

Impact of Genetic Relatedness of Parents on Reproductive Outcomes

Megan Lynch^{1,2}, Kristin A. Maloney^{1,2}, Toni I. Pollin^{1,2,4}, Elizabeth A. Streeten^{1,2}, Erik G. Puffenberger⁵, Kevin A. Strauss⁵, Alan R. Shuldiner⁶, Braxton D Mitchell^{1,2,3}

¹ University of Maryland School of Medicine, Program for Personalized and Genomic Medicine, Baltimore, MD

² University of Maryland School of Medicine, Department of Medicine Baltimore, MD

³ Baltimore Veterans Administration Medical Center Geriatrics Research and Education Clinical Center, Baltimore, MD

⁴ University of Maryland School of Medicine, Division of Cardiovascular Medicine, Baltimore, MD

⁵ Clinical Laboratory, Clinic for Special Children, Strasburg, Pennsylvania

⁶ Regeneron Genetics Center LLC, Tarrytown, NY

*Presenting author: mlynch@som.umaryland.edu

Background & Objectives: Genetically isolated populations that have arisen due to recent bottleneck events have reduced genetic variation that reflects the common set of founding individuals. Members of such populations share increased genetic relatedness and are often enriched for recessive disorders that are rare in the general population. In this report, we evaluate, in the Lancaster Amish community, the impact of genetic relatedness of couples on reproductive health outcomes.

Method(s) and Results: We first identified 234 highly penetrant recessive conditions with known variants segregating in the community (Plain Insight Panel [PIP]) and used exome sequencing data to identify couples who are carriers for a PIP variant in the same gene. Reproductive outcomes were assessed by questionnaire. In addition, we evaluated whether genetic relatedness of parents across the genome, assessed by kinship coefficient (R), was associated with reproductive health outcomes. We found 300 out of 1824 (16.4%) couples at risk of producing a child with an autosomal recessive disorder. Carrier couples were more likely to report stillbirths (8.3% vs. 4.8%, $p=0.02$) although the number of children (6.3 vs. 6.4, $p=0.8$) or number of pregnancies (7.7 vs. 7.6, $p=0.4$) did not differ between groups. The mean R coefficient (\pm SD) between spouses in the Amish is 0.073 ± 0.017 , a larger value compared to randomly mating outbred populations ($R < 0.005$). We found that a higher relatedness between spouses was positively correlated with number of children ($p < 0.0001$), pregnancies ($p < 0.0001$), and stillbirths ($p=0.03$), although not with the number of miscarriages ($p=0.4$).

Conclusions: We assessed the impact of known highly penetrant recessive variants on reproductive outcomes and the association of pregnancy outcomes with overall relatedness between parents. These results highlight a complex association between relatedness of parents and reproductive health outcomes in founder communities.



Conflict of interest disclosure: Megan T. Lynch, Kristin A. Maloney, Toni I. Pollin, Elizabeth A. Streeten, Erik G. Puffenberger, Kevin A. Strauss and Braxton D. Mitchell declare that they have no conflict of interest. Alan R. Shuldiner is an employee of Regeneron Pharmaceuticals, Inc. and receives compensation as salary and stock options.

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