

## When bad news are good news for neurodegenerative diseases

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FAP was initially called "the feet disease" due to the 1st symptoms appear in the lower limbs. Credit: How Soon Ngu

Some genetic diseases caused by an abnormal repeat in the DNA are known to become more severe with each new generation - this dreadful trait is called anticipation. Now a study by Portuguese researchers from



Porto University has proved, for the first time, the existence of anticipation in diseases caused by a different type of error in the fatal neurodegenerative disorder Familial Amyloid Polyneuropathy (FAP).

The discovery has two major implications: First, it opens the door to the possibility that many more diseases could show anticipation, including Alzheimer's and cancer. Second, and no less important, Carolina Lemos, Alda Sousa and colleagues' discovery that although FAP, a fatal incurable disease, becomes worse from generation to generation, there is a positive side. If we can unveil the mechanism of how disease worsens, we might be able to stop it, and also predict the age of disease onset to establish a transmission pattern to help patient management. And in fact, the study, published in the *Journal of Neurology, Neurosurgery and Psychiatry*, has already found an effect of gender on FAP onset with men having the disease and further unveiling this pattern.

FAP is a progressive and fatal <u>neurodegenerative disorder</u> without a cure or a clear mechanism. As in many age-related neurodegenerative disorders including Alzheimer's and Parkinson's, the disease is linked to deposits of a mutated protein on neurons which later die, compromising the functions they normally control. In FAP, the mutation occurs in a liver protein called transthyretin (TTR) and the affected neurons belong mostly to the autonomic nervous system, which controls many of our nonconscious visceral functions. As consequence, the initial symptoms include a tingling followed by loss of sensation in the lower limbs that spreads to the rest of the body as the nerve destruction continues, eventually reaching the autonomic functions crucial to our survival. This means trouble for things like breathing and heartbeat that, unless the disease is stopped, result in death in as little as 10 years.

The problem is that so far, there is no effective treatment for FAP – until recently, options were limited to liver transplants. Donor organs are



difficult to find, and the procedure implies life-long medication and the threat of tissue rejection. In 2011, a new drug called Tafamidis (which binds the <u>mutated protein</u>, stopping its aggregation) was made available, and while it only delays the disease's progression, if initiated early enough, it can arrest the nerve damage even if it cannot cure FAP.

To make things worse, although the disease is rare, it can have incredibly high incidence devastating entire communities in which it occurs. A good example is Póvoa de Varzim and Vila do Conde, two of the most affected areas of Portugal (where FAP was first described), where 1 in every 1000 individuals has the disease, and 1 in every 538 are carriers of the mutated gene.

All this indicates that the possibility that FAP had anticipation, if true, could represent a potentially important tool to understand the disease and, at a minimum, help patients' management.

With this aim in mind, the teams leaded by Alda Sousa decided to look into the largest database of FAP patients in the world, property of the Hospital de Santo António in Porto, Portugal. It documents 2440 FAP patients from 572 families over 70 years, since the disease was first described in the 60s in Portugal. From these, Lemos and colleagues used 926 pairs of parents and children, from 284 different families across Portugal. What they discovered was a remarkable pattern of disease transmission.

FAP normally appears in adulthood, but the researchers discovered that much depended on when the patients' parents had the disease. For example, while most parents with late-onset disease (after 50 years of age) had early-onset children (around 40 years of age), no early-onset parent had late-onset children. Furthermore, the risk of having a very early onset (before 30 years of age) was high for the children of parents with an early onset (around 40 years of age), but null for those with



parents developing FAP in their 70s. Finally, the older the parents were when the disease appeared, the lower the probability that their descendants developed early or very early disease. The results were analysed statistically to assure that the differences were real, and the conclusion indicated a clear pattern of children developing the disease earlier than their parents, proving that FAP showed anticipation.

Interestingly Lemos and colleagues also saw that women tended to have later disease than men, whether among parents or children, revealing an effect of gender on FAP onset. This was confirmed by the observation that sons from affected mothers had the larger anticipations (difference between parent-child age of disease onset), while father-daughter pairs showed almost none.

Until now, anticipation had only been proved in diseases caused by abnormal repeats of a piece of DNA, which are highly unstable, and, as they pass between generations, tend to multiply even more, causing an increase in disease severity. FAP, however, results from a point mutation (which if the TTR gene is seen like a beads necklace, it is a change in a single bead) and yet also shows anticipation. This proves anticipation as a real biological phenomenon, opening the possibility that it might exist in many other disorders.

Lemos says, "Our results can have some important implications for other diseases caused by point mutations as well, since these mechanisms of anticipation (independent of repeat expansions) are still mysterious." This suggests a new path in the study of neurodegenerative disorders linked to age, which not only show a similar disease mechanisms to FAP (deposits of abnormal proteins killing neurons) but which have already been suggested to have anticipation.

For those carrying the TTR mutation, to prove the existence of anticipation and a gender effect reveals a pattern of disease transmission



that will allow better counselling, and, most importantly, earlier detection and treatment, a crucial factor for Tafamidis 'effectiveness. Lemos says, "Now that we gained more insight into parent-of-origin effects, a strategy to identify genetic modifiers should focus on families, rather than individuals, aiming to unravel the mechanisms of anticipation"

Although what causes <u>anticipation</u> in FAP is still a mystery, there are suspicions that it could result from several interacting factors in different families, including effects from other genes, epigenetic mechanisms (inherited mechanism that do not involve DNA change, for example, an environmental influence) and/or hormonal effects. This last possibility has gained support with the present study showing that the age of disease onset seems to be different for women and men.

"Our current strategies are to search for genetic modifiers, within or closely linked to the TTR gene and to study candidate-genes, associated with TTR pathways that may also be influencing age of onset," says Lemos. "We are also looking for epigenetic mechanisms that may explain the observed variability in the different generations."

After all, if we can understand why neural death starts earlier, we might be able to stop it.

**More information:** "Overcoming artefact: anticipation in 284 Portuguese kindreds with familial amyloid polyneuropathy (FAP) ATTRV30M." Carolina Lemos, Teresa Coelho, Miguel Alves-Ferreira, Ana Martins-da-Silva, Jorge Sequeiros, Denisa Mendonça, Alda Sousa. *J Neurol Neurosurg Psychiatry* jnnp-2013-305383P. ublished Online First: 17 September 2013 DOI: 10.1136/jnnp-2013-305383

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