Update on Medical Genetics for Family Practitioners
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No disclosures

Objectives
• Introduction to the Maritime Medical Genetics Service (MMGS)
• Genetics 101
• Key Points in collecting a family history
• Review of Patterns of Inheritance
• Common indications to initiate genetic testing versus genetics referral

MMGS
• Based out of the IWK
• see prenatal cases, children, adults and men
• Serve all the Maritimes
• Clinical Service
• Family implications
• 6 Geneticists
• Mix of pediatric trained and medicine trained individuals with either
  2 year CCMG fellowship training or 5 year Royal College Medical
  Genetics program
• ~15 Genetic Counsellors
• MSc training in genetic counselling
• Nursing and dietitian

Services
• Telehealth services
• Travelling clinics to PEI and New Brunswick
• Geneticist on-call 24/7 IWK locating 902-470-8888
• Triage counsellor available during working hours
  • Field questions about referrals and testing

Our Clinics
• Major Clinics
  • Pediatric
  • Prenatal
  • General
  • Cancer
  • Metabolic and PKU
• Subspecialty Clinics
  • Huntington and neuropredictive
  • Cardiac
  • Connective Tissue Clinic
  • Deletion 22q11.2
  • Hemochromotosis*
What do we do?

- Goal is to tie issues together to make unifying diagnosis
- Draw on clues within patient’s family and medical history
- Patient rarely seen in isolation. Often impact on entire family
- Typically not for cure but treatment options are climbing
  - Anticipatory care
  - Educate
  - Empower
  - Allow for choices

Impact of Genetic Disease

- Up to 80% of mental handicap has a genetic component
- ~50% of first trimester spontaneous abortions are due to chromosomal abnormalities
- ~40% of infant mortality is due attributable to genetic factors
- ~20% of pediatric hospital admissions are due directly to genetic disorders
- ~5% of newborns have a genetic defect

Central Dogma of Molecular Biology

Wikipedia, Central Dogma of Molecular Biochemistry

1958

Forms of Inheritance

- Single gene inheritance
  - Mendelian* - autosomal dominant, autosomal recessive and X-linked
  - Non-mendelian
- Chromosomal disorders
- Multifactorial disorders*
- Environmental exposures

Autosomal Dominant

- A trait is dominant if it is phenotypically expressed in heterozygotes (as well as homozygotes).
- A single copy of the mutant allele is enough for the condition to be expressed.
Autosomal dominant

- Successive generations affected in a pattern of vertical transmission.
- Except for new mutations, every affected person has an affected parent.
- Affected persons are usually heterozygous.
- Each child of an affected person has a 50% chance of inheriting the abnormal gene.
- Unaffected individuals do not transmit.
- The two sexes are both affected and in equal numbers.
- Male to male transmission.
- Penetrance may not be 100%

Recessive

- A trait phenotypically expressed only in the homozygote.
- The mutant allele must be present on both chromosomes for expression.
Autosomal Recessive

- Horizontal pedigree pattern: a single generation affected; sibs may be affected but parents are not
- Both parents of an affected person are in fact heterozygous for the mutant gene
- Each sibling of an affected person has a 25% (1 in 4) chance of being affected
- The two sexes are affected in equal numbers
- There may be consanguinity—the probability increases as the rarity of the condition increases

X-linked Recessive

- No male to male transmission
- Generally only males affected
- Certainly incidence is much higher in males than females, as is severity
- All daughters of affected males are carriers
- All of the affected males in a kindred are related to each other through females: a diagonal pedigree
- One half of sons of carrier females affected

X-linked Recessive Mutations

- May be passed down through multiple generations (previous slide)
- May be new mutation in the mom (all of her cells)
- May be new mutation just in the egg

Multifactorial Inheritance

Familial Clustering of Diseases

A primary characteristic of genetic disease with complex inheritance is that affected individuals tend to “cluster” in families (familial aggregation)
Common Congenital Anomalies With Multifactorial Inheritance

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Population Incidence (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleft by whole/birth</td>
<td>0.6-1.7</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>0.4</td>
</tr>
<tr>
<td>Congenital diaphragmatic hernia defects</td>
<td>2</td>
</tr>
<tr>
<td>Congenital heart defects</td>
<td>0.2-3</td>
</tr>
<tr>
<td>Hexenvalve cartilage</td>
<td>0.7</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>1.0</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>0.2</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>Variable</td>
</tr>
<tr>
<td>Anomalous aortic arch</td>
<td>Variable</td>
</tr>
<tr>
<td>Supravalvar narrowing</td>
<td>Variable</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>0.3</td>
</tr>
</tbody>
</table>

The primary mechanism of clinical genetic investigation is the elucidation of the family history.

