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

SGNIPT FOR RECESSIVE CONDITIONS IS HERE TO STAY

October 25, 2023 @ **5** pm ET

Register

AN INSIDER'S GUIDE TO CLINICAL TRIALS

October 26, 2023 @ **2:00** pm ET

Register

ISSUE 17

NEWSLETTER

The little lit review

1 Incremental yield of whole genome sequencing over chromosome microarray and exome sequencing for congenital anomalies in prenatal period and infancy: systematic review and meta-analysis

N. Shreeve, C. Sproule, K. W. Choy, Z. Dong, K. Gajewska-Knapik, M. D. Kilby† & F. Mone

WHO: 18 studies encompassing 902 cases with congenital abnormalities that were or would have been identified prenatally; cases included fetuses, neonates and infants (up to one year of age)

OBJECTIVES:
1. Determine the incremental yield of WGS over CMA and/or ES
2. Evaluate the turnaround time (TAT) and quantity of DNA required for testing using WGS and ES.

Findings:

- The clinical genetic syndrome most commonly identified was Noonan Syndrome
- Incremental yield was greatest for the postnatal cohort with CMA analysis at 39%, prenatal cohort with CMA analysis at 16%, and exome sequencing cohort at 1%
- WGS appears to require less DNA than a stepwise testing strategy (QF-PCR/G-banding karyotype – CMA – ES) and potentially provides results in a shorter timeframe to facilitate decision making (though these were research WGS and commercial WGS may have different TAT); however, CMA and ES pathway utilizes less fetal DNA and has potential faster turn-around-times although it is associated with more VUS.
- Pediatric population may have greater yield as prenatal phenotyping is more difficult and affected by evolving fetal phenotypes

What variants are detected with WGS over WES?

intronic variation, repeat expansions, pathogenic copy number variants (CNVs) with greater resolution than that of CMA, structural DNA alterations and mitochondrial disorders

NEWSLETTER

The little lit review

Unexplained Female Infertility Associated with Genetic Disease Variants

Michael P Dougherty, Alexandra M Poch, Lynn P Chorich, Zoe A Hawkins, Hongyan Xu, Robert A Roman, Haitao Liu, Soumia Brakta, Hugh S Taylor, James Knight, Hyung-Goo Kim, Michael P Diamond, Lawrence C Layman

Of the paper's population of 197 patients with unexplained infertility, 6.6% or 13 patients had likely pathogenetic or pathogenic variants in one of ACMG's 59 actionable genes after whole exome sequencing (WES) . The first question is: what's the chance that someone in the general population would have a likely path or path variant in one of these genes? Of the nearly 50,000 people in the UK biobank and 20,000 in eMERGE biobank, the percents are 2% and 2.5%, respectively.

The authors included additional genes not among ACMG's 59 actionable genes. 10.6% of their cohort were identified to have LP/P variants in these genes. The authors state, "our findings support a genetic link between infertility and future medical illness."

Table 1.

Medically Actionable Genes with Pathogenic or Likely Pathogenic Variants Identified in the Study Population.

Gene	Genetic Disorder	Risk	PMID*
BRCA1	Breast, ovarian, and pancreatic cancer	Breast cancer, 40–87%; ovarian cancer, 16–86%; pancreatic cancer, 2.5%	28632866 (breast and ovarian), 35077220 (pancreatic)
BRCA2	Breast, ovarian, and pancreatic cancer	Breast cancer, 27–84%; ovarian cancer, 13–32%; pancreatic cancer, 2.5%	28632866 (breast and ovarian), 35077220 (pancreatic)
MYH11	Aortic dissection	17%	17666408
GLA	Fabry disease (cardiac, cerebro-vascular, and renal)	Neuropathic pain, 64%; kidney impairment, 33%; end-stage kidney disease, 1%; transient ischemic attack or stroke, 27%; tinnitus and hearing loss, 47%; gastrointestinal symptoms, 53%	15025684
PKP2	Arrhythmogenic right ventricular dysplasia or cardiomyopathy	11–47%	17010805
KCNQ1	Familial atrial fibrillation; long QT syndrome	Long QT syndrome, 73%; sudden death, 9.5%	12702160
SCN5A	Six different cardiac arrythmias; the Brugada syndrome	Syncope, 22–30%; sudden cardiac death, 10–20%	27472692, 27566755
RYR1	Central core disease of muscle; malignant hyperthermia	Malignant hyperthermia, 40.6%	31206373
APOB	Familial hypercholesterolemia	Hepatic steatosis, nearly 100%; severe hepatic steatosis witl occasional progression to cirrhosis, 5–10%	33983694
CACNA1S	Hypokalemic periodic paralysis	Hypokalemic periodic paralysis characterized by low potassi- um, myopathy, and recurrent episodic paralysis, 84–100%	15098604

*PubMed identification numbers (PMIDs) are provided for the reference or references from which the risk values were obtained.

