Genetic Considerations in Having Children

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- Hereditary cancer syndromes
- Connective tissue disorders
- Dermatology genetics
- Neurogenetics
- Cardiogenetics
- Autism genetics

- Mitochondrial genetics
- Metabolic disorders
- Vision and hearing disorders
- Bleeding/clotting disorders

...and many more!
Outline

• How babies are made (genetics refresher)
• Genetics of EDS
• Genetic testing basics
• Prenatal testing options
• Considerations for anyone having children

Terminology

• EDS: Ehlers-Danlos syndrome
• HSD: hypermobility spectrum disorder
• Genetic variant: difference in a gene from the typical genetic sequence
• Pathogenic: disease-causing
• Mutation: a new genetic variant (may or may not be pathogenic)
How Babies Are Made (Genetics)
Inheritance Patterns

• Autosomal dominant (AD)
• Autosomal recessive (AR)
• De novo (not inherited)
• Other (X-linked, mitochondrial, multifactorial)

Autosomal means not sex-linked
Autosomal Dominant (AD) Inheritance

Adapted from Greenwood Genetic Center

Autosomal Dominant (AD) Inheritance

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**Autosomal Dominant (AD) Inheritance**

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**Autosomal Recessive (AR) Inheritance**

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Autosomal Recessive (AR) Inheritance

Adapted from Greenwood Genetic Center
De novo variants (mutations)

- Every time cells divide to make new cells they copy their genetic information
- Sometimes the copy is not exact
- De novo variants happen when germ cells (sperm and egg) are produced
- We all have a few new variants in our genome that were not inherited from either parent
De novo variants (mutations)

Some conditions have higher rates of de novo mutations than others

- Polycystic kidney disease: 5% de novo
- Marfan syndrome: 25% de novo
- Classical EDS: 50% de novo

De novo variants are typically seen in dominant conditions

Once a person has a pathogenic variant it can be passed to their children
Summary

- For most genes, children inherit one copy from mom and one copy from dad
- Dominant conditions are caused by a pathogenic variant in one copy of a gene
- Recessive conditions are caused by pathogenic variants in both copies of a gene
- De novo variants can cause a dominant condition in a person with no family history

Genetics of EDS
### Inheritance of EDS

<table>
<thead>
<tr>
<th>Category</th>
<th>GENES</th>
</tr>
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<tbody>
<tr>
<td>Arthrochalasia EDS (AD)</td>
<td>COL1A1, COL1A2</td>
</tr>
<tr>
<td>Cardiac-valvular EDS (AR)</td>
<td>COL1A2</td>
</tr>
<tr>
<td>Classical EDS (AD)</td>
<td>COL5A1, COL5A2</td>
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<td>Classical-like EDS (AR)</td>
<td>TNXB</td>
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<td>Dermatosparaxis EDS (AR)</td>
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<td>CHST14</td>
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<td>Myopathic EDS (AD or AR)</td>
<td>COL12A1</td>
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<tr>
<td>Periodontal EDS (AD)</td>
<td>C1S, C1R</td>
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<tr>
<td>Spondyloystlastic EDS (AR)</td>
<td>SLC39A1</td>
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<tr>
<td>Vascular EDS (AD)</td>
<td>COL3A1</td>
</tr>
<tr>
<td>Hypermobility spectrum disorder (AD)</td>
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</tbody>
</table>
Points to Remember

• Even in the same family with the same genetic variant, people can have very different clinical features of the condition.

• Inheritance pattern (dominant or recessive) determines the chance that a person with a type of EDS will have a child who also has that type of EDS.
Points to Remember

• Even in the same family with the same genetic variant, people can have very different clinical features of the condition.

• Inheritance pattern (dominant or recessive) determines the chance that a person with a type of EDS will have a child who also has that type of EDS.

