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INTERNATIONAL RESEARCH AGENDA

LECTURE

DISCOVERY OF AN UNUSUAL HIGH NUMBER OF DE NOVO MUTATIONS IN SPERM OF OLDER MEN USING DUPLEX SEQUENCING

by Prof. Irene Tiemann-Boege, PhD

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Monday, 27th of January 2020 at 10 am

CMN Smoluchowskiego 17 street, seminar room nr **CMN_1/D/15**

Abstract

De novo mutations (DNM) are an important player in heritable diseases and evolution, yet little is known about the different mutagenic processes in our germline. We have adapted an ultra-sensitive sequencing technology, also known as duplex-sequencing (DS.), that renders sequence information on both DNA strands resulting in a detection sensitivity of one mutation in 10^7 sequenced bases. With these extremely low error-rates we identified accurately DNMs in a selected region of FGFR3 in sperm DNA from old and young donor groups. We have found within a ~6000 nucleotide-region, representing mainly exons of the FGFR3, highly mutable sites with mutation frequencies 4-5 orders of magnitude higher than genome average. Most of these mutations occur in different donor pools, are missense mutations, and are associated with congenital disorders or have been described in the COSMIC database to be associated with tumorigenesis. Mutations found in both old and young donor groups show higher frequencies in older donors, suggesting that these mutations expand in the male germline with paternal age. Our approach is an important strategy to identify driver mutations in genes of the receptor tyrosine kinase pathway. Driver mutations expanding in the male germline is one of the strongest mutagenic mechanisms described so far, and with unexplored consequences in a society with delayed parenthood.

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