LEUKODYSTROPHY GENETICS AND REPRODUCTIVE OPTIONS FOR AFFECTED FAMILIES

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Outline

- Genetics 101: Basic Concepts and Myth Busting
- Inheritance Patterns
- Reproductive Options
Genetics 101

Nucleotides:
- Adenine (A)
- Cytosine (C)
- Thymine (T)
- Guanine (G)

Flow of Information: DNA → RNA → Protein
We are at the tip of an iceberg

**GENOME:**
- 3 billion DNA letters
- ~25,000 genes
- 2,500 genetic tests

**KARYOTYPE:** 46,XX or 46,XY
Not All “Genetic” Testing is Equal
Different Methods and Scales of Testing

Unfortunately, we can’t always tell if a certain ‘gene spelling’ is truly a mistake
Nerve Cells and Myelin
Example: X-Linked ALD

- *ABCD1* gene on X chromosome

- More than 1000 different “spelling mistakes” have been found in X-ALD patients

- More than half of these are unique to each family

- Up to 7% did not inherit their mutations—occurred spontaneously ("de novo")

www.x-ald.nl
X-ALD Pathogenesis

Three-hit hypothesis on the physiopathogenesis of X-ALD.

Singh & Pujol, 2010
Biochemical Testing vs. Genetic Testing

- Cheaper
- Faster
- Can tell you what is actually happening in the body
- You don’t need to know all the possible spellings of the gene

- Higher cost
- Slower
- Genetic test may not always predict symptoms, age of onset, progression
- Can be more reliable for detecting mutation CARRIER
Genetic Myths

• Genetic conditions are always inherited

• X-linked disorders never affect women & girls

• Two people with the same gene mutation will always have the same symptoms

• When we find the gene for a disorder, we know what it does

• A ‘negative’ genetic test result means your symptoms aren’t genetic
## Checklist of Items to Discuss

### ✓ Nature/Scope
- Simple explanation of test
- Purpose = find genetic cause
- Possible result outcomes: +, −, VUS

### ✓ Benefits
- May identify the genetic cause/diagnosis
- Medical & psychosocial benefits to diagnosis

### ✓ Limitations
- Does not rule-out all genetic conditions
- Will not lead to definitive cure or treatment
- May need to test parents

### ✓ Risks
- Ambiguous results
- Unexpected/unrelated information
- Familial implications

### ✓ Costs
- Check with insurance!
GENETIC INHERITANCE PATTERNS
X-Linked Disorders

- Genetic carrier mother
- Non-carrier father
- Eggs: $X^C$ and $X^R$
- Sperm: $X^R$ and $Y$

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Autosomal Recessive
Autosomal Dominant

Unaffected mother

Affected or predisposed father with autosomal dominant faulty gene

Unaffected
dd

2 out of 4 chances 50%

Affected or predisposed
Dd

2 out of 4 chances 50%
REPRODUCTIVE OPTIONS FOR COUPLES AT RISK FOR AN INHERITED DISORDER
Different Options at Different Times

- Pre-conception
- Pre-implantation
- Pre-natal
- First trimester
- Second trimester
Options – if genetic cause is unknown

• Adoption

• Use of donor egg/sperm/embryo

• Natural conception
  • Use of ultrasound if anomalies detectable prenatally

• No further childbearing
Reproductive options— if known genetic diagnosis with available testing

- Adoption
- Use of donor egg/sperm/embryo
- IVF and Pre-implantation Genetic Diagnosis
- Natural conception with CVS/amnio
- Natural conception with NO prenatal diagnosis
- No further childbearing
Egg or Sperm Donation

Pre-conception

Pre-implantation

Pre-natal

First trimester

Second trimester
Egg or Sperm Donation

- Available from storage banks; frozen and stored

- Donor is tested for genetic conditions and infectious diseases including the AIDS virus

- Donors can be either anonymous or known; selected by prospective recipient or by the sperm bank

- Donor sperm can be inseminated directly into the uterus or used in IVF procedures

- Donor eggs are used in 10% of all IVF cycles in the United States, live birth rate is over 50%
Pre-implantation Genetic Diagnosis
Preimplantation Genetic Diagnosis (PGD)

- Genetic analysis of one or two cells from the early embryo conceived through *in vitro* fertilization (IVF)
- Allows only unaffected embryos to be transferred into the uterus
- First performed in 1989 in couples at risk of transmitting X-linked conditions
- Since 1990s has used FISH to detect specific, single-gene disorders
Applications

