetal Digital Pads

Sandal Gap Toes
Syndactyly

Webbed Neck

Sacral Dimple

Café-Au-Lait Spots

Chest Findings

Pectus Excavatum

Pectus Carinatum

Aplasia Cutis Congenita
Minor Anomalies

• One or two minor anomalies may not be associated with major anomalies.
• Single minor anomalies – certain ones are a “red flag” for a specific occult major anomaly.
• Be aware of patterns of minor anomalies – multiple malformation syndromes.
• Three or more minor anomalies – may be a nonspecific indication of major anomaly.

[Hoyme, 2013]

Specific Minor Anomaly as Marker of Occult Major Anomaly

• Pre-auricular pit or tag - Middle ear malformation, congenital hearing loss
• Café-au-lait spots – Neurofibromatosis, Legius Syndrome
• Hypopigmented patches – Tuberous sclerosis
• Hairy patch to sacrum – Tethered spinal cord
• Neck webbing – Turner syndrome, Noonan Syndrome

Patterns of Minor Anomalies Associated with Certain Conditions

• Trisomy 21
• Fetal Alcohol Syndrome
• Neurofibromatosis
• Williams Syndrome
• Marfan Syndrome
• Turner Syndrome

Lisch Nodules

https://www.google.com/search?q=Axillary+freckling&source=lnms&tbm=isch&sa=X&ved=0ahUKEwjqvu3X2NvZAhVDzlMKHd0bD4UQ_AUICigB&biw=1366&bih=662#imgrc=5F9OBMXpn3XxxM:
Case Study

• 2 yo male presents with concern for large right foot. Ht 75%, wt – 80%, HC 70 %. Pedigree includes no significant family history. Recently referred to orthopedics for enlarged right foot, x-ray and ortho evaluation “normal”.
• Exam reveals 3 cm healed, irregular shaped surgical scar to umbilical area. Right foot circumference at mid metatarsals 15 cm, left foot 12 cm.

What do you think?

Hypermobility

Summary

• Assessing growth and development during childhood is essential in primary care!
• Address developmental delays and signs of ASD; **always** screen as recommended!
• Assess family history/pedigree for patterns of conditions.
• Recognize minor and major anomalies
• Think genetically, be aware of genetic red flags!!
• Refer for genetic evaluation when indicated!!
Making the Genetics Referral

- Locate genetics services in the geographical area
- Cancer/hematology cases generally go to hematology/oncology service
- Cystic fibrosis generally goes to pulmonology service
- Clearly document reasons for referral – phenotypical findings, family history, use appropriate terminology
- Send all labs/diagnostic studies previously performed
- Follow the recommendations of the genetics provider

References

Whelan AJ; Ball S; Best L; Best RG; Ehnierrt SC; Ganschow P; Hopkin RJ; Mayesky J; Stallworth J. (2004). Genetic red flags: Clues to thinking genetically in medical practice. Primary Care Clinical Office Practice, 2004 Sep; 31(3): 497-508.