Shedding light on the state of genetic counseling for hereditary transthyretin-related amyloidosis

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Many forms of amyloidosis are caused by mutations in very specific genes that cause the misfolding of certain proteins, which ultimately misfold and aggregate. Though genetic diseases are normally not curable indefinitely, effective

treatments for amyloidosis exist. Thus, early detection via genetic counseling is extremely important. Credit: "202206 genetic counseling02" / Database Center for Life Science (DBCLS)

Early detection and treatment of hereditary transthyretin-related amyloidosis via genetic counseling are crucial. Yet, not all at-risk individuals seek genetic counseling, and management for presymptomatic carriers remains unclear. To tackle these knowledge gaps, a research team from Japan conducted a retrospective study on over 200 people who sought genetic counseling at a medical center, shedding light on the current advantages and limitations of current practices.

A paper reporting their findings, co-authored by Senior Assistant Professor Katsuya Nakamura, Dr. Tsuneaki Yoshinaga, and Dr. Yoshiki Sekijima from Shinshu University, was published online in the journal *Amyloid* on May 25, 2024.

Hereditary transthyretin-related amyloidosis (AATRv amyloidosis) is a rare inherited disorder in which the liver produces abnormal transthyretin (TTR) proteins due to a variant in the TTR gene. Like in other types of amyloidosis, these proteins tend to misfold and accumulate, forming harmful structures known as amyloid fibers. If left untreated, AATRv amyloidosis can cause problems in the heart and kidneys, as well as neurological damage.

Thanks to substantial progress in medical science, there are some treatment options available to people diagnosed with AATRv amyloidosis, such as getting a liver transplant or taking TTR stabilizer drugs.

If caught early, the progression of this disease can be slowed down. However, not everyone who is at risk of carrying a mutated TTR gene is willing to get proper genetic counseling for themselves or for their families, leaving many people potentially exposed to the damage caused by AATRv amyloidosis.

Against this backdrop, researchers from Japan decided to conduct a study aimed at gaining insights into the current status of genetic counseling and presymptomatic management among people at risk of developing AATRv amyloidosis.

In a retrospective study, the research team enrolled 202 participants who visited Shinshu University Hospital for genetic counseling regarding AATRv amyloidosis from April 1998 to March 2021.

"Despite the development of new and effective therapeutic drugs, we still encounter patients who are hesitant to share their genetic information with their families. Therefore, we decided to investigate the extent to which the at-risk family members of patients benefit from appropriate genetic care through genetic counseling," says Dr. Nakamura, explaining the motivation behind this work.

After analyzing the data recorded for these patients, the researchers found that 103 of the people who received genetic counseling (about 50%) were asymptomatic but at risk due to a family history of AATRv amyloidosis. Of them, only 83 actually underwent predictive testing, with 33 of them coming out positive. As for the other 20, the researchers could determine the reasoning behind their choices in most cases.

Worth noting, the team also monitored 31 of the 33 presymptomatic carriers, providing data on various aspects of their condition and treatment outcomes.

After reviewing the data, the researchers came to significant conclusions. They recognized that the way in which genetic testing is currently performed has several key limitations.

"As a result of the development of effective treatments and advances in disease elucidation, the number of presymptomatic carriers detected using targeted genetic approaches is expected to increase. Developing a less invasive and simpler method for monitoring that can be performed at any facility other than specialized amyloidosis centers is imperative," says Nakamura.

On the other hand, the findings suggest that a comprehensive clinical genetic approach combining genetic counseling, predictive genetic testing, and monitoring methods could be greatly beneficial for at-risk individuals.

Moreover, considering how stressful the mere possibility of carrying a diseased gene can be, the researchers emphasize that psychosocial support should also be provided collaboratively by genetic counselors and psychologists. Such guidelines may also be readily applicable to other genetic diseases.

"Ultimately, we hope many patients, at-risk individuals, and medical professionals can understand the significance of appropriately promoting this type of approach," concludes Dr. Nakamura.

More information: Katsuya Nakamura et al, Genetic counselling for at-risk family members with hereditary transthyretin amyloidosis: data from a single-centre study, *Amyloid* (2024). DOI: 10.1080/13506129.2024.2357094