

Abstract 72

MUTATIONS IN THE FOXG1 GENE CAUSE THE CONGENITAL VARIANT OF RETT SYNDROME.

Ilaria Meloni¹, Francesca Mari¹, Maria Antonietta Mencarelli¹, Ariele Spanhol-Rosseto¹, Rosangela Artuso¹, Dalila Rondinella¹, Nadia Bahi-Buisson², Juliette Nectoux², Robert Rubinsztajn², Thierry Bienvenu², Anne Moncla³, Brigitte Chabrol³, Laurent Villard⁴, Zita Krumina⁵, Judith Armstrong⁶, Ana Roche⁶, Mercè Pineda⁶, Bruria Ben-Zeev⁷, Eva Gak⁸, Francesca Ariani¹, Alessandra Renieri¹.

1 Medical Genetics, Department of Molecular Biology, University of Siena, Italy

2 Université Paris Descartes, CNRS (UMR 8104), Institut Cochin, Inserm U567, Paris, France

3 Inserm U910, Université de la Méditerranée, Assistance Publique Hôpitaux de Marseille, Hôpital de La Timone, Marseille, France

4 Inserm U910, Université de la Méditerranée, Faculté de Médecine de La Timone, Marseille, France

5 Medical Genetics Clinic of Latvian State, Children's University Hospital, Latvia

6 Hospital Sant Joan de Déu, Esplugues, Barcelona, Spain

7 Pediatric Neurology, Dana Children's Hospital, Tel Aviv Medical Center, Tel Aviv, Israel

8 Sagol Neuroscience Center, Sheba Medical Center, Tel Hashomer affiliated to the Sackler School of Medicine, Tel Aviv University, Israel

Rett syndrome is a severe neurodevelopmental disorder representing one of the most common genetic causes of mental retardation in girls. The classic form of the disease is mostly caused by mutations in *MECP2*. By candidate gene approach, we recently identified *FOXG1* as the gene responsible for the congenital variant of Rett. *FOXG1* encodes a brain-specific transcriptional repressor, essential for early telencephalon development, that exhibits an expression pattern in the postnatal cortex partially overlapping with that of *MeCP2*. Sixty *MECP2/CDKL5* mutation-negative European Rett patients (classical and variants), 43 patients with encephalopathy with early-onset seizures and 4 atypical Rett patients were analyzed for mutations in *FOXG1*. *FOXG1* mutations were identified in 4 patients, independently classified as congenital Rett variants from France, from Spain and from Latvia. Clinical data were compared with the two previously reported *FOXG1* mutated patients. In all cases there was an early onset of symptoms. In the perinatal period the girls were floppy, passive and easy to cry. Deceleration of head growth started before the fourth month and led to severe microcephaly. Motor development was severely impaired and the voluntary hand use was absent. In contrast with classic Rett, patients had poor eye contact. Typical stereotypic hand movements with hand-washing and hand-mouthing activities were constant and present all time. Some patients presented tongue movements. Jerky movements of upper limb were also present. Brain MRI showed corpus callosum hypoplasia in most cases, while epilepsy was a variable sign. Scoliosis was usually severe. Neurovegetative symptoms typical of Rett were frequently present.