Connecting the Dots: Clues to Common Genetic Diagnoses

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Objectives

• Recognize key features and red flags suggesting specific genetic conditions
• Ask specific follow-up questions based upon clinical indications
• Understand the collaborative effort needed to make a diagnosis
• Identify appropriate patients for genetics referrals

Case 1

• 10-year-old boy
• Referral reason – autism
• Review of medical history:
  • Normal motor milestones; mild speech delays
  • Otherwise healthy
• Physical examination – isolated macrocrania
Case 1 (continued)

- Referral to Genetics – differential diagnosis
- Fragile X syndrome
- Chromosomal abnormality
- Relevant family history
- Mother with thyroid cancer
- Maternal relatives with breast and renal cancers
- Genetics plan
- PTEN sequencing and deletion/duplication
- Genetic counseling

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PTEN Hamartomatous Tumor Syndrome (PHTS)

- Autosomal dominant inheritance
- Diagnostic spectrum including patients with Cowden Syndrome, Bannayan-Riley-Ruvalcaba Syndrome, PTEN-related Proteus Syndrome or Proteus-like Syndrome and an identifiable PTEN mutation
- Mucocutaneous lesions
- Increased risk of cancer
- Breast cancer
- Endometrial/uterine cancer
- Renal cancer
- Colorectal cancer

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PTEN Hamartomatous Tumor Syndrome (PHTS)

Surveillance:

- Annual thyroid screen and dermatologic examination
- Annual gynecological evaluation and breast screening
- Colonoscopy beginning at age 35 years
- Biennial renal imaging

At-risk family members:

- Refer for genetic counseling and testing
- Screening beginning at age 8-10 years
Case 1: Summary

Red flags for this diagnosis include:

- Autism
- Macrocrania
- Family history of breast, renal, or thyroid cancer

Case 2

15-year-old boy
Referral reason – renal angiomyolipomas incidentally detected on renal ultrasound exam
Review of medical history:
- Single hospitalization for abdominal pain
- Otherwise healthy
Physical examination – raised skin lesion on lower back (Shagreen patch)

Case 2 (continued)

Referral to Genetics
Suspect tuberous sclerosis complex
Genetics plan
- TSC1 and TSC2 sequencing and deletion/duplication analysis
- Genetic counseling
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**Tuberous Sclerosis Complex (TSC)**

- Autosomal dominant inheritance, variable expressivity
- Major Features:
  - Hypomelanotic macules (≥ 3, at least 5 mm diameter)
  - Angiofibromas (≥ 3) or fibrous cephalic plaque
  - Ungual fibromas (≥ 2)
  - Shagreen patch
  - Multiple retinal hamartomas
  - Cortical dysplasias
  - Subependymal nodules
  - Subependymal giant cell astrocytoma
  - Cardiac rhabdomyoma
  - Lymphangiomatosis
  - Angiomyolipoma
- Minor Features:
  - "Confetti" skin lesions
  - Dental enamel pits (≥ 3)
  - Intraoral fibromas (≥ 2)
  - Retinal achromic patch
  - Multiple renal cysts
  - Nonrenal hamartomas

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**Tuberous Sclerosis Complex (TSC)**

- Surveillance:
  - Cranial CT/MRI every 1-3 years
  - Renal imaging
  - Ophthalmology evaluation
  - Cardiac and pulmonology evaluations
  - Neurodevelopmental and behavioral evaluation
- At-risk family members:
  - Refer for genetic counseling (~ 65-70% of cases are de novo)
  - Genetic testing, as indicated

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**Case 2: Summary**

- Red flags for this diagnosis include:
  - Characteristic skin findings
  - Shagreen patch
  - Facial angiofibromas
  - Hypomelanotic macules
  - Ungual fibromas
  - Characteristic findings on imaging
    - Angiomyolipoma
    - Rhabdomyoma
    - Cortical tubers
  - Seizures, ID, DD
**Case 3**

