Genetics Review and Reproductive Options in Kennedy Disease

Alice Schindler, MS, CGC
Genetic Counselor, NIH/NINDS/Neurogenetics Branch

Heather Montie, PhD, Assistant Professor
Department of Bio-Medical Sciences
Philadelphia College of Osteopathic Medicine

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Chromosome to Gene to Protein

CELL → CHROMOSOME → DNA → GENE → PROTEIN
Androgen receptor gene (AR)
Trinucleotide Repeat Disorders

A trinucleotide is a group of 3 chemical bases within a gene. Trinucleotides code for amino acids. Amino acids are the building blocks of proteins.

Normal number of repeated trinucleotide segments within a gene = **Normal Protein Function**.

Mildly expanded number of repeated trinucleotide segments = **Normal Protein Function**.

Fully expanded number of repeated trinucleotide segments = **Abnormal or Absent Protein**.
**X-Linked Segregation, Carrier Mother**

- **Affected Male**
- **Carrier Female**
- **Normal Individual**

Diagram showing the segregation of the X chromosome in a carrier mother: 25% chance of an affected son (XY), 25% chance of a carrier daughter (XX), 25% chance of a normal son (XY), and 25% chance of a normal daughter (XX).
X-Linked Segregation, Affected Father

- Affected Male
- Carrier Female
- Normal Individual

Carrier Daughter: XX
Normal Son: XY
Carrier Daughter: XX
Normal Son: XY
Reproductive Options

**Affected Males**
- 0% chance affected Sons
- 100%/obligate Carrier Daughters
- Gamete (sperm) Donation
- Gamete Selection (sperm selection for male children)
- Use No Options
- No Children
- Adoption

**Carrier Females**
- Have a 50% **chance** to have affected sons and carrier daughters
- Prior to Pregnancy
  - Gamete (Egg) Donation
  - Gamete Selection (sperm selection for female children)
  - Pre-implantation Genetic Diagnosis (PGD)
- During Pregnancy
  - Ultrasound (for gender)
  - CVS/Amniocentesis
    - Usually not recommended for adult onset disorders
Reproductive Options

**Affected Males**
- Will not have affected children
  - 50% Unaffected Sons
  - 50% Carrier Daughters
- Gamete (sperm) Donation
- Gamete Selection (sperm selection for male children)
- Use No Options
- No Children
- Adoption

**Carrier Females**
- Have a *chance* to have affected sons and carrier daughters
- Prior to Pregnancy
  - Gamete (Egg) Donation
  - Gamete Selection (sperm selection for female children)
  - Pre-implantation Genetic Diagnosis (PGD)
- During Pregnancy
  - Ultrasound (for sex)
  - CVS/Amniocentesis
    - Usually not recommended for adult onset disorders
Factors affecting decision to get pre-conception or prenatal genetic testing

- Perceived risk
- Experience with disease
- Personality: behavioral beliefs (e.g. safety and accuracy) and perceived choice control
- SES factors
- Genetic Education and counseling
- Service delivery/Attitudes of health professionals
- Personal medical hx
- Family dynamics & what others did

(Biesecker et al., 2000; Lerman et al, 2002; Godino et al, 2013; Chen et al, 2017)
Transabdominal Chorionic Villus Sampling (CVS)

Ultrasound Probe

Chorionic Villi

Placenta

Amniotic Fluid

Uterine Wall

Bladder

Greenwood Genetic Center
Preimplantation Genetic Testing
Early human development

*in vitro*
Tissues for Preimplantation Biopsy

- Egg
- Cleavage stage
- Blastocyst

- Polar Body
- * Blastomere
- Trophectoderm
PGD-IVF

Heather Montie, PhD and John Hanlon
Disclosures

- John and I made a choice together after much discussion and education about all the choices we had to have a child.

- We DO NOT believe that everyone must make the same choices that we have made (nor should any of us).

- Every individual/family has the right to make the best decision for them without any judgment or opinion inserted by others.

- We fully support everyone’s decisions and are happy for anyone that chooses to not have children or to have children in any manner that is right for their family.

- We are also not spokespeople for any of the clinics or companies that are discussed in this presentation. They are only brought up because they were part of our journey.

- As a KD researcher, my choice to do PGD-IVF does NOT mean I have lost faith that we will find a therapy for KD soon.
Married September 2013

- Our family began with 2 dogs and a cat.
- But our fur-babies weren’t enough for us.
- We were ready to expand our family.
- I was 36 when we decided to have a baby.
- “advanced maternal age”
Kennedy’s Disease and my family

- I am an obligate carrier.
- My dad’s disease course was quite aggressive and coupled with his congestive heart failure, resulted in his death at the young age of 64 (2011).
- I chose a career path to research Kennedy’s Disease to help find a therapy, or even better, a cure.
What is PGD-IVF?

- Preimplantation Genetic Diagnosis & *In Vitro* Fertilization
- It is a screening test used to determine if genetic or chromosomal disorders are present in embryos produced through *in vitro* fertilization (IVF).
- PGD screens embryos before they are transferred to the uterus so couples can make informed decisions about their next steps in the IVF process.
  - Embryos unaffected by the genetic or chromosomal disorder can be selected for transfer to the uterus.
- Thousands of clinical PGD cycles have been performed worldwide, resulting in the birth of thousands of healthy babies.
In vitro fertilization (IVF)

- *In vitro* fertilization (IVF) is the joining of a woman's egg and a man's sperm in a laboratory dish.
- *In vitro* = “outside the body”

Why is the procedure performed?
- to help a woman become pregnant
  - to treat many causes of infertility
  - or for genetic reasons
PGD-IVF in a nutshell

- **Genetic Counseling (1-3 months)**
  - Determine the PGD tests to be done
  - Find a company that can test your genetic condition
    - may need time for company to develop a specific test for you

- **Initial tests of mother and father** to ensure there are no inherent fertility issues that also need to be addressed. *(1-2 months)*
  - woman’s hormone levels and cycle timing
  - ovary check (where follicles (eggs) are stored)
  - sperm health
PGD-IVF in a nutshell (cont.)