“To fail to take a good family history is bad medicine and will someday be criminal negligence.”
Dr. Barton Childs, 1982

Family history
3 generations
not only first degree relatives
ie grandparents, aunts, uncles and children

Pedigree Symbols

SCREEN for Familial Disease

- Some Concerns - “Do you have any (some) concerns about diseases or conditions that seem to run in the family?”
- Reproduction - “Have there been any problems with pregnancy, infertility, or birth defects in your family?”
- Early Disease, Death or Disability - “Have any members of your family died or become sick at an early age?”
- Ethnicity - “How would you describe your ethnicity?” or “Where were your grandparents born?”
- Non-Genetic - “Are there any other risk factors or non-medical conditions that run in your family?”

Seeking Out Red Flags
- Recurrent miscarriages (3 plus)
- Stillbirth, early infant death
- MR, learning difficulties
- Congenital anomalies
  - Heart defect, cleft palate
- Cancer and age at diagnosis
- Sudden or unexplained death at any age
- Known genetic condition in family

Family History
- Pedigree Symbols
- Ethnicity
- Proband/Index Case - affected individual through whom the family was obtained.
- Consultant = anyone who is consulting genetics

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Indications for Genetics Referral

- Family history of a known genetic disorder or recurrent condition
- Birth defects: major anomalies versus several minor differences
- Cognitive disability or developmental delay
- Chronic neurologic or neuromuscular childhood/adult disorders
- Dysmorphic facial features
- Short stature or overgrowth
- Ambiguous genitalia or abnormal sexual development

Indications for Genetics Referral

- Carrier status based on ethnicity (ex. thalasemia)
- Infertility, recurrent miscarriages
- Behavioural disorders (autism)
- Adult onset conditions of suspicious nature (young age of cancer diagnosis)
- Consanguinity
- Advanced maternal age
- Teratogen exposure
- Someone needs to think about it!

Genetic testing done by GP vs Genetics

- Family practitioner
  - Karyotype
  - Microarray
  - Specific testing such as hemochromatosis
- Triggers to send on to genetics
  - Pediatric example
  - Adult example
  - Cancer genetics

Karyotype for recurrent losses (>3)

46,XX, inv(2)(p23.1p25.1), t(2;9)(q33.2;q32)

Translocation
Inversion

Case Demonstrates

- Importance of general family history beyond presenting problem
- 1/500 people have chromosome rearrangement
- ~5% of recurrent (3 or more) early losses due to balanced translocation in parent
- Karyotype parents if 3 or more losses
  - 2 or more if advanced maternal age
- Importance of testing family member most likely to have abnormality even if result has no direct impact on them

**Microarray Technology**

CGH (Comparative Genomic Hybridization), CMA (Chromosomal Microarray)

- DNA based, virtual karyotyping
  - Does not require culturing or chromosomes
- Very high resolution coverage of the genome
  - 5-400 kb resolution versus 10mb for karyotype
- Detects imbalances only – gains and losses
  - Does not detect balanced chromosome rearrangements
  - Products of conception in some cases

**Microarray Testing**

- Indications
  - Largely replaced karyotype for most indications
  - Children with significant cognitive impairment and developmental delay and multiple congenital anomalies
  - Most of such kids linked up with pediatric services
- Considerations for informed consent
  - Normal result
  - Abnormal result
  - Unexpected result
  - Variant Uncertain Significance (VUS)
- Considerations for interpretation of results
  - Normal result does not equate no genetic diagnosis—may benefit from genetics assessment
  - Abnormal result or VUS should see genetics

**Microarray analysis: deletion 22q11.21**
Hemochromatosis “Clinic”

- 150 referrals per year
- Patient information session held annually in the spring
- Genetics, Hematology and GI
- Broadcast to Charlottetown, NB and other NS sites
- Best if patients come to session with genetic test results
  - All physicians can order hemochromatosis genetic testing*
- Letter sent back to patient and referring MD with information specific to patient

What is Hereditary Hemochromatosis?

