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Discovery of somatic recombination events in APP and analysis of its occurrence

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Motivation and Aim: Neurodegeneration is one of the most severe diseases. And it was distinguished that it is caused by protein misfolding into a specific amyloid structure and following aggregation and loss of function. Amyloid structure represents a cross-∝-structure, possessing uniquely stable and resistant features. Several proteins are known to cause neurodegeneration, from which amyloid ∝ (A∝) is the most crucial. Despite the urgency of disease, any effective therapy and even diagnostic system have not been created yet. Recent diagnostics system is based on already identified genetic markers – mutations in specific proteins-coding genes: amyloid precursor protein (APP), presenelin 1, presenelin 2. Which, indeed, lie in the protein misfolding processes and following aggregation and amyloidization. Though do not possess high specificity.
Recently, a new mechanism of APP amyloidization and, thus neurodegeneration development, was proposed [1, 2]. It was shown that neurodegeneration could be initiated by an event called somatic recombination. Commonly, this event is described as being responsible for antibody variation production and immune system reactivity. And is contributed by abnormal exon-exon recombination of specific V, D and J segments, leading to the formation of non-canonical splice variants. However, the exact mechanism and recombination positions have not been designated. In this work we created a new algorithm for somatic recombination searching and provided hypotheses of possible mechanisms.
Methods and Algorithms: We utilized open-access genomic sequencing data of human brain (SRR7905480 ID) to search in it all possible paired exon-exon combinations of APP gene. Before the search the filtration of raw data with 23-mers generated from APP sequences was implemented. After which the alignment of combinations on filtered genome by bwa algorithm was provided. From gained overlappings only with the highest coverage were taken into the following analysis. With obtained coordinates the insertion regions were determined. Further each insertion was analyzed on correlation with structural genomic elements, which was taken from annotation data. And the intersection of coordinates was applied as the method. For each insertion the area up and down ~100 bp was also searched for. Gained distributions then were compared with Kolmogorov-Smirnov test to define significant correlations, including the domain information of Aβ protein from PDB database.
Results: We established that, indeed, amyloid precursor protein is affected by somatic gene recombination events in the human genome. From all possible pair-to-pair exons combinations only 5 % have a high raw reads coverage. From which combinations of exon 7 with exons 6, 9 and 10 appeared to be the most frequent. We also identified that recombinations were spread through the whole genome of chromosome 21 with a

tendency to the start of the APP gene. We additionally estimated the correlation between insertion positions distribution and structural genome elements which revealed the association between recombination insertions and such structural elements as: VDJ-segments, recombination patterns and mobile genetic elements.

Conclusion: Based on these findings, we proposed that indeed somatic gene recombination exists in the case of APP gene. And the whole genome of chromosome 21is affected by APP exons recombinations. The most recombinant exon 7 could possess a sufficient role in recombination events and even disease development. And these events could be caused by sided VDJ-segment recombinations and mobile genetic elements transposition.

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