New mutation linked to ovarian cancer can be passed down through dad

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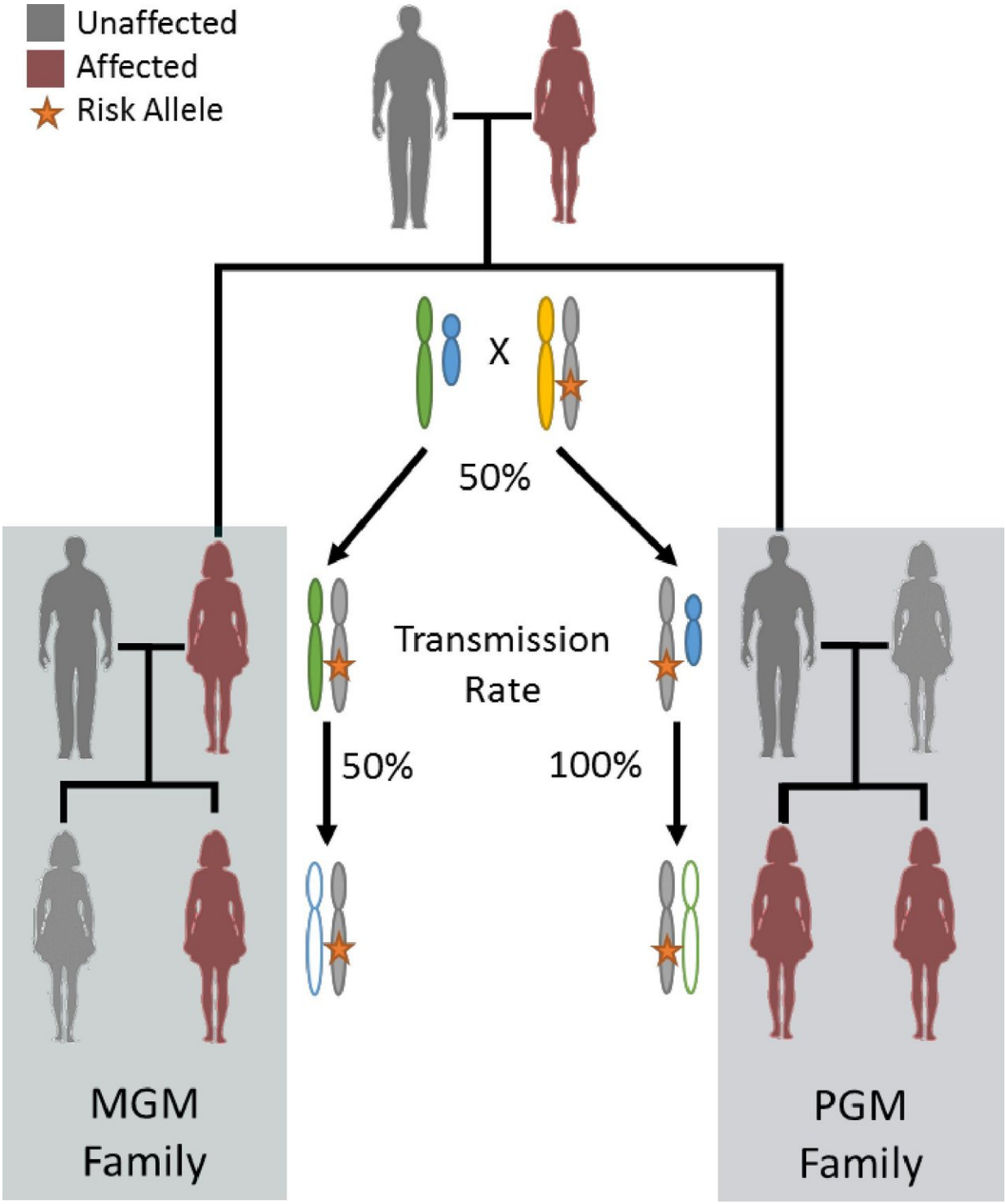

Fig 1. X-linked model. Schema for X-linked inheritance when cancer status is specific to women (all carrier men are effectively disease censored). Two family patterns with a pair of first-degree affected women are the maternal grandmother (MGM) family and the paternal grandmother (PGM) family.

Stratton's paradox implies that PGM families are more likely under X-linkage because a father must pass the variant to all of his daughters. The rates are equal if the variant is autosomal. Credit: Kevin H. Eng and colleagues

A newly identified mutation, passed down through the X-chromosome, is linked to earlier onset of ovarian cancer in women and prostate cancer in father and sons. Kunle Odunsi, Kevin H. Eng and colleagues at Roswell Park Comprehensive Cancer Center in Buffalo, New York, report these findings February 15th, 2018, in *PLOS Genetics*.

In earlier studies, researchers noticed that when a woman develops ovarian cancer, her sister faces a higher risk of also developing the disease than her mother, an observation they found difficult to explain. This observation led Eng and colleagues to investigate whether genes on the X-chromosome, potentially passed down through the father, may contribute to his daughters' risk of ovarian cancer.

Using the Familial Ovarian Cancer Registry, a donor-funded resource based at Roswell Park, the researchers collected information about pairs of granddaughters and grandmothers and sequenced portions of the X-chromosome from 186 women affected by the cancer. They found that cases of ovarian cancer linked to genes inherited from the paternal grandmother had an earlier age-of-onset than cases linked to maternal genes, and were also associated with higher rates of prostate cancer in fathers and sons. Additional sequencing led the researchers to identify a previously unknown mutation on the X-chromosome that may be associated with cases of ovarian cancer that develop more than 6 years earlier that average.

The study proposes that a gene on the X-chromosome may contribute to a woman's risk of developing ovarian cancer, independently of other

known susceptibility genes, such as the BRCA genes. Future studies will be needed, however, to confirm the identity and function of this gene. This observation suggests that there may be many cases of seemingly sporadic ovarian cancer that are actually inherited, and may lead to improved cancer screening and better genetic risk assessment.

"Our study may explain why we find families with multiple affected daughters: because a dad's chromosomes determine the sex of his children, all of his daughters have to carry the same X-chromosome genes," says Eng, an assistant professor of oncology in Roswell Park's Department of Biostatistics and Bioinformatics. What we have to do next is make sure we have the right gene by sequencing more families. This finding has sparked a lot of discussion within our group about how to find these X-linked families. It's an all-or-none kind of pattern: A family with three daughters who all have ovarian cancer is more likely to be driven by inherited X mutations than by BRCA mutations."

More information: Eng KH, Szender JB, Etter JL, Kaur J, Poblete S, Huang R-Y, et al. (2018) Paternal lineage early onset hereditary ovarian cancers: A Familial Ovarian Cancer Registry study. *PLoS Genet* 14(2): e1007194. doi.org/10.1371/journal.pgen.1007194

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