- An inherited form of iron overload due to high absorption of iron
- Accumulation of iron in various tissues:
  - Liver, heart, pancreas, skin, joints
- Most common genetic condition affecting Canadians
  - ~ 1/250

Complications

- Asymptomatic or mild fatigue
- Hepatomegaly, cirrhosis or hepatocellular carcinoma
- Diabetes mellitus, loss of libido or testicular atrophy
- Arthropathy, chondrocalcinosis or synovitis, osteoporosis
- Cardiomyopathy and dysrhythmias
- Bronze or metallic gray pigmentation

Who Should Consider Genetic Testing?

- Any adult who has a relative with hereditary hemochromatosis
- Any adult who has abnormal results of iron studies
  - Ferritin and transferrin saturation
- Testing children is not recommended:
  - adult onset disease
  - testing requires informed consent
  - Not associated with juvenile hemochromatosis

How is Genetic Testing Done?

- Tests for the C282Y and H63D mutations
- Testing for other mutations -only research basis
- 10-20% of hemochromatosis NOT explained by the HFE gene
- Any physician can order and blood sample sent to QE II Hospital, Halifax

Who Develops Hemochromatosis?

- Not everyone with mutations on both genes develops the disease
- Risk to develop disease - mutation dependent
  - C282Y / C282Y (\(\text{C} / \text{C}\)) ~ 50-100%
  - C282Y / H63D (\(\text{C} / \text{H}\)) ~ 5%
  - H63D / H63D (\(\text{H} / \text{H}\)) ~ 1%
- Women tend to develop disease later in life
- Typically, carriers of 1 mutation do not develop hemochromatosis
Tests for Hemochromatosis

- C282Y/C282Y; C282Y/H63D; H63D/H63D
- Ferritin > 300-1000 ug/ml/L
- % saturation > 55% in men
  > 45% in women
- If ferritin < 300-no treatment required-recheck ferritin in a year

When to begin phlebotomy treatment

Examples when to refer

- Peds case
- Adult case
- Cancer cases
  - Breast cancer
  - Colon cancer/ multiple polyps

History

- Pregnancy
  - Unplanned, 20 year old G2A1
  - Smoking exposure
  - Threatened labour 27 weeks
- Delivery
  - SVD 34 weeks
  - Growth parameters at 25th percentile
  - NICU 3 weeks for feeding

Physical Exam

- Age appropriate
- Growth
  - Height 3rd percentile
  - Weight 25th percentile
  - Head circumference 50th
  - Wearing size 18 months
  - Large anterior fontanelle 3 X 5 cm

History

- Twin A
  - Asthma, orchectomy, ENT
  - CT head normal for large fontanelle
- Twin B
  - Well
  - CT head normal for large fontanelle
  - Development appropriate for both
  - Family history non-contributory
    - Mother pregnant
What’s Missing?

Diagnosis
- Large fontanelle, short stature, dental anomalies and hypoplastic scapula
  - Cleidocranial Dysplasia
- AD inheritance, typically de novo mutation
  - RUNX2 gene
- Complications
  - Recurrent ear and sinus infections
  - Hearing loss
  - Orthopedic issues-scoliosis, genu valgum, osteoporosis
  - Dental anomalies
  - Injury due to open fontanelles
  - Normal intelligence and lifespan

Case Demonstrates
- Multiple anomalies can raise red flag
  - Need not be major anomalies
  - 2 or more minor anomalies can signify major anomaly
  - 2 or more anomalies, major and 2 plus minor anomalies or several minor anomalies warrant referral
- Child with syndrome does not need to have MR or learning difficulties
- Genetic diagnosis determines recurrence risk
  - Unknown diagnosis and parent unaffected: up to 25%
  - This case nominal recurrence risk
- Cannot correct underlying genetic defect but can guide care
  - Dental and ENT intervention
  - Helmet use and osteoporosis screening

Inheritance
- Autosomal dominant
  - Offspring at 50% risk
  - Mutation in EYA1 gene identified in 40%
- 90% of cases inherited from affected parent
- Limited family history information
- Variable within and between families
  - Impossible to predict severity
- Surprised and worried by association of renal disease
  - Not reassured that major structural anomalies likely detected by ultrasound as cannot predict renal function
  - Major determinant in pregnancy planning

