

## **The Sex Controversy in Alzheimer's Disease: Are we Looking at the Wrong Chromosome?**

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Alzheimer disease (AD) is the most common cause of senile dementia [1] and represents a complex and progressive neurodegenerative disorder of the human brain. Among the first genetic lesions found to be specifically associated with Alzheimer's disease are aberrations in chromosome number and/or structure, primarily in chromosomes 21,14 and 1 and secondary changes in the sex chromosomes [2]. So, when looking on the research that has been done on AD one can ask: "Are we on the right track by focusing on the genetic switch that brings Familial Alzheimers Disease (FAD) and Sporadic Alzheimers disease (SAD) to be expressed through genes that are only located at the chromosome 21 and / or 14/1?".

Simply, are we looking at the right chromosome/s, like 21 and 14, or are we missing something in this complex picture that we call AD?

Extensive research has been done on how the APP gene on chromosome 21 wakes up neurodegeneration in neuronal cells that leads to FAD and/or SAD [1] (for review see MA Smith., *et al.* 1998). So, how does this explain the sex differences in AD. Women are 1,5 x more prone to AD and also deteriorate faster than men once the onset of the diseases becomes detectable [3]. One hypothesis state that these differences are acquired by the aging of the ovaian-pituitary axis and their related hormones [4]. Supplemental hormonal therapy addresses these issues [5], but still shows that more knowledge is needed or there is a more fundamental change in the cell. Second, the results of hormone replacement studies suggest strongly that hormone replacement increases AD risk, the opposite of what was predicted [5].

### **The X chromosome**

The candidate for our mystery chromosome is the X chromosome. The X chromosome is unique, it harbors 5% of the genes in the genome, of which more than 50% are related to neuronal issues [6]. Aging activates a number of instabilities that may affect the X chromosome. The most prominent is aneuploidy [7-10], then centromere instabilities or premature centromere separation [11] thus altering the secondary role of cohesion in neurons that are always in the interphase. These changes affect the topological arrangement of the X chromosome of which expression of genes can be affected [12,13]. Interestingly these changes are found to be reflected in the peripheral blood lymphocytes [7,8].

On the hand of epigenetics, alteration on the centromeres and skewing of the X chromosome [14] have been detected in cerebral cortex and in peripheral blood lymphocytes of women with AD [7,9]. Centromere cohesion proteins have been proposed as an mechanism of the re-entry cell cycle activation in Alzheimer's disease [10,15,16].

Looking at the another part of the story, or the hand of genetics, is the finding by Minerva., *et al.* [17] in a Genome wide association study (GWAS) study that women do express a risk gene on the X chromosome, the protocadherine 11 or PCDHX11 gene (PCDHX proteins are very alike cadherin neuronal receptors. These receptors are known to group at the synaptic junction and interestingly are related to presenilin dependent processes).

The GWAS study showed that an alteration of five SNIPs on the X chromosome in a gene named PCDH 11 to be a susceptibility gene for AD. Still, other authors haven't confirmed these first GWAS studies [18,19]. One of the reasons that we postulate is that PCDHX11 is highly associated with X chromosome skewing, an epigenetic alteration of the inactivation process of the X chromosome, suggesting a hypothesis that an epigenetic alteration on the inactivation centers of the X chromosome (or skewing) relates not only to aging, but might be a novel property that puts women at greater risk of AD than men [14].

Wilson., *et al.* 2007 [20] showed that PCDHX11 replicates asynchronously in male and female cells. Replication asynchronization is often associated with allele specific mode of expression which originates from imprinting, chromosome X inactivation or other mechanism that may go toward monoallelic expression. These processes might be the cause of the discrepancies between the GWAS studies concerning the PCDHX11 gene.

Most importantly, the line of work based on the sex hormone hypothesis has not led to treatments for AD, suggesting a need to consider alternative hypotheses linking female sex and AD risk. Findings from several lines of research implicate sex differences in the stress response as a promising candidate [21]. Takayuki K and Shigeru O, 2013 reported that Bisphenol A (BPA) changed the expression of X chromosome inactivation regulating factors, thus altering the expression levels of X linked neurodevelopmental related genes. An extensive review has been published linking stress to aneuploidy [22]. Therefore, environmental factors, such as endocrine disruptors can alter the epigenetic expression of the X chromosome in women, giving a strong molecular mechanism of women's susceptibility to AD pathogenesis.

### Conclusion

To understand AD in the context of aging we may state in reference to chromosome 21, and 14, the X chromosome becomes important not due to its genetic alterations but to its unique epigenetic properties to manifest instability such as premature centromere division, aneuploidy, asynchronous replication, territorial imbalances and X chromosome skewing.

To our view these overall changes give a new view into the sex difference in AD and ultimately, these sex differences could be put fruitfully to use by guiding the development of biomarkers sensitive to early signs of AD neurodegeneration.

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