OF ZEBRAS AND HORSES: A PRIMER ON GENETICS IN ADULT MEDICINE

JOYCE SO MD, PHD, FRCPC, FCCMG

Advances in Internal Medicine

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DISCLOSURE

I have no relevant financial relationships with any companies related to the content of this course.
OBJECTIVES

• Learn about current clinical genetic testing
• Learn about when medical patients warrant genetic assessment and investigation
• Learn about the implications of genetic diagnosis on treatment, management and family planning
HISTORICALLY SPEAKING...

• Incapacitating bouts of “madness”, abdominal colics, port wine-coloured urine, rambling speech degenerating into obscenities and hallucinations

• Acute-onset and –recovery

• Bilious attacks

• Gout

• Sheer insanity

• Acute intermittent porphyria
ACUTE PORPHYRIAS

A treatable genetic condition!
BIOCHEMICAL TESTING

Blood, urine or other tissue levels of substrates and/or metabolites in a biochemical pathway that has been disrupted by an underlying genetic defect

Enzyme activity assays in leukocytes, erythrocytes, fibroblasts or other tissues

Example: acute intermittent porphyria due to mutations in HMBS (hydroxymethylbilane synthase)

- Increased urine porphobilinogen and 5-aminolevulinic acid
- Decreased erythrocyte HMBS (aka porphobilinogen deaminase) enzyme activity
Blue bloods... red urine...

- two living descendants of father George II with laboratory confirmation of elevated urinary porphyrin metabolites
FIND THE ZEBRAS!

Genetic conditions: individually rare, collectively common → >10 000 single gene disorders estimated to affect 1 in 100 individuals at birth on a global basis (WHO Genomic Resource Centre, 2012)
Psychiatric bipolar disorder since 20s
Endocrine calcium disturbance since birth
Neurologic seizures since 20s

Microdeletion 22q11.2 (DiGeorge syndrome)
WHEN TO SUSPECT A GENETIC CONDITION

- When there are “unrelated” multisystemic findings
GENETIC CONDITIONS ARE OFTEN MULTISYSTEMIC

• Pertinent past medical history often drowned out by details of acute medical history

• Multisystemic issues (particularly if they are rare problems) may suggest an underlying genetic disorder

• Often missed on history when focus is primarily on acute condition
  • E.g. Asking about childhood surgeries could lead to “discovery” of congenital anomalies
22q11.2 DELETION SYNDROME

- A common copy number variant (CNV) syndrome, 1 in 4000-6000 live births
- Cardiac defects
- Abnormal facies (deep-set eyes, “hooded” eyelids, tubular nose, facial asymmetry)
- Thymic hypoplasia (immunodeficiency)
- Cleft palate (velopharyngeal insufficiency)
- Hypocalcemia
- 22q11.2 deletion
- Neurodevelopmental disorder
- Renal defects/dysfunction
- Psychiatric manifestations (30%)
CHROMOSOMAL TESTING

Fluorescence In Situ Hybridization

probe DNA
Labeling with fluorescent dye
Denature & Hybridize

22q11.2 deletion
Normal 22
CHROMOSOMAL MICROARRAY (SNP ARRAY)
CHROMOSOMAL MICROARRAY (SNP ARRAY)
CHROMOSOMAL TESTING

Karyotype + FISH
• Slower: cultured cells
• Low-resolution: detects large copy number variants
• Detects balanced and unbalanced rearrangements

SNP array
• Faster: test done on DNA
• High-resolution: detects small copy number variants
• Detects amount of genetic material, not location
Depression at 40
Tremors at 60
Balance difficulties at 63

FMR1 400 5’ UTR CGG repeats
(Fragile X syndrome)

FMR1 150 5’ UTR CGG repeats
(premutation carrier)

DD, IQ 58, ADHD, OCD, social anxiety, depression, self-injury, repetitive and aggressive behaviours, poor social skills

