Chromosome gains and losses in the human brain are probably less important than previously thought

In general, each human cell contains 46 chromosomes: 23 chromosomes from each parent. Before a cell divides all chromosomes are duplicated. The cell has several mechanisms to ensure that during cell division the chromosomes are evenly distributed over the two daughter cells. However, when one of these mechanisms fails, a cell can lose or gain copies of one or more chromosomes. The resulting incorrect number of chromosomes is called aneuploidy.

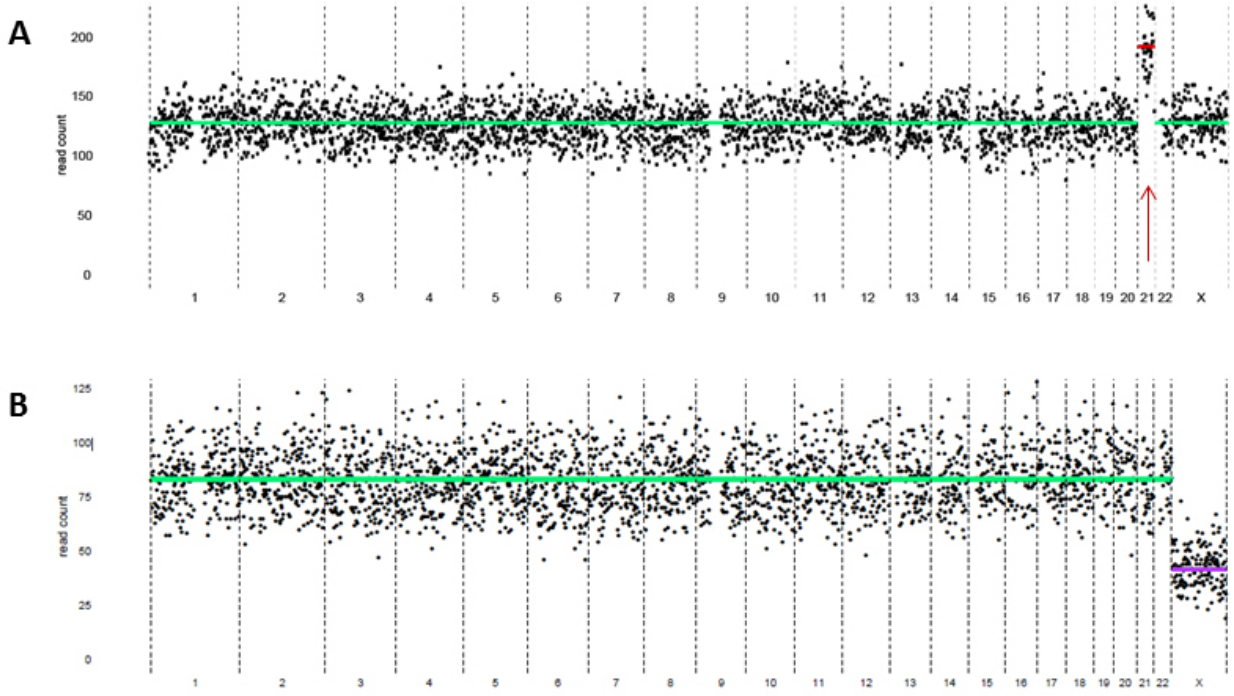

Fig. 1. A) A cell from a woman with Down syndrome: this cell has 3 copies of chromosome 21 and two X chromosmes. B) A cell from a man with Alzheimer's disease: this cell is not aneuploid and has one X chromosome. Colours represent the number of copies present of each chromosome. Purple; one copy, green; two copies, red; three copies.

Aneuploidy is mostly known from systemic trisomies such as Down syndrome, people having an extra copy of chromosome 21, and cancer. Interestingly, aneuploid cells have also been found in the human brain. Studies suggest that the number of aneuploid cells is increased in brains affected by Alzheimer's disease. Based on these studies it has been hypothesized that aneuploid cells can play a role in Alzheimer's disease. If a cell has an extra chromosome, the genes on this

chromosome will likely be transcribed and translated into proteins. These extra proteins have to be processed to prevent the formation of protein aggregates. However, when cells are unable to deal with the protein imbalance, this can lead to protein aggregation. Alzheimer's disease is characterized by such protein aggregates in the brain. The possibility that aneuploidy in brain cells could therefore be involved in Alzheimer's disease seemed an interesting possibility.

In our study we describe a single-cell sequencing (sc-seq) method to very precisely count the number of copies of each chromosome present in an individual cell. We isolate cells, cut the DNA in small pieces and 'read' the fragments, called sequencing. We then determine for each of these fragments from which chromosome the fragment came. By counting the number of fragments of each chromosome we can thus determine how many copies of each chromosome were present in individual cells. This is a major improvement compared to previous methods that mostly rely on the binding of short fluorescently-labeled DNA fragments to a specific spot on a chromosome (Fluorescence in situ hybridization, FISH). In contrast to FISH, we can determine the copy number of *all* chromosomes in a cell and along the full length of the chromosomes. We confirmed the accuracy of our method by sequencing single cells from an individual with Down syndrome and clearly detected the extra copy of chromosome 21.

When we then counted the chromosomes in large numbers of individual brain cells from elderly people with and without Alzheimer's disease, we found very limited aneuploidy in healthy aged individuals and no increase in Alzheimer's patients, despite the high accuracy of our method.

Our results are in line with other sc-seq studies, which also report low levels of aneuploidy in the normal human brain. Our study is the first that uses sc-seq to investigate aneuploidy both in normal brain as well as brain affected by Alzheimer's disease. In our study, we sequenced more than 1500 cells, many more than the previous sc-seq studies. However, our results are in contrast with the earlier FISH studies that showed substantial aneuploidy in human (Alzheimer's) brain samples. We can think of two possible explanations: 1) FISH has a higher background, due to failure to bind or non-specific binding of the labeled DNA fragments, resulting in false positive aneuploid events or 2) we cannot formally exclude that we missed rare cells that were responsible for the aneuploid events detected in the FISH studies.

In conclusion, we report low levels of aneuploidy in human neurons, with no increase in Alzheimer's disease. Therefore, our results do not support an important role of aneuploidy in the normal human brain and the pathogenesis of Alzheimer's disease.

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