# Beyond Mendel: Study sheds new light on well-established theories of genetic inheritance

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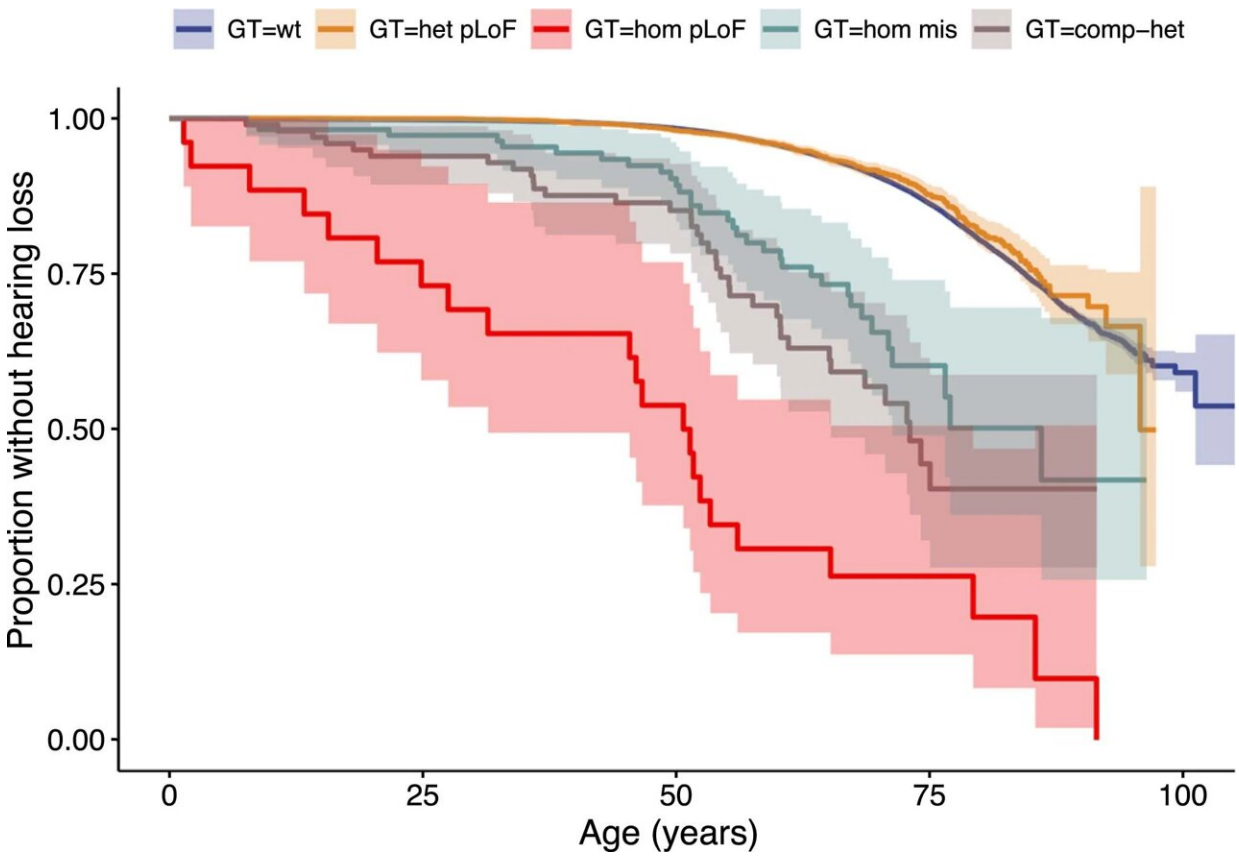


Age at first disease diagnosis of variant carriers in *GJB2* (survival plot). Wt, wild type; het, heterozygous; hom, homozygous; comp-het, compound heterozygous; GT, genotype. Genotypes of a known pathogenic missense and pLoF variant in *GJB2* associated with hearing loss. Comp-het carry both the pathogenic missense and pLoF variant on different alleles. Credit: *Nature* (2023). DOI: 10.1038/s41586-022-05420-7

A large-scale biobank-based study performed in Finland has discovered several new disease genes as well as new insights on how known genetic factors affect disease. The study highlights an underappreciated complexity in the dosage effects of genetic variants.