LD, anxiety, depression, behavioural difficulties

Menopause at 40

Severe autism, non-verbal
WHEN TO SUSPECT A GENETIC CONDITION

• When family history is suggestive
It’s All in the Family

Important to take a comprehensive family history

Ask about:

• Brain disorders (neurodevelopmental, neurological, psychiatric)

• “Things that run in the family”

• Congenital anomalies: any family members born with “something unusual” (cleft lip/palate, extra fingers/toes, club feet, holes in the heart…)

• Multiple pregnancy losses/stillbirths

• Family members with similar findings to patient
FMR1-RELATED DISORDERS

• Caused by triplet repeat (CGG) expansions in 5' UTR of X-linked FMR1 gene

• Fragile X syndrome: >200 CGG repeats
  • 1:4000 males, 1:8000 females

• Premutation carriers: 55-200 CGG repeats
  • ~1:178 females, 1:400 males
  • Premature ovarian failure in 20% of females
  • Tremor-ataxia syndrome in males (40%) > females (16-20%)
    • 2-4% males with adult-onset cerebellar ataxia
  • Increased risk of neuropsychiatric diagnoses, even without frank manifestations of the known FMR1-related disorders
    • Autism, ADHD, mood disorders, bipolar disorder, schizophrenia
FXTAS

WM lesions in splenium of CC (or postmortem intranuclear inclusions)

Cerebral WM lesions

Moderate to severe generalized atrophy

WM lesions in middle cerebellar peduncles

- Intention tremor
- Cerebellar ataxia
- Parkinsonism
- Moderate to severe ST memory deficits
- Executive function deficits
- Neuropathy

Cerebral WM lesions
Age (y)

23

13

Clumsy, uncoordinated, slurred speech, repetitive hand movements, psychiatric SSx unresponsive to medical therapy

MRI brain: mild diffuse atrophy

Basic metabolic investigations normal

Abdominal U/S: splenomegaly

8

LD

Non-dysmorphic; O/E dysarthria, tremor, vertical supranuclear gaze palsy, dystonia, ataxia

Basic metabolic investigations normal

Abdominal U/S: splenomegaly

340x502

MRI brain: mild diffuse atrophy

Basic metabolic investigations normal

Abdominal U/S: splenomegaly

390x361

Lyso-SM509 biomarker: increased

403x393

Abdominal U/S: splenomegaly

Lyso-SM509 biomarker: increased

509x238

Tx/miglustat

Anxiety

15

Trichotillomania

Episodic auditory and visual hallucinations

18

OCD

Clumsy, uncoordinated, slurred speech, repetitive hand movements, psychiatric SSx unresponsive to medical therapy

Follow-up

↓ trichotillomania, OCD, dysarthria, dystonia, vSNGP; improved gait and coordination

23

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NPC1/NPC2 sequencing: two pathogenic variants in NPC1

Niemann-Pick disease type C

326x281

OCD

NPC1/NPC2 sequencing: two pathogenic variants in NPC1

Niemann-Pick disease type C
WHEN TO SUSPECT A GENETIC CONDITION

• When there is unexplained regression/cognitive decline
CHANGE OVER TIME

• Important to dig in the past (beyond acute presentation) and establish chronology

• Neurodegenerative

• Neurometabolic
  • Possibility of targeted therapies
Defective transport and recycling of unesterified cholesterol

NIEMANN-PICK DISEASE TYPE C
NP-C

Systemic involvement

Neonatal Cholestasis
- Liver
- Neonatal splenomegaly

Niemann-Pick C

Neurological involvement

- (Early) Infantile
  - Delay in motor milestones
  - Hypotonia
  - Speech delay
  - Cataplexy

- Late Infantile
  - Gait problems
  - Clumsiness

- Juvenile
  - School problems
  - Ataxia
  - (Seizures)
  - (Cataplexy)

- Adult
  - Psychiatric problems
  - Ataxia
  - Dystonia
  - Dementia

Hepatosplenomegaly
- Absent in ~15% of cases
- Age of onset is variable
- May regress with age