• Each type of EDS is a different condition. Having one type of EDS does not increase your risk to have a child with a different type of EDS.
Genetic Testing Basics
Gene sequencing

Reference: GTAGTACCTC TATGAACGAAAGG

GTAGTACCTC GATGAACGAAAGG

Deletion/duplication testing

Reference: GTAGTACCTC TATGAACGAAAGG

GTAGTACCTC AAGG

Gene
Genotyping (most consumer ordered tests)

Reference: GTAGTACCTCTTATGAACGAAAGG

- Accuracy is less certain (false positives, false negatives, failed reads)
- Health risks identified are often small or do not account for personal/family history
- Third party interpretation services are totally unregulated
If you choose to have genetic testing

- Get help from someone who has experience with genetic testing
- Ask about cost and insurance coverage
- Choose a lab that offers clinical testing

Possible test results

Positive:
A pathogenic genetic variant is identified
Possible test results

**Negative:**
No genetic variant is found (or only common and clearly benign variants)

Possible test results

**Variant of uncertain significance:**
A genetic variant is found but there is not enough evidence to classify it as pathogenic (harmful) or benign (harmless)
Possible test results

Variant of uncertain significance:
A genetic variant is found but there is not enough evidence to classify it as pathogenic (harmful) or benign (harmless)

Variants of uncertain significance are common

The lab will notify your provider if they reclassify the VUS
Possible test results

**Variant of uncertain significance:**
A genetic variant is found but there is not enough evidence to classify it as pathogenic (harmful) or benign (harmless)

- Variants of uncertain significance are common
- The lab will notify your provider if they reclassify the VUS
- 90% of VUS's turn out to be benign (harmless)

What can you do with test results?

- Confirm or rule out a diagnosis
- Reproductive planning
- Test family members
- Participate in research or clinical trials
Prenatal Testing Options

Prenatal testing options

1st trimester  2nd trimester  3rd trimester
Prenatal testing options

1st trimester: PGD
2nd trimester: CVS
3rd trimester: Amnio

Preimplantation genetic diagnosis (PGD)

- May also be called PGT-M (preimplantation genetic testing – monogenic)
- In vitro fertilization to create embryos in a lab
- Embryos are tested for the known genetic variant
- An embryo without the variant can be transferred
Preimplantation genetic diagnosis (PGD)

- PGD is expensive ($15,000 per IVF cycle)
- Insurance rarely covers IVF or embryo testing
- Some couples will not have any unaffected embryos to transfer
- Some couples will have embryos left after they are done having children
Chorionic villus sampling (CVS)

- Sample of cells from the placenta
- Around 11 weeks of pregnancy (first trimester)
- Can also screen for missing/extra chromosomes
Amniocentesis

- Sample of amniotic fluid from around the fetus
- Around 16-20 weeks of pregnancy (second trimester)
- Can also screen for missing/extra chromosomes and open neural tube defects
Cell-free DNA

- Not used for single gene disorders (yet) but often offered in pregnancy to screen for missing/extra chromosomes
- Uses a blood sample from mother
- Anytime after 10 weeks of pregnancy

What else to know?

- Some families choose to have a child without testing for a known genetic condition in the family
- Even if testing determines that a pregnancy is affected with a condition, it doesn’t tell us what the condition will look like for that child
- There are many ways to become a parent – some families choose to use a sperm/egg donor, adopt, or become foster parents
Pregnancy management

• Talk about your plan for pregnancy with your health care providers
• Talk about your diagnosis with your OB/GYN provider
• Ask about your medications, including non-prescription supplements
• Pregnancy is hard on all bodies – take care of yourself!

Considerations for Anyone Having Children
Carrier screening

Carrier screening for recessive and X-linked genetic conditions is usually offered to all couples

- Carrier frequency for cystic fibrosis is 1/25
- Carrier frequency for spinal muscular atrophy is 1/50

Some ethnic groups have higher carrier frequencies for certain conditions

Risks in any pregnancy...

- Congenital heart defect (1/100)
- Down syndrome (1/700)
- Cleft lip (1/940)
- Spina bifida (1/2800)

We don’t understand all the genetic/environmental factors that affect risk
Resources

- National Society of Genetic Counselors (www.nsgc.org)
- American College of Medical Genetics and Genomics (www.acmg.net)
- American College of Obstetricians and Gynecologists (www.acog.org)

https://www.healthymiamidade.org/committees/florida-healthy-babies/
Thank You!

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