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Centro Riferimento Regionale per il controllo e la cura della Sindrome di Down e delle altre patologie cromosomiche e genetiche
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Research Project Title: ***"DE***ciphering ***N***eurodevelopmental **D**isorde***R***s through the ***ITE***ms of undiagnosed rare diseases. The **DENDRITE** Study"

Background

During the past decade, advances in genetic research have enabled genome wide discovery of chromosomal copy-number changes and single-nucleotide changes in patients who developed neurodevelopmental disorders. These technological advances — which include array comparative genomic hybridization, single-nucleotide-polymorphism genotyping arrays and next generation sequencing — have transformed the approach to the identification of etiologic genes and genomic rearrangements. In the meantime the most recent acquisitions, such as the Whole Exome/Whole Genome massively sequencing technologies, have transformed our understanding of genomic variation and its relevance to health and disease enabling the rapid discovery of single-gene causes across disciplines and, deserving as blueprint to widen the scope of new diagnostic and therapeutic tools. Expanding the current knowledge into neurosciences represents the future major goal in research since its related diseases, especially those that arise during the developmental age, have been highlighted as the most frequent reasons for medical referral and/or diagnostic workup. Indeed, neurodevelopmental disorders have an incidence of 1 in 66 to 1 in 100 children in Western countries and a delay in diagnosis has been associated with an indirect increased financial cost to families. Early and appropriate access to interventions have been the

only so far demonstrated to gain patients' long-term outcomes and, to reduce lifetime costs for individuals, families and society. Thus, since taken together they represent one of the most health burdens in the current clinical arena, our research project will contribute to bridge the existing gap of their molecular basis and etiologic factors.

Rationale and Aims

Accurate diagnosis is the cornerstone of good medical care. However, the chance of achieving a genetic diagnosis for a child with severe developmental delay is low where no diagnosis is apparent after routine investigation – yet the majority of children with developmental disorders fall into this category. Although individually rare, collectively these conditions represent a significant burden for individuals, families, and health services. In the past decade whole genome microarray analysis has already proven valuable for identification of large pathogenic copy number variants (mostly deletions and duplications) in children with developmental disorders, but most children remain yet undiagnosed. In many cases, the condition is caused by a de novo mutation that occurs spontaneously in the affected child somewhere in the genome, and if there is no family history for the condition the genetic basis of the diagnosis can be easily overlooked. Whole Exome/Whole Genome massively sequencing technologies have transformed our understanding of genomic variation allowing the rapid discovery of several single-gene disorders especially in the neurodevelopmental field. In this view scientists need robust datasets to generate high-quality genomic data, filtering out a very large number of probably benign variants, prioritizing plausibly pathogenic variants, and linking these findings to individual clinical data for interpretation and appropriate clinical follow-up. Indeed, health-related findings from a human genome could potentially include thousands of variants pertaining to hundreds of different conditions, almost none of which provide clinically useful information for a specific individual. Hence, first step toward addressing the above mentioned challenges is to separate potential genomic findings into those that are pertinent to a particular disease investigation and those that are non-pertinent (or incidental) to that disease. Hence, the major aim of this study will be the DNA collection from small amounts of blood and/or saliva of trios (proband and his/her parents) and/or quads (proband, his/her parents and siblings) belonging to a homogeneous patients' cohort that have been subjected to an extensive diagnostic workup, in accordance to the current guidelines (CGH array, inherited errors of metabolism examinations, etc..) which failed in recognize any known etiologic causes. This workflow will generate a neurodevelopmental disorders' DNA series

accustomed to be tested thorough Whole Exome/Whole Genome massively sequencing technologies both in-house and/or in collaboration across National and International Network and Consortia (i.e. The ASID - Autism Spectrum/Intellectual Disability international consortium), high specialized leading Academic Medical Centers and or/ teaching Research Hospitals (such as University of Washington's Department of Genome Science, USA and/or The Seattle Children Hospital, USA) and/or joining relevant ongoing project (such as The University of Washington PANGEA Project - Project Assessing New Genetic Exploration in Autism) in order to communicate pertinent findings to individual research participants and minimizing those incidental findings that will not communicate to the participants.

Patients' recruitment

Probands and his/her parents and/or siblings will be recruited if the patient meets at least 2 of the following criteria:

1) Neurodevelopmental disorder diagnosis

2) Congenital anomalies

3) Abnormal growth parameters (height, weight, occipitofrontal circumference)

4) Dysmorphic features

5) Unusual behavioral phenotype

6) Genetic disorder of significant impact for which the molecular basis is currently unknown or those disorders whose neuro-phenotype is known being less impinged than the observed one in the probands' framework.

These criteria are focused on congenital or early onset phenotypes, and are specifically designed to maximize the chance of finding a highly penetrant monogenic cause for the child's condition. This study will be performed collecting small amounts of blood and/or saliva from trios (proband and his/her parents) and/or quads (proband, his/her parents and siblings). Samples will be achieved under patients and/or parents' consent (hereby attached) according to the Helsinki Doctrine for Human Experimentation and according to the Italian Laws which including also the "Codex on the protection of personal data" (DL n°196, 30/06/2003). Feedback of only potentially neurodevelopmental/syndromic causal variants will be reported to the families and communicate

with appropriate counselling regarding recurrence risk, likely prognosis, and potential clinical management. Moreover DNA samples, clinical, diagnostic and genetic information collected could be shared with National and International registries, network and consortia (stated above) with the dual aims of assisting the translation of new high-throughput genomic technologies into clinical practice, and elucidating the underlying genetic architecture of developmental disorders. However, all this information will be stored in a de-identified, coded, way to keep proband's personal identity a secret. Finally, the de-identified information could be shared also with an NIH repository called Database of Genotypes and Phenotypes (dbGaP) that has been established to archive, as well as share with qualified scientists, data from studies centered on the interaction of genotype and phenotype.

Expected results, including potential therapeutic/clinical applications

Despite substantial progress on understanding the role played by deleterious variants and their effector proteins on pathological mechanisms of cognitive disorders, few therapeutic interventions have been proposed so far. In this context connecting clinical and functional data underlying NDD disorders represents a fundamental step in research and diagnostic field. Overall, we expect that our research projects will give new insights in the physiopathology of NDD disorders. The characterization of the molecular bases underlying these conditions, through recent genomics technologies, will open a new window on the dynamics that constantly shape and reshape our central nervous system and that are impinged in neurodevelopmental disorders.

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