- 12-year-old girl
- Referral reason: red raised skin lesions on upper back
- Review of medical history:
  - Recurrent otitis media
  - Otherwise healthy
  - Biopsy by dermatologist is consistent with a leiomyoma

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**Case 3 (continued)**

- Referral to Genetics
  - Suspect hereditary leiomyoma and renal cell carcinoma
- Family history:
  - Sibling with similar lesions
  - Mother had hysterectomy at age 35 due to fibroids
- Genetics plan:
  - FH sequencing and deletion/duplication testing
  - Genetic counseling

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**Hereditary Leiomyoma and Renal Cell Carcinoma (HLRCC)**

- Autosomal dominant inheritance
- Cutaneous leiomyomas (76%)
  - Diagnosed between 10-47 years (average 25)
  - Located on trunk, extremities, and, occasionally, the neck or face
  - Can be painful
- Uterine fibroids:
  - Present in nearly all females
  - Occur at younger age than general population (<30 vs. 45)
- Renal cell carcinoma (aggressive)
  - ~15% lifetime risk of RCC
  - Diagnosed between 11-90 years (average 41)
Hereditary Leiomyoma and Renal Cell Carcinoma (HLRCC)

**Surveillance:**
- Dermatologic evaluation every 2 years
- Annual gynecologic evaluation
- Annual abdominal MRI or CT

**At-risk family members:**
- Refer for genetic counseling and testing
- Screening beginning at age 8-10 years

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**Case 3: Summary**

Red flags for this diagnosis include:
- Biopsy results consistent with leiomyoma
  - Cutaneous
  - Uterine
- Family history of
  - Uterine fibroids
  - Similar skin lesions
  - Renal cell carcinoma

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**Case 4**

- 5-year-old girl referred to neurologist
- Referral Reason
  - Three episodes of dizziness and vomiting
- Review of medical history
  - Congenital bilateral sensorineural hearing loss
- Next steps
  - Brain MRI
    - Initially showed only minimal white matter abnormalities
    - Neurologist concerned about seizures
      - Follow up brain MRI several years later disclosed enlarged vestibular aqueduct (EVA)
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Case 4 (continued)

- Referral to Genetics – differential:
  - Hearing loss only
  - Connexin 26
  - Hearing loss panel
  - Hearing loss and EVA
  - SLC26A4 gene analysis
  - Branchio-oto-renal syndrome (BOR)
- Family history:
  - Sister with congenital hearing loss
  - No congenital hearing loss in other family members
- Genetics plan:
  - SLC26A4 sequencing and deletion/duplication testing
  - Genetic counseling

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Pendred Syndrome/DFNB4

- Autosomal recessive inheritance
- Gene: SLC26A4
- Major features:
  - Congenital hearing loss
  - Non-progressive
  - Enlarged vestibular aqueduct (EVA)
  - Goiter
  - Onsets between late childhood and early adulthood
  - 10% have abnormal thyroid function
  - Accounts for 10% of all hereditary hearing loss

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Pendred Syndrome/DFNB4

Management:

- Hearing aids
- Consideration of cochlear implants
- Standard treatment of abnormal thyroid function
- Avoid weightlifting and contact sports

Surveillance:

- Annual (at minimum) assessment of hearing and endocrine function
- Baseline thyroid ultrasound with periodic surveillance
- At-risk family members:
  - Site-specific genetic testing
Case 4: Summary

Red flags for Pendred/DFNB4:

• Hearing loss AND
• EVA
• Brain MRI or high resolution CT to assess temporal bone anatomy
• Goiter

Case 5

• 3-year-old boy referred to autism evaluation
• Pregnancy history
• Unremarkable
• Review of medical history
• Developmental delays
• Hand flapping
• Friendly demeanor
• Gaze aversive
• Review of systems otherwise negative

Case 5 (continued)