Vertical supranuclear gaze palsy
- 75%

www.niemann-pick-c.com
SINGLE GENE DISORDER TESTING

All exons = exome (1% of genome)

mRNA → protein
SINGLE GENE DISORDER TESTING

Example: NP-C caused by mutations in NPC1 or NPC2

- Mutations could be detected by
  - Sanger sequencing of NPC1 and NPC2 genes
  - Lysosomal disorders gene panel
  - Whole-exome sequencing

- Important to phase if 2+ variants detected in genes associated with recessive disorders

- Biochemical testing
  - Fibroblast filipin staining
  - Oxysterol profile
Heterochromia iridum
Hypertelorism
Achondroplasia (*FGFR3* mutation)
- Macrocephaly, frontal bossing, midface hypoplasia
- Rhizomelic shortening
- Bowed legs
- Brachydactyly
- Exaggerated lordosis
Cleidocranial dysplasia (RUNX2 mutation)

- Broad forehead, hyperteloric (due to open metopic suture)
- Oligodontia (due to delayed/failed eruption of permanent dentition)
- Narrow, sloping shoulders and apposition of clavicles (due to absent clavicles)
- Moderate short stature (163 cm at 16 yo)
WHEN TO SUSPECT A GENETIC CONDITION

- When there are dysmorphic features
DETECTING FACIAL DYSMORPHISMS: BOTTOM LINE

• If you think the patient has unusual or unique facial features, they probably do.

• “Who do you (does he/she) resemble the most in your family?”

• Often, if they look unique, they will say they don’t resemble anyone in their family.
IMPLICATIONS OF GENETIC DIAGNOSIS

• But I should.....
DETECTION OF AT-RISK FAMILY MEMBERS AND FAMILY PLANNING
TARGETED THERAPEUTICS — METABOLIC DISORDERS

• Phenylketonuria: low-protein diet — dietary management; Kuvan (sapropterin) — cofactor
• Ornithine transcarbamylase deficiency — sodium phenylacetate, sodium benzoate - scavengers
• Acute intermittent porphyria: hemin — substrate inhibitor
• Fabry disease: Fabrazyme (agalsidase beta) — enzyme replacement therapy
• Niemann-Pick disease type C: Zavesca (miglustat)
TARGETED THERAPEUTICS — SINGLE GENE DISORDERS

- Episodic ataxia: acetazolamide, 4-aminopyridine
- Tuberous sclerosis: mTOR pathway inhibitors (rapamycin derivatives)
- Neurofibromatosis type 1: Koselugo (selumetinib) — FDA approval 04/2020
- Spinal muscular atrophy: Spinraza (nusinersen) — antisense oligo
- RPE65-related retinitis pigmentosa: Luxturna (voretigene neparvovec-rzyl) — gene therapy!
BARRIERS TO ACHIEVING A GENETIC DIAGNOSIS

• Not “thinking genetic” on the differential to begin with

• Complexity of modern genetic testing - daunting task to arrange testing and interpret results

• Not knowing how to refer patients and/or bring up the topic of genetics referral with patients

• Lack of awareness and interest from many providers
WHY WE SHOULD LOOK FOR ZEBRAS.....

• Many genetic diagnoses are likely missed in adults
  • Recognizing red flags

• Many genetic conditions, especially metabolic, are treatable

• Earlier implementation of management and treatment will lead to significantly better outcomes for mental and physical health

• Diagnosis of a proband will allow accurate recurrence estimations for patient and family members
ADULT GENETICS AT UCSF

• Adult Genetics and Preventive Genomics Clinic (Mount Zion) – MD + GC
  • Ambulatory referral is available on Apex
  • Future: joint adult genetics clinics with cardiology and psychiatry

• eConsult is available on Apex

• Inpatient consults are available
  • Consider eConsult if unsure or quick question
LET'S FIND THE ZEBRAS!