

Loss of Y chromosome in blood cells associated with developing Alzheimer's disease

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Men with blood cells that do not carry the Y chromosome are at greater risk of being diagnosed with Alzheimer's disease. This is in addition to an increased risk of death from other causes, including many cancers. These new findings by researchers at Uppsala University could lead to a simple test to identify those at risk of developing Alzheimer's disease.

The results are presented today in American Journal of Human Genetics.

The loss of the Y chromosome (LOY) is known to affect up to 20 percent of men who are aged over 80, and is the most common genetic mutation acquired during a man's lifetime. Professors Lars Forsberg and Jan Dumanski, from the Department of Immunology, Genetics and Pathology at Uppsala University, and colleagues from Sweden, France, the UK, the US and Canada, investigated loss of the Y chromosome in over 3200 men with an average age of 73, and an age range of 37-96. Around 17 percent of them showed LOY in blood cells, and this increased with age. The researchers found that those with an existing diagnosis of Alzheimer's disease (AD) had a higher degree of LOY, and that LOY was also a marker for the likelihood of developing the disease during the follow-up period.

'The idea for this research project came to me when I was writing our first paper on the relationship between LOY and the development of nonblood cancers. In thinking about the process known as immunosurveillance - the body's ability to fight disease development throughout life - I found that it had been well studied in AD, and hence it occurred to me that LOY might be involved in this disease too,' says Lars Forsberg.

Using standard molecular techniques, the identification of LOY in blood is easy to determine when it occurs in 10 percent or more of blood cells with a nucleus containing DNA. As well as being relatively common in older men, it also occurs less frequently in those who are younger.



Since women do not carry a Y chromosome, and men have, on average, shorter lives, it is possible that LOY may be related to the earlier death of men. However, the researchers say, the mechanisms and causes for their findings are still not properly understood. They are currently investigating the functional effects of LOY, and looking at its role in different groups of men and in other diseases, in order to understand better which types of cancer are associated with LOY, as well as whether there is a link with early signs of dementia, for example <u>mild cognitive impairment</u>.

Another question to be answered relates to how LOY in blood cells can be related to disease in other organs.

'The blood cells we studied are involved in the immune system, and the fact that LOY in them is associated with disease in other tissues is striking. We therefore hypothesise that the loss of LOY in blood cells leads them to lose part of their immune function,' says Jan Dumanski.

Previous research by the same group has shown that smoking greatly increases the risk of acquiring LOY, by as much as 400 percent. However, smoking appears to have a transient effect, and is also dosedependent, so quitting could reverse the effect. This could be important to emphasise in smoking-cessation programmes, the researchers say.

More difficult to tackle is the question of diagnosis and treatment of serious conditions such as AD and cancer. This is currently based on identifying clinical symptoms, and the development of diagnostic tools for their earlier detection could lead to strategies aimed at preventing their development before symptoms occur. For example, in the future it might be possible to use an LOY test to identify men at risk and then carry out oncological or neurological evaluations to try to detect early, mild, symptoms of disease. LOY might also become an important diagnostic tool in combination with other biomarkers that may be used to



predict risks for various diseases.

'The addition of LOY testing in the general population could give medical practitioners the possibility of using preventive strategies in men at risk. For example, in cancer, primary tumours are usually not deadly; it is the metastatic process that it normally responsible for deaths. If we could predict which men have an increased risk of cancer, we could watch them closely for the development of disease and also use appropriate preventive treatments. In short, the widespread use of LOY testing could radically decrease male mortality rates, and even perhaps eliminate the difference in life expectancy between the sexes,' says Lars Forsberg.

More information: *American Journal of Human Genetics*, Dumanski et al.: "Mosaic loss of chromosome Y in blood is associated with Alzheimer's disease" www.cell.com/ajhg/fulltext/S0002-9297(16)30149-5, DOI: 10.1016/j.ajhg.2016.05.014

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