- **Stimulation “Super-ovulation”** (to induce multiple eggs to mature) (hormone injections multiple times a day for 3-4 weeks) *(2-4 months)*

- **Egg retrieval** (anesthetized) *(1 day)*
PGD-IVF in a nutshell (cont.)

- **Fertilization** (same day as retrieval; unless choose to freeze eggs for future) (6 days)

- Partner must be on site for their contribution
- Fertilized eggs grown in culture for 5 days
  - (to blastocyst stage)
  - calls from clinic daily to explain status
    - many embryos lost during this process (normal) (may start with 20 but end with only 5)
- at day-5, viable blastocysts have some cells removed to test
  - 2 weeks – 1 month for results
  - blastocysts are frozen
Superovulation and retrieval may be repeated here

At least 1 month rest for woman’s cycle to settle back to normal

Preparation for transfer of genetically normal blastocyst (hormones to prep the uterus and drugs to inhibit ovulation) (1 month)

Transfer (1 day)
**PGD-IVF in a nutshell (cont.)**

- Pregnancy test *(9 days later)* (about 23-43% chance of pregnancy)
  - If positive, CELEBRATE!

- Woman must take progesterone shots daily (thickens uterine wall) for 10 weeks to help maintain pregnancy.

- At 10-15 weeks, chorionic villi or amniocentesis re-testing for gene anomaly *(if one chooses to do so)* (can also test for chromosomal anomalies at this time) *(my insurance covered this $875)*

- **In total:** 6-12 months *(if everything works 1st time)*
  - Plus another 37.5 weeks of pregnancy *(more time if there is a failure at any point)*
IVF risks and side effects

- IVF involves large amounts of physical and emotional energy, time, and money.

- Many couples dealing with infertility suffer stress and depression.

- Fertility medicines may induce:
  - bloating, abdominal pain, mood swings, headaches, and other side effects. (memory loss, anxiety, lack of patience)
  - Most IVF medicines must be given by injection
    - several times a day
    - repeated injections can cause bruising
IVF risks and side effects (cont.)

- During the treatment:
  - many doc visits (1-3 a week) (major commitment of time)
    - blood draws and ultrasounds to check hormone levels and egg maturation
  - The last week before egg retrieval is very painful.

- In rare cases, fertility drugs may cause ovarian hyperstimulation syndrome (OHSS).
  - buildup of fluid in the abdomen and chest
  - severe cases require draining of the fluid with a needle
IVF risks and side effects (cont.)

- Risks of egg retrieval include reactions to anesthesia, bleeding, infection, and damage to structures surrounding the ovaries, including the bowel and bladder.

- There is a risk of multiple pregnancies when more than one embryo is placed into the womb.
  - Carrying more than one baby at a time increases the risk of premature birth and low birth weight.
  - IVF embryos have an increased chance of dividing
    - So even if 1 is transferred; it could become twins!
  - It is unclear whether IVF increases the risk of birth defects.
Risks of failure at each stage of PGF-IVF

- Super-ovulation
  - may not lead to any mature follicles to be retrieved; or very few
- IVF may not lead to any viable blastocysts after 5 days in culture
- Genetic testing may reveal no genetically normal embryos
- Embryos may not survive thaw
- Transfer of an embryo may not lead to pregnancy
- If pregnancy is successful, there are still risks of loss that occur with any pregnancy
IVF monetary costs

- IVF is very costly.

- Some states have laws that say health insurance companies must offer some type of coverage.
  - But, most insurance plans do not cover infertility treatment.
  - Some insurance plans will pay for injectable hormones. ($5,000-$7,000)

- Fees for a single IVF cycle include costs for medicines, surgery, anesthesia, ultrasounds, blood tests, processing the eggs and sperm, embryo storage, and embryo transfer.

- The exact total of a single IVF cycle varies, but may cost more than $12,000 - $19,000, plus the $5,000-$7,000 for hormones, plus genetic screening ($5,000-$6,000).

**Total** = $22,000-$32,000

A little happy note: You can deduct whatever amount is above 10% of your gross income from your federal taxes
Our IVF journey......

Enson Edward Hanlon

12-13-15
Our IVF journey......

- We transferred a frozen embryo in January, 2017.
- Unfortunately it didn’t result in a pregnancy.
- We had one embryo left........
Our IVF journey: *March*

3-7-17

11-16-17!
Thanks!

- My father Edward Montie, my husband John Hanlon, our son Enson Edward Hanlon, and our daughter coming soon!
- Our whole family for their support
- RMA-Jefferson
- Genesis Genetics
- Jefferson OB/GYN
- The KDA for allowing us to share our story.

montihea@hotmail.com
heathermon@PCOM.edu

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- The whole NIH KD family for always being there for all of us!
References

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- RMA of Philadelphia

- PennMedicine

- Genesis Genetics
  - http://genesisgenetics.org/pgd/