An international team of scientists led by researchers at the University of Helsinki and the Broad Institute of MIT and Harvard examined the effects of 44,370 genetic variants on more than 2000 diseases in almost 177,000 Finnish biobank participants. The study focused on so-called coding genetic variants, i.e. variants that are known to change the protein product of the gene.

The results of the study, published in *Nature* on January 18, 2023, convey that the reality of genetic inheritance is more complex than the Mendelian inheritance laws taught in biology classes all around the world.

What is special about the study, apart from the size of the data set, is that the team searched at scale specifically for diseases that one only gets if one inherited a dysfunctional genetic variant from both parents (recessive inheritance).

"Researchers usually only search for additive effects when they try to find common genetic variants that influence disease risk. It is more challenging to identify recessively inherited effects on diseases as you need very large sample sizes to find the rare occasions where individuals have two dysfunctional variants," explains Dr. Henrike Heyne, first author of the study from the Institute for Molecular Medicine Finland FIMM, University of Helsinki (now group leader at HPI, Germany).

However, the extensive FinnGen study sample, collected from Finland,

offers an ideal setting for such studies. The Finnish population has experienced several historical events that have led to a reduction of the population size and also been relatively isolated from other European populations. For this reason, a subset of dysfunctional and therefore potentially disease-causing genetic variants are present at higher frequencies, making the search for new rare disease associations of recessive inheritance easier.

Acknowledging this benefit, the researchers performed genome-wide association studies (GWAS) on 2,444 diseases derived from national healthcare registries, testing both additive and recessive inheritance models.

As a result, the team was able to detect known and novel recessive associations across a broad spectrum of traits such as retinal dystrophy, adult-onset cataract, hearing loss and female infertility that would have been missed with the traditional additive model.

"Our study showed that the search for recessive effects in genome-wide association studies can be worthwhile, especially if somewhat rarer genetic variants are included, as is the case in the FinnGen study," says Henrike Heyne.

In addition, the dataset has provided a new perspective on the inheritance of known disease variants. For rare disease genes, inheritance is traditionally almost exclusively described as recessive or dominant. The study shows, however, that the reality is somewhat more diverse.

The researchers found, for example, that some variants that are known to cause genetic disease with recessive inheritance also have some attenuated effects when only one disease-causing variant is present, which other studies confirm. They also find genetic variants with

beneficial effects (protecting from heart arrhythmia or protecting from hypertension) in genes that are associated with severe disease.

These results demonstrate that the so-called Mendelian laws based on the experiments with peas done in 1856, in a monastery garden near Brno (today Czech Republic) by the monk Gregor Mendel do not fully capture all aspects of inheritance of rare diseases.

"With the increased usage of carrier screening in the general population, whereby many individuals are learning that they are carriers for multiple pathogenic variants, understanding which of those variants may have mild health effects could be incredibly important for these individuals," says Heidi Rehm, an author on the paper and Professor of Pathology at Massachusetts General Hospital and Medical Director of the Broad Clinical Lab.

The study could contribute to the integration of the traditionally separate but more and more overlapping scientific fields that study either the effect of rare genetic variants on rare disease or the effect of common genetic variants on common disease. The results demonstrate how large biobank studies, particularly in founder populations such as Finland, can broaden our understanding of the sometimes more complex dosage effects of genetic variants on disease.

"This study highlights the importance of integrating the large-scale biobank approach with detailed insights that emerge from rare disease studies. A more complete understanding of the role of genetic variation in each gene only emerges when we take account of all of the perspectives and insights from diverse study designs," says Mark Daly, senior author on the paper and Director of the Institute for Molecular Medicine Finland (FIMM) and faculty member at Massachusetts General Hospital and the Broad Institute.

**More information:** Henrike Heyne, Mono- and biallelic variant effects on disease at biobank scale, *Nature* (2023). DOI: 10.1038/s41586-022-05420-7. www.nature.com/articles/s41586-022-05420-7

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