

Genetic analysis of developmental dyslexia in an Italian cohort: preliminary data

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Developmental dyslexia (DD) is a neurodevelopmental disorder defined as a persistent failure to acquire efficient reading skills despite normal intelligence, sensory capabilities, and adequate education. DD is a heritable multifactorial disorder where genetics and environment factors affect the neurobiological, neuropsychological, and behavioral level of a person.

We aimed to characterize, from a genetic point of view, a cohort of Italian children with isolated DD or DD coupled with dysorthographia and/or dysgraphia and/or dyscalculia. We created a panel of the most common and best characterized genes involved in DD: *CMIP*, *CNTNAP2*, *CYP19A1*, *DCDC2*, *DIP2A*, *DRD2*, *DYX1C1*, *FMRI*, *GCFC2*, *KIAA0319*, *KIAA0319L*, *MRPL19*, *ROBO1* and *S100B*. These genes were sequenced by a Next Generation Sequencing (NGS) platform of Life Technologies company (Ion Torrent Personal Genome Machine). Using a custom bioinformatics pipeline we prioritized the identified variants to validate by Sanger sequencing.

So far, 63 families with at list one child affected by DD were involved in the study. We collected saliva samples from 36 children with DD and 46 children with DD accompanied by Specific Learning Disorders (SLDs) (plus 10 adults). A total of 92 samples were collected (63 children; 19 brothers and sisters; 6 parents; and 4 other relatives). In our series females/males ratio is 1:1.6 (31:51). A total of 71 DNA samples (2 children certificated without DD; 64 affected children and 5 affected brothers and sisters) were sequenced by NGS.

Overall, we identified 5286 variants in 4 genes. A custom bioinformatics pipeline coupled by a HotSpot panel composed by all known SNPs (dbSNP v144) in the target regions was applied. Prioritizing the 5286 identified variants by the pathogenicity and the literature, we selected 145 of them. These variants are present in 58 children and distributed in 11 genes/regions: *CMIP*, *CNTNAP2*, *DCDC2*, *DIP2A*, *DRD2*, *DYX1C1*, *DYX1C1-CCPG1*, *GCFC2*, *KIAA0319*, *KIAA0319L*, *ROBO1*.

Interestingly, we confirmed 4 strongly DD-associated polymorphisms identified in 50 children: 1) rs57809907 in *DYX1C1* gene (a stopgain variant in 15 children); 2) rs17819126 in *DYX1C1* gene (a nonsynonymous variant in 5 children); 3) rs3743205 in *DYX1C1-CCPG1* 5' UTR overlapping region (a ncRNA exonic variant in 9 children); and 4) rs4504469 in *KIAA0319* gene (a nonsynonymous variant in 42 children).

Moreover, we identified 7 novel variants (MAF \leq 0.0016), with 2 stopgain, 2 splicing and 3 frameshift variants, in 33 children and 7 novel nonsynonymous variants (MAF \leq 0.0021) in 7

children to validate with Sanger sequencing. Finally, 2 of the nonsynonymous variants were also candidate as potential causative variants for alternative splicing.

Summarizing, we performed a first mutation screening in 71 Italian children using a custom DD-related gene panel. The unknown variants identified, but not yet confirmed, could be or not to be related with DD or DD with other SLDs. A largest cohort must be screened and finally an accurate genotype-phenotype association must be done.

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