The genomic architecture of inherited DNA variants

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You have your mother's eyes and your father's smile, but genetics is much more than just what's on the surface. In a study that spans more than a decade, researchers at Baylor College of Medicine have looked at

generations of families in a specific population to reveal the role newly inherited DNA variants play on recessive disease traits, and in the process, they have created a population specific database revealing unique DNA information unseen in larger cohorts.

The findings, now published in *Genetics in Medicine Open*, revealed a correlation between occurrences of complex genetic disorders in those families with increased levels of consanguinity when compared to unaffected populations. Consanguinity is when both parents contribute similar genetic markers to an offspring, such as by sharing a common ancestor, and the genetic information from both the genome inherited from the father and that from the mother are identical.

"We observed that the areas on the chromosome known as ROH, regions of homozygosity, were longer in those individuals in which there was a higher degree of parental consanguinity when compared to those with less," said Dr. Zeynep Coban-Akdemir, postdoctoral associate in molecular and human genetics at Baylor and currently assistant professor at UTHealth School of Public Health as well as co-lead author on the study.

"We can see what is happening when consanguinity is at play and also when new genetic variations are introduced into the family unit of the clan or tribe representing more distant ancestors."

Dr. Xiaofei Song, a former Baylor graduate student now working as an assistant professor at Moffitt Cancer Center, said, "We further applied a statistical method to systematically assess the impact of these genetic variations on disease. Our results indicate that the newly introduced genetic variations can better explain the clinical features observed in our patients." Song also is co-lead author on the study.

"The published study contributes to the field of both rare disease and

population genomics. From a trainee perspective, the article provides a valuable resource for comprehending fundamental concepts of human genetics and applying diverse computational methods to elucidate these concepts," said Ph.D candidate Tugce Bozkurt-Yozgatli, with the Acibadem University in Istanbul, Turkey.

Coban-Akdemir, who worked in the Lupski Lab at Baylor where the research was conducted, says this is an important part of the findings because it reveals how genes act within different populations and clans to contribute to different recessive genetic disorders.

The population studied was a cohort of individuals originating from Turkey that is known to have different variations in genetic markers when compared to other populations from greater Europe.

Researchers created and analyzed a database of variants derived from exome sequencing, a genomics assay providing a glimpse into genetic variation genomewide, of 773 unrelated volunteers who were affected with various suspected rare Mendelian disease traits, which are diseases caused by a mutation in a single gene and clearly passed down from one generation to the next in accordance with Gregor Mendel expectations.

They were compared to another database created by the same researchers of 643 unaffected relatives.

Roughly half of the genetic variants in this Turkish group are not present in greater European control populations that are found in shared databases commonly used by genetic researchers.

"This group of Turkish individuals and families gives us insight into genetics that the average population doesn't provide. What we found in this Turkish population is very unique. Not only is this group underrepresented in larger databases, but it shows us that they have an

enriched genetic variation that is only seen within this population when compared to European populations," Coban-Akdemir said.

Dr. Davut Pehlivan, assistant professor of pediatrics—neurology at Baylor, said on a single individual there are about 40 million Watson-Crick base pair variations within our DNA.

"The Human Genome Project opened the doors for researchers to investigate entire genomic DNA complement using next-generation sequencing technology. However, more struggles appeared with these advancements. For example, it is hard to pinpoint which variant is causing disease among 40 million variations of our DNA. Studying healthy populations helps us to eliminate many of these common variations from consideration. Thus, we studied both patients and their healthy relatives in the Turkish population," Pehlivan said.

"There are a lot of changes in the genome, and we don't fully understand the meaning of all of those details, but the data from this population study will help all investigators around the world who are trying to interpret the results of other variants in the human genome DNA."

Pehlivan described gathering the information and families wanting to participate in genomics research beginning in 2010, traveling long distances to rural areas where the patients were mostly located, a human interest story itself, to make sure the database and clinical information would show an accurate representation for these families.

"We discovered more than 200 genes that contributed to the existing body of disease gene associations. This will help us get closer to understanding, in this population and in others, what is causing these diseases and the human biological perturbation underlying a broad scope of diseases.

"Our studies will open new avenues of research in human biology and genome biology and eventually help to potentially bring nucleic acid treatments, something used to develop the COVID vaccine, to the patients and families" Pehlivan said.

"This team of researchers is not just helping the population that they studied, but their findings also can be applied to many populations. We all are very different individuals on this planet, yet our genes act very similarly, and we all share a common humanity. So, understanding how genetic disorders work helps us to support affected families across the globe," said Dr. James R. Lupski, the Cullen Foundation Endowed Chair in Genetics and Genomics at Baylor.

In the past, Coban-Akdemir and Dr. Claudia M.B Carvalho, previously with Baylor and currently in her own laboratory at the Pacific Northwest Research Institute (PNRI) in Seattle who also contributed to this study, have worked on studying variants of genes to identify causes of diseases through production of truncated or altered proteins that take on a new or different function. Their work also focused on databases of populations with and without genetic disease.

Their current work reflects the importance of diversity and inclusion as work continues to reveal causes of genetic diseases.

More information: Zeynep Coban-Akdemir et al, The impact of the Turkish population variome on the genomic architecture of rare disease traits, *Genetics in Medicine Open* (2024). DOI: 10.1016/j.gimo.2024.101830

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