Case Demonstrates
- Many adults with congenital anomalies that have not been investigated
  - Never too late to investigate
- Genetic diagnosis can direct other investigations and treatment
  - Proteinuria and hematuria
  - Needs ongoing renal screening
  - Significant impact on family planning decisions
- Information can empower patients to make informed decisions
  - Often may not be information they were hoping to hear
- Must respect patient’s autonomy to act on information we provide
  - Sometimes conflict as to who is our patient, patient with condition or partner with pregnancy
Proportion of cancer due to genetic factors

Inherited Causes of Cancer Make Up 5-10% of All Cancers

General Red Flags

- Suspicious History in Referred Patient with Cancer
  - Tumour type/location
  - Multiple primary malignancies
  - Young age at diagnosis
  - Strong family history
  - Testing offered if certain criteria met or chance of finding mutation >10%

- Known Mutation in Family (referred patient does not necessarily have cancer)
  - Closest affected relative determines risk of inheriting mutation
  - Predictive testing
  - Testing of blood (DNA) sample for just the specific mutation identified in the family
  - Yes or No answer

Hereditary Breast and Ovarian Cancer

- Diagnosed with breast cancer < age 40
- Diagnosed with triple negative breast cancer < age 50
- Diagnosed with ovarian cancer < age 60
- Diagnosed with both breast and ovarian cancer at any age
- Diagnosed with bilateral breast cancer, with 1st diagnosis < age 50
- Male breast cancer at any age
- Diagnosed with breast cancer < age 50 and a relative on the same side of the family with ovarian cancer
- Ashkenazi Jewish ancestry with a personal or family history of breast and/or ovarian cancer
- French Canadian or Icelandic ancestry with breast cancer < age 50
- Two or more 1st and/or 2nd degree relatives diagnosed with breast cancer before the age of 50
- Two or more 1st and/or 2nd degree relatives diagnosed with ovarian cancer at any age
- Personal and/or family history of pancreatic cancer

Key points in who to refer

- Patient must have cancer to be offered testing!!
  - Otherwise results less informative
  - Exception: families with a mutation already identified and testing is predictive
  - Applies to all Hereditary cancer families
- Best person to test may not always be the person referred
  - Woman with breast cancer at age 49 with a niece who was 32 at diagnosis

Hereditary Colorectal Cancer

- Hereditary Non-polyposis Colon Cancer
  - HNPCC
- Lynch syndrome
- Familial Adenomatous Polyposis (FAP)
  - Other polyposis syndromes

Hereditary Colorectal Cancer Red Flags

- Colorectal cancer at less than 50
- Colonic polyps at less than 40
- An individual with a personal and/or family history of multiple cases of the following primary cancers:
  - Colorectal, gastric, small bowel adenocarcinoma, endometrial, ovarian, urinary tract
- Familial adenomatous polyposis (FAP) suggested on colonoscopy
- Individual with 10 or more adenomatous polyps
What if no mutation is identified?

- Most patients do not have a mutation
- Variant of unclear significance (VOUS)
  - Base screening on family history, generally screening begins 10 years younger than youngest age of diagnosis for close relatives
- "good news with fine print"
- Only true negative is in context of predictive testing
- Lynch syndrome clinical diagnosis in absence of a mutation

Take Away

- Genetic issues can cross a lifespan
  - Not just children that are candidates for genetic disorders and can benefit from diagnosis
  - Impact for individual and other family members
- Options for genetic testing by Family Practitioners
  - Issues of informed consent and result interpretation
  - Remember: normal genetic testing does not necessarily mean no genetic condition
  - Genetic testing rarely 100%
  - Many individuals with genetic disease under specialist care (pediatricians) but may be transferred back to primary care/ included in communication and care plan
- Numerous flags to prompt a referral to genetics
  - Recognizing inheritance patterns and collecting family history can provide crucial flags as to who may have a genetic disorder
  - Depend on family practitioners to identify patients as probands but also to identify and send in at-risk family members (particularly for more remote histories of cancer)

Get in Touch With Us

902-470-8754 Main Line
902-470-8709 Fax Line

Dad -> Bb
Offspring -> bb

Thank you!