

Abstract 4

MUTATIONS IN HUMAN RAB39B GENE ARE RESPONSIBLE FOR X-LINKED NON-SPECIFIC MENTAL RETARDATION

Maila Giannandrea¹, Veronica Bianchi¹, Maria Lidia Mignogna¹, Alessandra Sirri², Francesca Cogliati³, Silvia Russo³, Lidia Larizza³, Hilger H Ropers⁴, Jozef Gecz⁵, Charles E Schwartz⁶, Arjen PM de Brouwer⁷, Hilde van Esch⁸, Martine Raynaud⁹, Jamel Chelly¹⁰, Daniela Toniolo² and Patrizia D'Adamo¹

Dulbecco Telethon Institute, Dibit - San Raffaele Scientific Institute, Milano, Italy¹.

Dibit - San Raffaele Scientific Institute, Milano, Italy².

Istituto Auxologico Italiano, Milan, Italy³.

Department of Human Molecular Genetics, Max Planck Institute for Molecular Genetics, Berlin-Dahlem, Germany⁴.

SA Pathology, Women's and Children's Hospital, North Adelaide, South Australia, Australia⁵.
JC Self Research Institute of Human Genetics, Greenwood Genetic Center, Greenwood, South Carolina, USA⁶.

Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands⁷.

Centre for Human Genetics, University Hospital Leuven, Leuven, Belgium⁸.

Unité de Génétique CHU Bretonneau, Tours, France⁹.

Institut Cochin (IC), Département de Génétique et Pathologie Moléculaire GDPM, Equipe de Génétique et Physiopathologie du Retard Mental GPRM, Paris, France¹⁰.

X-linked non-specific mental retardation (XLMR) is a common human disorder characterized by mental handicap as the only clinical symptom. Different mutations in 30 X-linked genes have been identified to date. Recently, we identified two independent mutations in Rab39b gene in two MRX families. The first mutation affects the 5' splice junction of intron 1 (GT/AT) and the second one produces a premature stop codon. However, each mutation leads to a Rab39b loss of function. Rab GTPases act as molecular switches between an active GTP-bound state and an inactive GDP-bound conformation. More than 60 different Rab proteins are known, and their general role is to control the intracellular trafficking in the exocytic, endocytic and recycling pathways. Between the Rab proteins, some have a well-known function in specific vesicular traffic pathways, while the role of some others is still not identified. Rab39b is one of the Rab proteins with unknown function and to understand how the lack of Rab39b could be involved in the pathology of XLMR, we characterized its expression profile and its cellular localisation and identified a possible role in neuronal cells. In situ hybridisation and Rab39b mRNA expression profiling by real-time PCR revealed that Rab39b is predominantly expressed in brain, particularly in neurons. In order to identify the vesicular traffic route regulated by Rab39b, we over-expressed the protein in HeLa, Cos7 and mouse hippocampal neurons. The co-localization with markers of Golgi compartments, suggested an involvement in the Golgi-related traffic. Moreover, in mouse hippocampal neurons we observed the presence of Rab39b positive punctae along neurites. Finally, to mimic the effect of human mutations, we down-regulated Rab39b on hippocampal neurons by shRNA technology. Preliminary results showed that a 70% reduction of Rab39b did not affect the dendrite and axon formation. In contrast, we observed an enlargement of the cell body and growth cones plasma membrane. These results suggested that the role of Rab39b in neurons is to mediate retrograde trafficking important for neuronal polarization.