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Hyung-Goo Kim et al., J Spine Neurosurg 2018, Volume 7
DOI: 10.4172/2325-9701-C7-030

International Conference on
ALZHEIMERS, DEMENTIA AND RELATED NEURODEGENERATIVE DISEASES
December 03-04, 2018 Madrid, Spain

Comparative genomic mapping implicate LRRK2 for intellectual disability and autism at 12q12 and HDHD1 as well as PNPLA4 for X-linked intellectual disability at Xp22.31

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We report a genomic and phenotypic delineation for two chromosome regions with candidate genes for syndromic intellectual disability at 12q12 and Xp22.31. Fine mapping of six unreported small informative Copy Number Variations (CNVs) narrowed down the chromosomal interval to one gene LRRK2 at 12q12. Expression studies revealed high levels of LRRK2 transcripts in whole human brain, cerebral cortex and hippocampus. RT-qPCR assays revealed that LRRK2 transcripts were dramatically reduced in our micro deletion patient compared to his healthy grandfather with no deletion. The decreased expression of LRRK2 may affect protein-protein interactions between LRRK2 and its binding partners, of which 8 have previously been linked to intellectual disability. These findings corroborate with a role for LRRK2 in cognitive development and thus, we propose that intellectual disability and autism displayed in the 12q12 micro deletion patient are likely caused by LRRK2. This is in stark contrast to the late-onset Parkinsonism caused by the same gene with an average onset age of 53 years. We identified one additional minimal candidate region demarcated by a micro deletion DCP250361 at 12q12. Among the four genes deleted, we propose TWF1 as a likely candidate gene for intellectual disability and craniofacial anomalies. Furthermore, we refined the known candidate gene region encompassing three genes to one gene NELL2 with one micro deletion patient DCP139. Through the genomic and clinical delineation of six reported and nine unreported cases at Xp22.31, we propose HDHD1 and PNPLA4 for X-linked intellectual disability. High transcript levels of these two genes in the human brain substantiate their role in intellectual functioning.

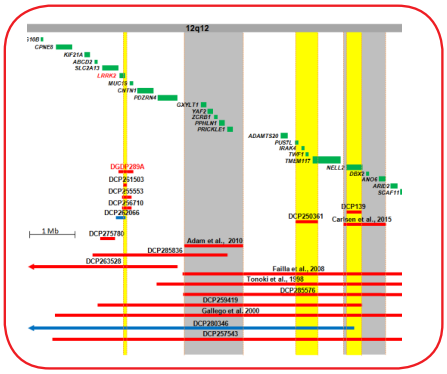

Figure 1: Comparative deletion mapping of CNVs at 12q12. Twenty four genes residing in this 8.2 Mb chromosomal region are displayed. 13 unreported DECIPHER cases and our micro deletion DGDP289A is displayed with five published cases. DGDP289A has a micro deletion involving only LRRK2 and MUC19. CNV mapping with three micro deletions and one micro duplication from DECIPHER database along with DGDP289A suggest LRRK2 as a likely candidate gene. Micro deletions are represented by red bars, while micro duplications are in blue. The four chromosomal segments with gene deletions likely producing clinical features such as developmental delay/intellectual disability and autism are highlighted in yellow (new candidate gene regions) and in gray (reported candidate region).

Biography

Hyung-Goo Kim is a Senior Scientist at Qatar Biomedical Research Institute. His current focus is in identifying new disease genes for neurological disorders to elucidate their underlying mechanism.

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