ISSUE 17

NEWSLETTER

The little lit review

Unexplained Female Infertility Associated with Genetic Disease Variants

Michael P Dougherty, Alexandra M Poch, Lynn P Chorich, Zoe A Hawkins, Hongyan Xu, Robert A Roman, Haitao Liu, Soumia Brakta, Hugh S Taylor, James Knight, Hyung-Goo Kim, Michael P Diamond, Lawrence C Layman

No.	Gene	Cytoband	HGVS Coding	Protein change	Variant type	Affected Exon	Gnomad Frequency (%)	ACMG Call	Race
1	*ALPL*	1p36.12	c.1363G>A	p.Gly455Ser	Missense	12 of 12	0.041	P	Caucasian
2	*ANXA11*	10q22.3	c.112G>A	p.Gly38Arg	Missense	38 of 506	0.008	P	Caucasian
3	*ATM*	11q22.3	c.3538del	p.Val1180Ter	Stop gained	1180 of 3057	0	P	Caucasian
4	*BEST1*	11q12.3	c.404C>T	p.Ala135Val	Missense	4 of 9	0.04	P	Caucasian
5	*C1QTNF5*	11q23.3	c.-2366+1G>A	-	Splice site	-	0.003	P	Caucasian
6	*CFHR5*	1q31.3	c.678del	p.Glu226AspfsTer7	Frameshift	5 of 10	0.001	P	Black
7	*CLCN7*	16p13.3	c.2299C>T	p.Arg767Trp	Missense	24 of 25	0	P	Caucasian
8	*DUSP6*	12q21.33	c.566A>G	p.Asn189Ser	Missense	2 of 3	0.068	P	Caucasian
9	*ERCC6*	10q11.23	c.3607_3608insGGGCTGGCTGCTTAAGGTCCACCTTA	p.Lys1203ArgfsTer33	Frameshift	18 of 21	0	P	Caucasian
10	*GBA*	1q22	c.1226A>G	p.Asn409Ser	Missense	10 of 12	0.27	P	Black
11	*IMPG2*	3q12.3	c.3023-6_3030dup	p.Ala1011PhefsTer2	Stop gained	15 of 19	0.002	P	Caucasian
12	*KCNJ11*	11p15.1	c.185C>T	p.Thr62Met	Missense	1 of 753	0	P	Caucasian
13	*MEF2A*	15q26.3	c.836C>T	p.Pro279Leu	Missense	8 of 11	0.118	LP	Caucasian
14	*PKD1*	16p13.3	c.12391G>T	p.Glu4131Ter	Stop gained	45 of 46	0.003	P	Asian
15	*PSEN1*	14q24.2	c.617G>C	p.Gly206Ala	Missense	7 of 12	0.051	P	Caucasian
16	*RAD51C*	17q22	c.577C>T	p.Arg193Ter	Stop gained	4 of 9	0.004	P	Caucasian
17	*SLC25A4*	4q35.1	c.523del	p.Gln175ArgfsTer38	Frameshift	2 of 4	0	P	Caucasian
18	*TTN*	2q31.2	c.73254_73255del	p.Glu24419IlefsTer2	Stop gained	276 of 313	0.017	LP	Caucasian
19	*TTR*	18q12.1	c.424G>A	p.Val142Ile	Missense	4 of 4	0.59	P	Black
20	*VWF**	12p13.31	c.2561G>A	p.Arg854Gln	Missense	20 of 52	0.9	P	Caucasian*

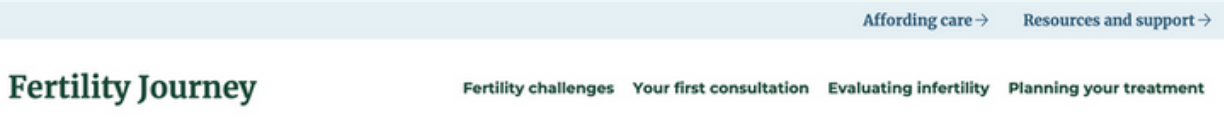
Table S5: AD pathogenic variants not included in the 59 MAG genes, which could affect health. 20 P/LP variants were identified in 21 individuals.

What's considered unexplained infertility?

Healthy couple, >1 year, normal uterine cavity, 1 patent fallopian tube, >9 menses/year, motile sperm count >5 million in the ejaculate

NEWSLETTER

Community Content:



This week's community content spotlight is for Fertility Journey - a straightforward, quick overview of the fertility process.

Modern Reproduction Content: