Genetic studies of children with mental retardation

Saideh Rajaei
Department of Medical and Clinical Genetics, Institute of Biomedicine
The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden, 2013

Mental retardation (MR) is characterised by significant limitations in intellectual function and adaptive behaviour. It is estimated that MR affects up to 3% of the population in Europe. Patients with MR are an aetiologically heterogeneous group. Approximately 25-35% of the patients have a genetic diagnosis. In the last decade, the introduction of molecular karyotyping has proved to add new and important data for MR diagnosis.
In this thesis, we have undertaken extensive genetic analysis for two groups of children with MR. In the first study, a group of fourteen clinically diagnosed early infantile onset Rett Syndrome patients were included. The aim for this patient group was to identify possible pathogenic genetic variations. The second study was population-based and included children (born 1987–1998; 46 000 children) living in the Swedish County of Halland in 2004. 133 patients with SMR were identified and then divided in four categories depending on timing of onset; prenatal, perinatal, postnatal and undetermined timing. 23 patients within the prenatal group (included 82 patients in total), were still undiagnosed. The aims were; firstly to investigate whether the aetiological prevalence and co-morbidity of SMR, as well as the male: female ratio in Scandinavia had changed over time. Secondly, to investigate the impact of new genetic methodology, like molecular karyotyping, on the number of diagnosed children with SMR.
In the early infantile onset RTT patients we found a *MECP2* deletion (1/14) with the initial screening, and molecular karyotyping (SNP array) found three (3/14) copy number variations with uncertain significance.
The SMR study showed the same prevalence as previous Scandinavian studies (2.9 per 1000). The molecular karyotyping resulted in diagnosis of 5/19 patients of the previously undiagnosed patients from the prenatal group, which increased the frequency of diagnosed patients from earlier 4% (using traditional analysis methods) to 22.5% (this study). Furthermore, we identified *MECP2* duplication syndrome in a female patient with mild to moderate MR and two brothers from the SMR study. These results imply that *MECP2* duplication is a pathogenic CNV in both genders, thus, there are phenotypic differences in females and males. Risk for recurrence is 50% for boys and less for girls because of incomplete penetrance.
In conclusion, this thesis investigates the genetic causes of two specific groups of patients with mental retardation. This follow up is essential for prognosis, management, and genetic counselling which permit prenatal diagnosis and determination of recurrence risk.

Key words: *Mental retardation, Rett syndrome, RTT, early onset infantile RTT, MECP2, SMR, SNP array, copy number variations, CNV, MECP2 duplication syndrome*

ISBN: 978-91-628-8614-1 *http://hdl.handle.net/2077/31714*

Genetic studies of children with mental retardation

Akademisk avhandling

Som för avläggande av medicine doktorsexamen
vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen
försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg
fredag den 8 mars 2013, kl 13:00

av
Saideh Rajaei

Fakultetsopponent: Professor Jaqueline Schoumans Pouw,
Intitute génétique medicale, Université de Lausanne, Switzerland

Avhandlingen baseras på följande arbeten:

I. Rajaei S, Erlandson A, Kyllerman M, Albage M, Lundstrom I, Karrstedt EL, Hagberg B. Early infantile onset "congenital" Rett syndrome variants: Swedish experience through four decades and mutation analysis. *J Child Neurol. 2011 Jan;26(1):65-71.*

II. Lundvall M, Rajaei S, Erlandson A, Kyllerman M. Aetiology of severe mental retardation and further genetic analysis by high-resolution microarray in a population-based series of 6- to 17-year-old children. *Acta Paediatr. 2012 Jan;101(1):85-91.*

III. Rajaei S, Kyllerman M, Albåge M, Erlandson A. Copy-number variations in early infantile onset Rett syndrome variants. *Manuscript in preparation*

IV. Rajaei S, Lundvall M, Hallböök T, Kyllerman M, Stefanova M, Erlandson A. *MECP2* duplication syndrome in three patients with aspects on phenotype and implications for genetic counselling. *Manuscript in preparation*

Göteborg 2013

UNIVERSITY OF GOTHENBURG