B·DEBATE International Center for Scientific Debate BARCELONA

Sant Joan de Déu HOSPITAL MATERNOINFANTIL - UNIVERSITAT DE BARCELONA

Sant Joan de Déu Research Foundation

JUDITH ARMSTRONG

CV

PARTICIPANT AT:

CONNECTING THE GROWING BRAIN

UNDERSTANDING NEUROPAEDIATRIC DISEASES THROUGH SYNAPTIC COMMUNICATION

November, 26th-27th, 2015, Barcelona

Judith Armstrong, Facultative-Research scientist, Hospital Sant Joan de Déu, Barcelona, Spain

The research group in Rett syndrome has more than 20 years of experience. Dr. Armstrong is formed entirely in the field of Neurogenetics and hereditary neurological disease started in the studies of fragile X syndrome, work done during the past year in the Laboratory John F. Instituttet Kennedy, Denmark, under the direction of Dr. Grønskov and that meant obtaining a Masters degree in Human Genetics. She completed her doctoral training with Rett syndrome at Hospital Sant Joan de Deu de Barcelona, under the direction of Dr. Monros and the turning of the Tissue Bank for Neurological DNA of ICS Institute of Neuropathology (2003-2007), Hospital de Bellvitge under the direction of Dr. Ferrer and Dr. Volpini. Today and since 2008 she is Facultative-Research scientist in Section of Genetics and Molecular Medicine, Hospital Sant Joan de Deu de Barcelona and belongs to CIBERER U-703, responsible for research and molecular diagnosis of Rett Syndrome. Along with Dr. Pineda and since 2008, has resumed research projects in the RTT in the area of Molecular Genetics at the Hospital Sant Joan de Deu de Barcelona.The Rett Syndrome Group of the Hospital Sant Joan de Deu is a center of reference at national level, both clinical and molecular, logging more than 500 cases of RTT patients with clinical and genetic diagnosis confirmed

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ABSTRACT

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Genetic Tools Focused on Diagnosis

NGS technology has enabled to develop methodologies for the capture of all the genome coding regions (>20,300 coding gene in GRCh28), termed as whole-exome sequencing (WES). The success in WES comes by the exome-captured regions and its coverage. The weakest point in WES is that the capture of target sequences is not uniform across the genome. In consequence, a fraction of the coding regions could remain unsequenced. False-negative and false-positive rates are higher than in targeted panels, adding a layer of complexity and uncertainty to the diagnosis. Post NGS, powerful bioinformatics tools are used to assess all the high throughput data. The sequence analysis follows specific and versatile bioinformatics pipelines with quality control steps, read cleaning, assembly, annotation and SNP calling. Variant analysis is a constant game of filtering in and out depending on the specific traits of a pedigree. Generally, selecting an inheritance mode and ruling out common SNPs present in the databases, the list of candidate genes reduces drastically. Subsequent study and selection of candidates implicates the fusion of biological and clinical criteria. Whole-genome sequencing (WGS) overpasses these limitations of the WES, since the capture step is not necessary. However, its application in the clinical diagnosis is at present very limited. Nevertheless, these two approaches may be optimal for elucidation of molecular basis of new diseases. Targeted-capture NGS strategies may be of choice for a first step molecular studies of intellectual disability, autism spectrum disorder, neuropaediatric diseases in general and for Rett syndrome (RTT) in particular. Because the targeted region is smaller, gene panel strategies present an improvement in contrast to WES, as better sequence coverage can be achieved. For clinical diagnosis, this approach is highly valuable not only for detecting mutations, but also for being capable to rule out candidate genes as causative of the pathology, and consequently, a positive or negative diagnostic report for physicians and families may be done. Thus, the lack of false-negative results assures a major reliability, indispensable in the diagnostic field. Deeper coverage also favors the detection of copy number variants, which should also be ruled out in target genes, taking into account that NGS approaches do not display all kinds of genetic variation susceptible to cause a disease. Our experience in clinical and genetic diagnostic with RTT using targeted-NGS by panel of genes allow us to study a larger number of genes associated with RTT simultaneously, significantly reducing response time and the cost of the study. It also allows us to study other related clinical RTT and thus to redirect the clinical diagnosis to another disease genes: Angelman syndrome, Pitt-Hopkins syndrome, Dravet syndrome,....Verification by Sanger sequencing of the progenitors of the mutations detected by NGS remains essential for their characterization as well as perform functional studies.

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