NEWSLETTER

This newsletter centers on reproductive topics with a genetics focus. If there is an organization or upcoming webinar you'd like me to include in a future newsletter, please feel free to reach out at genetics@modernreproduction.org.

Sign up for the newsletter here

Webinars

AFFIRMING SEX AND GENDER DIVERSITY IN GENETICS PRACTICES, POLICIES, AND LAWS: A CALL TO ACTION

12/8/23 12PM EST

Register

NEXT-GENERATION SCREENING – THE PROMISE AND PERILS OF DNA SEQUENCING OF NEWBORNS AT BIRTH: A WORKSHOP

On Demand

ISSUE 21

NEWSLETTER

The little lit review

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Agenesis of the corpus callosum: What to tell expecting parents?

Pascale Tsai, Shiri Shinar

Genetic Testing:

- Microarray (captures common trisomies and microcell/dups) with a diagnostic yield of 11.1-12.5%.
- Whole Exome Sequencing (captures single gene conditions) with a diagnostic yield of 30% for isolated ACC and 49% for non-isolated cases.
- NIPT is of limited utility as it will not often include single gene conditions associated with ACC

Core Neuropsychological Syndrome:

- Delayed cognitive processing
- Reduced interhemispheric transfer of sensory motor information
- Decreased complex information analysis and unacquainted task performance, with increased vulnerability to more demanding cognitive tasks.

Prenatally detected and postnatally confirmed isolated ACC:

- 83/128 children with normal outcomes
- 45/128 children with a degree of neurodevelopmental complications
  - vision problems (up to 33%of cases)
  - delayed speech development (up to 29%)
  - seizures (up to 25%)
  - feeding problems (up to 20%)
  - impaired hand-eye coordination
  - sociobehavioral disorders such as attention-deficit-hyperactivity disorder (ADHD).

TABLE 1 Some genetic conditions

Genetic disorders
Chromosomal anomalies
Trisomy 18 (Edwards syndrome)
Trisomy 13 (Patau syndrome)
Trisomy 21 (Down syndrome)
Mosaic trisomy 8
Others
Non-chromosomal conditions
Dandy-Walker malformation
Aicardi syndrome
Andermann syndrome
Joubert syndrome
X-linked hydrocephalus
Walker-Warburg syndrome
Mowat-Wilson syndrome
Tubulinopathies
Inborn errors of metabolism

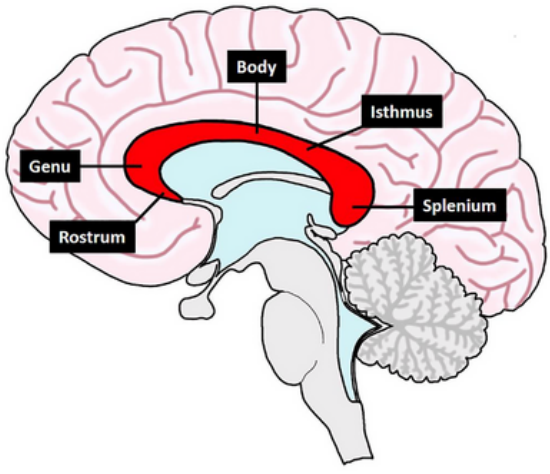


FIGURE 1 All parts of the corpus callosum in a midsagittal plane. [Colour figure can be viewed at wileyonlinelibrary.com]

ISSUE 21

NEWSLETTER

The little lit review

Expanded carrier screening on sperm donors

Lauren Isley, MS, CGC, Pamela Callum, MS, CGC, Jennifer Luque, MS, CGC, Jessica Park, MS, CGC, Kara Baldwin, MS, CGC

Current Overview of Screening donors per ACMG's 2021 guidelines:

- For screening oocyte donors include the conditions: cystic fibrosis, spinal muscular atrophy, hemoglobinopathies, and Fragile X .
- Expanded carrier screening can be considered.
- Given the probability of screening positive for expanded carrier screening, donors do not need to be excluded based on this status only. However if there are possible health complications related to the carrier status, then they may be ineligible on a case-by-case basis.

