

## Abstract 60

### MUTATIONS IN *IQSEC2*, A GUANINE NUCLEOTIDE EXCHANGE FACTOR FOR ARF6, CAUSE NON-SYNDROMIC MENTAL RETARDATION

Cheryl Shoubridge<sup>1,2</sup>, Patrick Tarpey<sup>3</sup>, Fatima Abidi<sup>4</sup>, Sinitdhorn Rujirabanjerd<sup>1</sup>, Jackie Boyle<sup>5</sup>, Marie Shaw<sup>1</sup>, Alison Gardner<sup>1</sup>, Anne Proos<sup>6</sup>, Helen Puusepp<sup>6</sup>, Lucy Raymond<sup>7</sup>, Charles Schwartz<sup>4</sup>, Roger Stevenson<sup>4</sup>, Gill Turner<sup>5</sup>, Mike Field<sup>6</sup>, Anna Hackett<sup>5</sup>, Andy Futreal<sup>3</sup>, Mike Stratton<sup>3</sup>, Jozef Gécz<sup>1,2</sup>

Genetics and Molecular Pathology, SA Pathology<sup>1</sup> and Department of Paediatrics, The University of Adelaide<sup>2</sup>, Adelaide, Australia; Cancer Genome Project, Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK<sup>3</sup>; J.C. Self Research Institute, Greenwood Genetic Center, Greenwood, South Carolina, USA<sup>4</sup>; GOLD NSW, Hunter Genetics, Newcastle, Australia<sup>5</sup>; RNSH, Kolling Institute of Medical Research, St Leonards, NSW<sup>6</sup>; Cambridge Institute of Medical Research, Cambridge CB2 2XY, UK<sup>7</sup>

As part of the recently completed effort of X-chromosome exon re-sequencing in families with X-linked mental retardation (Tarpey et al., Nat Genet 41(5):535-43, 2009) we have identified unique changes in the guanine nucleotide exchange factor (GEF) for the Arf family of GTP-binding proteins, the *IQSEC2* gene (also known as *BRAG1*). We identified four unique single nucleotide substitutions. Three of these; c.2587C>T/p.R863W (MRX1), c.2402A>C/p.Q801P (MRX18) and c.2273G>A/p.R758Q (an unpublished US family) occur within the Sec7 domain of *IQSEC2*. The fourth change, c.1075C>T/p.R359C (an unpublished Australian family) lies in the IQ domain of *IQSEC2*. All four changes segregate with the MR phenotype in the respective families and were not found in 200 other cases from the study or >200 controls. Mouse *Iqsec2* has been found at excitatory synapses as part of the postsynaptic protein complex with PSD-95 and NMDA receptors and functions as a GEF for Arf6 and also Arf1 (Sakagami et al., Neurosci Res 60(2):199-212, 2008). We show that the Sec7 domain changes affect *IQSEC2* protein function through compromised GEF activation of ARF6. Based on this data we postulate these changes to be deleterious to the function of *IQSEC2* and suggest that *IQSEC2* is a novel gene implicated in non-syndromic XLMR. We predict that these *IQSEC2* mutations impact on the ARF6 mediated regulation of dendritic differentiation through actin cytoskeleton organisation and membrane traffic.

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