- Single gene disorders
- Chromosome translocations
- Numerical chromosome abnormalities
- Sex selection
PGD Procedure

- Hormonal regulation of ovulation
- Transvaginal sonogram guides egg retrieval
- Fertilization by intracytoplasmic sperm injection (ICSI)
- Embryo biopsy
- Perform genetic diagnosis upon single cells from 6 to 12 embryos
- Embryo transfer (up to 4 embryos)
Cost of PGD

- Average cost of one IVF cycle is $3,500 [avg. # of cycles = 3]
- PGD adds another $2,000-$7,000 to that cost
- One cycle of IVF is successful about 10-35% of the time (success rates improve for couples who have had more than 2-3 cycles)
- Insurance plans may not reimburse for this procedure
IVF Success Rates

- 30 - 35% for women under age 35
- 25% for women ages 35 to 37
- 15 to 20% for women ages 38 to 40
- 6 to 10% for women ages over 40

As of 2010, the CDC quotes a 96-98% accuracy rate for PGD in the United States
Triple screening
Chorionic villus sampling
Screening vs. Diagnostic Tests

- Screening test:
  - Purpose is to detect early disease or risk factors for disease in large numbers of apparently healthy individuals

- Diagnostic test:
  - To establish the presence (or absence) of disease as a basis for making decisions about future course of action
First Trimester Screening – NOT for leukodystrophies

• Performed at 11 1/7 - 13 6/7 weeks gestation

• Nuchal translucency sonogram
  • Detection rate for NT alone ~70%

• Maternal serum
  • Free β-hCG & PAPP-A

• Combined detection rate ~95%
  • False positive rate 4-5%
Nuchal Translucency

- Gestation 11 1/7 to 13 6/7
- Ideal time 12 1/7 to 13 6/7
Diagnostic Testing for Known Genetic Defects: Chorionic Villus Sampling (CVS)

- Transcervical or transabdominal aspiration of a portion of the tissue surrounding the fetal gestational sac
- 10-13 weeks from last menstrual period
- Ultrasound scan: fetal viability, gestational age, guide biopsy
- Risks: miscarriage ~1/175 (less than 1%) at JHH, infections ~1/1000
- Placental mosaicism in 1% of samples
Transcervical Chorionic Villus Sampling

- Ultrasound Probe
- Placenta
- Chorionic Villi
- Amniotic Fluid
- Uterine Wall
- Biopsy Catheter
- Bladder
- Cervix
Transabdominal Chorionic Villus Sampling (CVS)

- Ultrasound Probe
- Chorionic Villi
- Placenta
- Amniotic Fluid
- Uterine Wall
- Bladder
Diagnostic Testing in the Second Trimester Amniocentesis

- 16-18 weeks after last menstrual period

- Ultrasound Scan:
  - Gestational Age
  - Fetal Viability
  - Locate Amnio site
  - Anomaly screen

- 20-30cc of fluid withdrawn

- Risks: miscarriage ~1/300 (at JHH)
Cell-Free Fetal DNA in Maternal Blood

Bodurtha & Strauss (2012)
“Decisions usually involve risk.”
Issues

• Think about how you’ve handled uncertainty in the past

• Timing is key – allow time to grieve past losses or adjust to new diagnosis

• Different family members do not always agree

• Numerical risk is interpreted differently by different people

• Cost and insurance constraints

• Pregnancy termination may or may not be acceptable
The Future

The mission of ALD Connect is to rapidly translate scientific advances into clinical research and new treatments for individuals with X-linked adrenoleukodystrophy (ALD).
RESOURCES FOR FAMILIES

- ALD Connect [Coming Soon]: http://www.aldconnect.org/
- The Genetic Alliance: http://www.geneticalliance.org/
- Children’s Rare Disease Network: http://www.crdnetwork.org/index.php
- SWAN – Syndromes Without A Name: http://www.undiagnosed-usa.org/
- Positive Exposure – Celebrating the Spirit of Difference: http://positiveexposure.org

- Gene Reviews: http://www.genereviews.org
- National Society of Genetic Counselors: http://www.nsgc.org/
- American College of Medical Genetics: http://www.acmg.net
- American Society of Human Genetics: http://www.ashg.org
Thank You! Questions?

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