

Report from Genetic syndromes of the RAS/MAPK pathway; from Bedside to Bench and Back. Berkeley, California, August 1-2, 2009

This was the second research symposium organised in association with the International Costello Syndrome Support Group (ICSSG) and Costello Syndrome Family Network (CSFN) meeting, the first having occurred in Portland in 2007. This year there were as well an overlapping CFC International meeting, a Californian NF1 group meeting and the Noonan Syndrome Support Group meeting.

The research symposium was convened by Dr Kate Rauen from the University of California in San Francisco and Lisa Schoyer from the Costello Syndrome Family Network.

The meeting aimed to bring together clinicians and scientists working on the RAS pathway. The clinical review session was of necessity brief, and included reviews of Noonan syndrome by Judith Allanson, NF1 and Legius syndrome by David Stevenson, Costello syndrome by Karen Gripp and CFC syndrome by Giovanni Neri.

In Noonan syndrome, the responsible gene can now be identified in 70 % of patients. There are few genotype/phenotype correlations to guide testing. In SOS1 mutations, short stature may be less marked and the skin phenotype more striking. In RAF1 mutations, there is a high (75%) incidence of cardiomyopathy, and lentiginos may be striking. In LEOPARD syndrome, although mutations in PTPN11 are the commonest cause, mutations in BRAF and RAF1 have also been reported.

The review of Costello syndrome was informed by Karen Gripp's prospective study, commenced in July 2003. This has confirmed the malignancy risk as 15%, predominantly for embryonal rhabdomyosarcoma (60%) in children less than 6 years. There has been a single rhabdomyosarcoma in an adolescent. Neuroblastoma and bladder carcinoma in adolescence each account for 15 % of the observed tumours. Mutation testing has confirmed the presence of more severe and milder phenotypes, associated with less common mutations.

For CFC, mutation analysis has confirmed a high prevalence of cardiac involvement (80%), both hypertrophy (40%) and congenital heart disease (PS, ASD, VSD the commonest). Severe and often very prolonged feeding difficulty is common, as are seizures, abnormalities of the optic disc, cryptorchidism, renal malformations, and the well described differences of skin and hair.

Frank McCormick provided an excellent overview of the RAS/MAPK pathway. Although the relationship between Ras, Raf, Mek, Erk has been known for some time, it is relatively recently that the importance of PI 3' kinase in Ras signalling has been discovered. Development of treatments that interfere with pathway activity has been difficult because of the tight regulation of the pathway, and in particular the existence of feedback loops at a number of levels. Prediction of a therapeutic response requires knowledge of the upstream and down stream mediators and effects of each mutated protein, and these may be tissue or indeed cell specific.

A number of speakers addressed the biochemical and functional characteristics of the component genes, SHP2, Neurofibromin, SOS1, RAF1, BRAF, MEK and RAS. The available data confirms that the mutation consequences are not only mutation specific, but tissue and cell dependent. In addition, mutations of different function in animal models can produce identical phenotypes (ie gain of function identical to loss of function).

Marco Tartaglia presented an identical mutation in a new pathway gene, SHOC2, in 25 of 410 cases with a phenotype consistent with a pathway disorder but no known mutation. The cases included those described by Mazzanti et al (Am J Med Genet 2003) as "Noonan like syndrome with loose anagen hair."

Several speakers presented animal models of different pathway components. David Guttman discussed the mouse model of NF1 optic gliomas. Studies have shown that the only Ras hyperactivated in NF1 deficient glioma cells is KRas, with rapamycin (mTor) as the target pathway, demonstrating again tissue and cell specific effects.

The current therapeutic options for treatment of RAS/MAPK disorders were reviewed, both in terms of treatment trials and lessons to be learnt from chemotherapy.

This was an excellent and stimulating meeting. For those interested, the next research symposium in North America is being planned for the first weekend in August in Chicago in 2011.

Bronwyn Kerr, September 2009

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