Study:

- Retrospective analysis of a single sperm bank practices from 7/2017-12/2021 in which 261-283 conditions were screened for each donor
- 19/966 donors were identified to have a carrier status that could confer health risks
- Only the two donors with LDLR variants exhibits symptoms related to the conditions - the conditions have older age onset, variability expressivity, and reduced penetrance.

TABLE 1: CLINICALLY SIGNIFICANT HETEROZYGOSITY FOR AUTOSOMAL RECESSIVE CONDITIONS

NUMBER OF POSITIVE DONOR APPLICANTS	GENE	ASSOCIATED AR DISEASE	ASSOCIATED POTENTIAL HEALTH RISKS (HETEROZYGOTES)
3	*ATM*	Ataxia telangiectasia	Moderately increased risk for breast cancer[10]
1	*NBN*	Nijmegen breakage syndrome	Possible increased risk for certain types of cancer, particularly in the presence of a specific founder mutation. Conflicting evidence exists[10]
2	*FH*	Fumarase deficiency	Increased risk of developing hereditary leiomyomatosis and renal cell cancer[11]
2	*LDLR*	Familial hypercholesterolemia	Increased risk for coronary artery disease and myocardial infarction[12]
1	*TNXB*	Ehlers-Danlos syndrome	Increased risk for joint hypermobility, recurring joint dislocations, and chronic joint pain[13]

TABLE 2: CLINICALLY SIGNIFICANT HEMIZYGOSITY FOR X-LINKED CONDITIONS

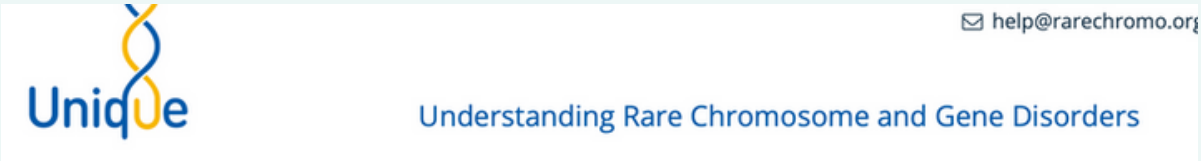
NUMBER OF POSITIVE DONOR APPLICANTS	GENE	ASSOCIATED X-LINKED DISEASE	ASSOCIATED POTENTIAL HEALTH RISKS (HEMIZYGOTES)
1	*DMD*	Duchenne muscular dystrophy	Delayed motor development and progressive muscle weakness, cardiomyopathy, and cognitive impairment[14]
1	*F9*	Factor IX deficiency	Prolonged or excessive bleeding following injury or trauma, joint bleeds, and deep muscle hematomas[15]

TABLE 3: CLINICALLY SIGNIFICANT COMPOUND HETEROZYGOSITY OR HOMOZYGOSITY FOR AUTOSOMAL RECESSIVE CONDITIONS

NUMBER OF POSITIVE DONOR APPLICANTS	GENE	ASSOCIATED AR DISEASE	ASSOCIATED POTENTIAL HEALTH RISKS (COMPOUND HETEROZYGOTES/ HOMOZYGOTES)
2	*BTD*	Biotinidase deficiency	If untreated, neurological abnormalities, vision problems, hearing loss, and cutaneous abnormalities[16]
1	*CAPN3*	Limb girdle muscular dystrophy 2a	Weakness and atrophy of the proximal limb-girdle muscles, joint contractures[17]
1	*NEB*	Nemaline myopathy	Progressive weakness of the proximal muscles, particularly those in the face/neck[18]
1	*CYP21A2*	Congenital adrenal hyperplasia (due to 21-hydroxylase deficiency)	Excessive adrenal androgen biosynthesis resulting in virilization and salt-wasting (classic form); hyperandrogenism resulting in possible hirsutism, menstrual cycle changes and infertility (non-classic form)[19]
1	*SLC25A13*	Citrin deficiency	Neonatal intrahepatic cholestasis (newborns), failure to thrive and dyslipidemia (older children), hyperammonemia wiith neuropsychiatric symptoms (adults)[20]
1	*HBA1/2*	Alpha thalassemia	Generalized edema, severe anemia, neonatal death (Hb Bart syndrome); spleen and liver enlargement, jaundice, bone changes (HbH disease)[21]
1	*USH2A*	Usher syndrome type 2a	Congenital, bilateral sensorineural hearing loss and progressive, bilateral retinal degeneration[22]

