A Quest for the genes: Down syndrome and Alzheimer disease

A summary of the article by Frances Wiseman, Laura J. Pulford, Victor L. J. Tybulewicz, Elizabeth M.C. Fisher by Claudia Cannavo*

Down syndrome is a complex condition characterized by intellectual disability, facial dysmorphology, and a range of other phenotypes that vary across the population. It is caused by the presence of three copies of chromosome 21, which is called trisomy 21. Since people with Down syndrome develop Alzheimer disease more frequently than the general population, it may be suggested that one of more of the genes present on chromosome 21 cause the development of AD. The APP gene is the main candidate; however, our group hypothesized that other genes on chromosome 21 could also contribute to disease development. The authors wanted to test this hypothesis by comparing a mouse model of AD with a mouse model of AD that had an extra partial copy of chromosome 21, with the APP gene missing. Using this model the team showed that an extra copy of chromosome 21 genes other than APP worsens some aspects of AD pathology. This is an important step towards increasing our understanding of the causes and mechanisms of AD in people who have DS.

Background

Down syndrome (DS) is a genetic disorder caused by an extra copy of human chromosome 21 (Hsa21), and people with DS have a greatly increased risk of developing Alzheimer disease (AD) in later life (1). AD is a neurodegenerative disorder and the most common cause of dementia, accounting to up to 80 % of cases. It heavily affects memory, behavior, mood and, eventually, basic vital functions. People who have AD experience a decline in cognitive function and develop amyloid plaques and neurofibrillary tangles, toxic protein aggregates in their brain which cause damage to brain cells (2). AD represents an enormous burden for individual affected, their caretaker's and society. There is no current known cause nor treatment for it, which makes it essential to focus on its research.

Hypothesis

Since AD occurs more frequently in people with DS than the general population, it is likely that one or more genes found on chromosome 21 can promote the development of AD. The APP gene, which produces the APP protein from which amyloid plaques are formed, is located on chromosome 21. Having three copies of APP in the absence of trisomy 21 causes AD without DS, confirming the importance of APP in the development of AD. The authors of the paper hypothesize that an extra copy of all genes on chromosome 21 except for APP might show a different development of AD.

Methods

To test their hypothesis, the authors compared a mouse model of amyloid beta (Aß) accumulation (tgAPP) to a mouse model of Aßaccumulation that also had a triplication of 75% of chromosome 21 genes (trisomic;tgAPP). Importantly, the additional 75% of Hsa21 did not include the APP gene, which was thus present in two copies. This made the trisomic;tgAPP mouse model ideal to assess the effect of trisomy of chromosome 21 genes other than APP. The tgAPP mouse develops amyloid plaques that model the early stages of AD development. Aß is one of the derivatives of APP, and the main component of amyloid plaques. It can be present inside the cells or outside; in addition, it can exist in different lengths that have different toxicity for the brain. In the paper, these characteristic elements of AD pathology were analyzed to assess how the extra copy of

* Claudia Cannavo
email: skgtcc6@ucl.ac.uk
Department of Neuromuscular Diseases, Institute of Neurology, UCL

chromosome 21 altered the development of amyloid pathology.

Results

The study resulted in several interesting findings. First, the trisomic;tgAPP mouse presented an increased number of amyloid plaques compared to the tgAPP mouse (Figure 1). In addition, the deposition of Aß inside cells was also increased. Furthermore, the ratios of the type of Aß fragments (long versus short) were altered by trisomy 21 and this was shown to correlate with increased Aß aggregation. These results suggest that other genes on chromosome 21 can contribute to the development of AD in people who have DS. The study also gives insights on possible mechanisms of AD development in the context of trisomy 21. In fact, no change was found in the clearance of Aß or in the activity of the proteins that produce Aß and other fragments from APP (Figure 2). Thus, it is very likely that the increase in number and size of amyloid plaques in the trisomic;tgAPP mice is due to the augmented production of Aß42, the longer and more toxic fragment of Aß.

Discussion

The importance of the study lies in the use of the known genetic origin of DS, which also leads to AD, to understand more of the unknown causes and mechanisms of AD. In addition, some of the changes observed by the authors – for example, the increased accumulation of amyloid plaques in trisomic;tgAPP mice – has also been observed in people with DS. Since the authors hypothesize that the changed ratios in Aß fragments could explain the more severe AD pathology observed in the trisomic;tgAPP mice, it could be interesting to verify this factor in the DS population. Together, data from mice studies and patients could lead to a more focused attempt to determine which gene or genes on Hsa21 contribute to the development of AD, thus providing great insights into the mechanisms of both AD and DS.

From Science to Society

Our research wants to pin down the genetic causes of AD in the DS population to gain a better understanding of the mechanisms of AD development. By acting on the specific pathways that lead to the formation of AD pathology, it could be possible to slow disease development by targeted therapy suitable for the specific needs of people who have DS.

Conclusion

Chromosome 21 genes other than APP have a role in the development of Alzheimer disease pathology in Down syndrome. Further studies could identify the identity of these genes and the mechanisms altered.

References

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Take home message

- Down syndrome (DS) is caused by trisomy of chromosome 21. Since people with Down syndrome also develop Alzheimer disease (AD), this suggests that one or more of the genes present on chromosome 21 causes the development of AD. The APP gene is the main candidate.

- The paper shows that chromosome 21 genes other than APP could contribute to the development of AD in people who have DS, and provides insights on possible mechanisms leading to AD pathology.

- An increased knowledge of the genetic causes of AD in DS could potentially lead to a comprehension of the mechanisms of AD development, thus increasing the chances of finding a cure for AD in people who have and also do not have DS.