"Identification of a gene causing Infantile Spasms in individuals with Williams-Beuren syndrome and large deletions"

The hemizygous deletion of a 1.55 Mb region of chromosome 7q11.23 causes the neurodevelopmental disorder Williams-Beuren syndrome (WBS) (1). WBS is characterized by numerous physical, cognitive and behavioural symptoms, but seizures have been only rarely reported and are thought to be unrelated to the deletion (2). Larger deletions have been reported, often with one breakpoint that is identical to those associated with the common WBS deletion (3-7). We have performed fine mapping and genotype-phenotype correlation in a collection of more than 30 individuals with larger deletions of 7q11.23, most of which extend toward the telomere. Fine mapping of the deletions in these cases has been performed using both quantitative real-time (qRT) PCR and comparative intensity analysis with Affymetrix SNP microarrays (8). By aligning the deletions along the genomic structure of this region of the chromosome, we have defined a new locus for Infantile Spasms, spanning the MAGI2 gene. The MAGI2 protein is part of the synaptic scaffold of neuronal dendrites and axons and is proposed to be involved in the trafficking of ionotropic glutamate receptors to the post-synaptic membrane (9,10). The identification of a causative gene should allow the development of the first genetic mouse model of Infantile Spasms and eventually lead to the development and testing of targeted, effective medications for this severe epilepsy, both in its isolated form and in children with WBS.

References

1. Morris, C.A. (2006). The dysmorphology, genetics, and natural history of Williams-Beuren syndrome. In Williams-Beuren syndrome: Research, evaluation, and treatment, C.A Morris, H. Lenhoff and P. Wang, eds. (Johns Hopkins University Press, Baltimore, MD) pp. 3-17.

2. Tercero, M.F., Cabrera Lopez, J.C., Herrero, M.M., and Rodriguez-Quinones, F. (2005). Williams-Beuren syndrome and West "syndrome:" causal association or contiguous gene deletion syndrome? Am. J. Med. Genet. A, *133*, 213-215.

3. Mizugishi, K., Yamanaka, K., Kuwajima, K., and Kondo, I. (1998). Interstitial deletion of chromosome 7q in a patient with Williams syndrome and infantile spasms. J. Hum. Genet. *43*, 178-181.

4. Wu, Y.Q., Nickerson, E., Shaffer, L.G., Keppler-Noreuil, K., and Muilenburg, A. (1999). A case of Williams syndrome with a large, visible cytogenetic deletion. J. Med. Genet. *36*, 928-932.

5. Morimoto, M., An, B., Ogami, A., Shin, N., Sugino, Y., Sawai, Y., Usuku, T., Tanaka, M., Hirai, K., Nishimura, A. et al. (2003). Infantile spasms in a patient with Williams syndrome and craniosynostosis. Epilepsia *44*, 1459-1462.

6. Stock, A.D., Spallone, P.A., Dennis, T.R., Netski, D., Morris, C.A., Mervis, C.B., and Hobart, H.H. (2003). Heat shock protein 27 gene: chromosomal and molecular location and relationship to Williams syndrome. Am. J. Med. Genet. A *120*, 320-325.

7. Ferland, R.J., Gaitanis, J.N., Apse, K., Tantravahi, U., Walsh, C.A., and Sheen, V.L. (2006). Periventricular nodular heterotopia and Williams syndrome. Am. J. Med. Genet. A, *140*, 1305-11.

8. Marshall, C.R., Noor, A., Vincent, J.B., Lionel, A.C., Feuk, L., Skaug, J., Shago, M., Moessner, R., Pinto, D., Ren, Y. et al. (2008). Structural variation of chromosomes in autism spectrum disorder. Am. J. Hum. Genet. *82*, 477-488.

9. Deng, F., Price, M.G., Davis, C.F., Mori, M., and Burgess, D.L. (2006). Stargazin and other transmembrane AMPA receptor regulating proteins interact with synaptic scaffolding protein MAGI-2 in brain. J. Neurosci. *26*, 7875-7884.

10. Chen, L., Chetkovich, D.M., Petralia, R.S., Sweeney, N.T., Kawasaki, Y., Wenthold, R.J., Bredt, D.S., and Nicoll, R.A. (2000). Stargazin regulates synaptic targeting of AMPA receptors by two distinct mechanisms. Nature *408*, 936-943.