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Unexplained Female Infertility Associated with Genetic Disease Variants

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

Data can be obtained by contacting the first author.

To the Editor:

Infertility affects 10 to 15% of persons in the United States. In approximately 30%, the cause is unexplained. Infertility has been suspected to be a harbinger of poor health outcomes, because both men and women with infertility have increased risks of cardiovascular disease, cancer, and death.[1,2] Recently, the National Institutes of Health released a funding opportunity announcement stating that infertility could be physiologically or genetically linked to other conditions.

We hypothesized that genetic disease creates a predisposition to infertility and subsequent medical illness. We sequenced the exomes of 197 women with unexplained infertility to identify pathogenic and likely pathogenic variants in genes deemed medically actionable by the American College of Medical Genetics and Genomics.[3] Among these medically actionable genes, 59 included pathogenic or likely pathogenic variants involved in cancer, cardiovascular disease, inborn errors of metabolism, and miscellaneous disorders (see the Methods section in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

We found 15 heterozygous pathogenic or likely pathogenic variants (14 of which were confirmed by Sanger sequencing) in medically actionable genes among 13 of 197 women with unexplained infertility (6.6%; 95% confidence interval [CI], 3.6 to 11.0); this percentage was significantly greater than the corresponding 2% of 49,960 persons in the U.K. Biobank[4] (odds ratio, 3.3; 95% CI, 1.7 to 5.8; P<0.001) and 2.5% of 21,915 persons from the eMERGE Network[5] (odds ratio, 2.60; 95% CI, 1.35 to 4.59; P = 0.001) (Tables S1 and S2 in the Supplementary Appendix). When we evaluated infertility according to race (11 White persons, 1 Black person, and 1 Asian person), we found a significantly greater percentage of White participants with pathogenic or likely pathogenic variants in medically actionable genes in our study sample than in the U.K. Biobank (odds ratio, 3.61; 95% CI, 1.76 to 6.68; P<0.001) or the eMERGE Network (odds ratio, 2.83; 95% CI, 1.37 to 5.27; P = 0.003) (the study was not powered to detect differences in the other races).

Four women (2.0%) had pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2*, which suggested a high risk of breast or ovarian cancer (Table 1). Subgroup analysis showed that the prevalence of pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* was significantly higher among women with unexplained infertility than among persons in the U.K. Biobank (odds ratio, 7.68; 95% CI, 2.04 to 20.45]) but not persons in the eMERGE Network (odds ratio, 2.99; 95% CI, 0.80 to 7.93). Six women (3.0%) had six different pathogenic or likely pathogenic variants (in five genes) associated with the risk of cardiovascular disease, and three women (1.5%) had pathogenic or likely pathogenic variants in genes causing miscellaneous disorders. One person had two pathogenic or likely pathogenic variants, and one had a pathogenic variant in *GLA* that can cause X-linked Fabry's disease (Table 1). Numerous rare variants of uncertain significance were also found in medically actionable genes (Table S4).

We investigated other highly penetrant pathogenic or likely pathogenic variants associated with serious life-altering phenotypes and identified 20 such variants in 21 participants

(10.7%), none of whom were among the 13 who had pathogenic or likely pathogenic variants in medically actionable genes; we confirmed the variants by Sanger sequencing (Table S5). These variants cause neurologic, ophthalmologic, renal, and hypogonadal disorders, among others (Table S3), which were much more common in our study population of women with unexplained fertility than in the general population (Tables S6 and S7).

Our findings support a genetic link between infertility and future medical illness. Pathogenic variants in medically actionable genes are highly penetrant and hereditary and have substantial effects on health. The fact that most of the variants we found among the women in our study were in genes that (when variant) confer a risk of hereditary cancers and cardiovascular disease is consistent with previous findings. Links between infertility and medical illness are plausible for cancer (*BRCA1* and *BRCA2*) but are less clear for cardiovascular disease (see the Supplementary Discussion).

The strengths of our study include the large sample of rigorously characterized women with unexplained infertility, the exome sequence analysis (which is unbiased), and the confirmation of variants by Sanger sequencing. Weaknesses include the homogeneous sample (predominantly White women) and the lack of detailed family history and follow-up. Although we do not recommend exome sequencing for women with unexplained infertility at this time, our finding that approximately 17% of the women with infertility in our study had pathogenic or likely pathogenic variants suggests that future medical illness may have a genetic component.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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.