NEWSLETTER

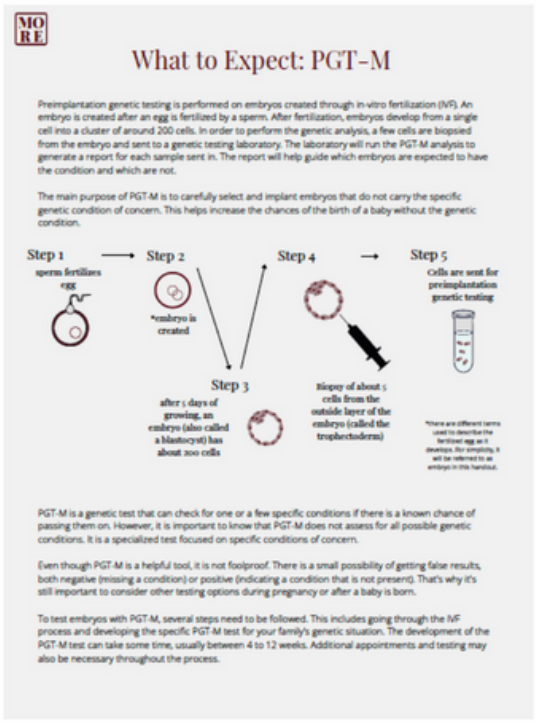
Community Content:



Unique provides numerous support resources for families. They're golden resource for providers to use are the fact sheets on numerous chromosomal conditions.

Modern Reproduction Content:

Modern Reproduction offers brochures and factsheets to download without lab branding. Check them out here. If there's a brochure/factsheet you'd like created, let me know at genetics@modernreproduction.org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What to Expect: PGT-M

Preimplantation genetic testing is performed on embryos created through in-vitro fertilization (IVF). An embryo is created after an egg is fertilized by a sperm. After fertilization, embryos develop from a single cell into a cluster of around 200 cells. In order to perform the genetic analysis, a few cells are biopsied from the embryo and sent to a genetic testing laboratory. The laboratory will run the PGT-M analysis to generate a report for each sample sent in. The report will help guide which embryos are expected to have the condition and which are not.

The main purpose of PGT-M is to carefully select and implant embryos that do not carry the specific genetic condition of concern. This helps increase the chances of the birth of a baby without the genetic condition.

Step 1 sperm fertilizes egg
Step 2 *embryo is created
Step 3 after 5 days of growing, an embryo (also called a blastocyst) has about 200 cells
Step 4 Biopsy of about 5 cells from the outside layer of the embryo (called the trophectoderm)
Step 5 Cells are sent for preimplantation genetic testing

*there are different terms used to describe the fertilized egg as it develops. For simplicity, it will be referred to as embryo in this handout.

PGT-M is a genetic test that can check for one or a few specific conditions if there is a known chance of passing them on. However, it is important to know that PGT-M does not assess for all possible genetic conditions. It is a specialized test focused on specific conditions of concern.

Even though PGT-M is a helpful tool, it is not foolproof. There is a small possibility of getting false results, both negative (missing a condition) or positive (indicating a condition that is not present). That's why it's still important to consider other testing options during pregnancy or after a baby is born.

To test embryos with PGT-M, several steps need to be followed. This includes going through the IVF process and developing the specific PGT-M test for your family's genetic situation. The development of the PGT-M test can take some time, usually between 4 to 12 weeks. Additional appointments and testing may also be necessary throughout the process.

Handout: What to Expect PGT-M