• Referral to Genetics
• Dysmorphic features identified on physical examination
  • Long face
  • Large ears
  • Mild joint hypermobility
• Family history
  • Mother experienced menopause at age 36 years
  • Paternal grandfather diagnosed at age 64 years with Parkinson’s-like symptoms
• Our plan
  • Chromosome analysis
  • Fragile X analysis (PCR and Southern blot)
  • Microarray
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**Fragile X Syndrome**
- Nontraditional X-linked inheritance
- Trinucleotide repeat with maternal anticipation
- Both males AND females can be affected
- Gene: FMR1
- Full mutation major features:
  - Intellectual disability
  - Characteristic appearance
  - Large head, long face, prominent forehead and chin, protruding ears
  - Behavioral abnormalities
  - Autism or autistic features
  - Social anxiety
  - Seizures

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**Fragile X Syndrome**
- Fragile X premutation carrier features:
  - Fragile X Tremor Ataxia Syndrome (FXTAS)
  - Often misdiagnosed as Parkinson's Disease
  - Fragile X Premature Ovarian Insufficiency (FXPOI)
  - Can lead to early menopause
- Importance of identification
  - Ends the diagnostic odyssey
  - Provides accurate recurrence risks
  - Tests at risk family members
  - Therapy
  - Medication
  - Support resources

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**Case 5: Summary**
- Red flags for this diagnosis include:
  - Individuals with full mutation
  - Developmental delays
  - Autism
  - Dysmorphic features
  - Individuals with premutation
  - Early menopause
  - Tremors, ataxia, “Parkinson’s Disease”
Case 6

- 14-year-old boy referred to gastroenterology
- Review of medical history
- Rectal bleeding
- Referral Reason
  - Passing of polyp
- Next steps?
  - Colonoscopy

Case 6 (continued)

- Referral for genetic counseling
- Suspect polyposis syndrome
- Family history
  - Mother with frequent nosebleeds
  - Maternal grandfather with colon cancer diagnosed in his 60s
- Genetics Plan
  - Gene panel for colorectal cancer predisposition genes
  - Results disclosure appointment
  - Prognosis
  - Recurrence risk

Combined Juvenile Polyposis Syndrome (JPS) and Hereditary Hemorrhagic Telangiectasia (HHT)

- Gene: SMAD4
- Autosomal dominant inheritance
- 25% de novo mutation rate
- Major features:
  - JPS: GI bleeding, gastric and colorectal polyps (juvenile hamartomas)
  - HHT: mucocutaneous telangiectasias, arteriovenous malformations (AVMs), telangiectasias, epistaxis, and intracranial bleeding
Combined Juvenile Polyposis Syndrome (JPS) and Hereditary Hemorrhagic Telangiectasia (HHT)

- Management
  - CBC to screen for anemia
  - Echocardiogram to screen for pulmonary shunting/AVM
  - Brain MRI to screen for cerebral AVM
  - Colonoscopy and upper endoscopy in mid-teens or at the time of initial symptoms
  - Repeat every 3 years if negative
- Testing of family members
  - Predictive testing may be appropriate in children because surveillance for some potential complications begins in early childhood

Case 6: Summary

- Red flags for this diagnosis include:
  - Juvenile colonic polyps
  - Telangiectasias
  - Frequent nosebleeds

Identifying Appropriate Genetics Referrals
Assessing the Key Features

- Family history questions
- PHTS
- HLRCC
- FXS
- Medical history questions
- Combined JPS/HHT
- Imaging
- TS
- Pendred/DFNB4

Refer to Genetics!

Division of Genetics

Physicians
- Richard Erbe, MD
- Luther Robinson, MD
- Laurie Sadler, MD

Genetic Counselors
- Laura Fisher, MS, CGC
- Melissa Samons, MS, CGC

Nutritionist
- Jessica Briggs, RD

Components of a GC Appointment

- Information gathering
- Establishing or verifying a genetic diagnosis
- Risk assessment
- Provision of information/education
- Psychosocial assessment and counseling
- Support resources
- Testing
- Follow-up