

Report from M62 and Northern Genetics Forum, Manchester, 2nd July 2009

The M62 meeting, held six monthly in Manchester, welcomed attendees from as far afield as Dublin, Newcastle and Cardiff in July in addition to those from the core centres of Liverpool, Leeds, Manchester, Sheffield and North Wales. During the day we followed our usual format of a set piece on a designated chromosomal disorder, an invited talk and a discussion topic, interspersed with case presentations from the various centres. At this meeting, which is a little more informal than the national meeting, we encourage trainees in particular to present cases and give presentations to a friendly audience.

The chromosome presentation by Alison Kraus from Leeds was on the 15q24 microdeletion syndrome. This was first reported as a recurrent microdeletion syndrome by Sharp et al. (Hum Mol Genet 2007 Mar 1:16(5):567-72) with several further cases reported since then. Though the facial features are subtle, seeing a montage of all the reported cases convinced us that the face is recognisable, with the high hairline and the downslanting palpebral fissures being particularly noticeable. Other features which might provide a clue to this condition are the joint laxity/connective tissue features and the presence of diaphragmatic hernia as a marker, recently highlighted by Van Esch et. al. The 15q24 microdeletion is another imbalance which occurs due to non-allelic homologous recombination, with duplications of the same region also having been reported.

Our invited speaker was Philip Murray from the Department of Endocrine Sciences at the University of Manchester and he gave an overview of 3M syndrome, concentrating particularly on the genetic and endocrinological aspects of this disorder. Mutations in CUL7 at 6p21 which is involved in assembly of an E3 ubiquitin protein ligase complex were first identified in this condition in 2005 but the condition has since been shown to be heterogeneous. Murray worked with the group in Manchester to identify a second locus at 2q35-q36.1. A gene OBSL1 was identified within this region and Murray demonstrated elegantly how loss of OBSL1 leads to downregulation of CUL7, suggesting that both proteins act in the same molecular pathway. Patients with OBSL1 mutations are phenotypically indistinguishable from those with CUL7 mutations. All are of short stature with a relatively well-preserved head size, and have classical features of anteverted nares, frontal bossing and mid-face hypoplasia. Prominent heels were also present in both groups. Work is ongoing, with the possibility of further genes being identified. Those who have families to contribute to this study can contact Philip.murray@manchester.ac.uk.

And what about the cases? We had about 30-40 cases, including some which were very instructive. These included conditions which are relatively new to dysmorphologists such as an infant with SMARD, spinal muscular atrophy with respiratory distress. SMARD is heterogeneous, with SMARD1 caused by mutations in IGHBP2 gene usual causing respiratory distress with an onset between six weeks and six months and it was pointed out that eventration of the diaphragm is a good marker for this condition. Some infants present with multiple congenital contractures. Another interesting presentation concerned two patients with learning disability, multiple naevi and fleshy palms to the hands where a diagnosis of CFC syndrome had been suspected in both. In fact they both turned out to have the recurrent 17q21 microdeletion syndrome,

A family was presented where a child had presented with bilateral cleft lip and palate and lip pits. There was no family history of clefting or lip pits. The diagnosis of Van der Woude syndrome seemed clear and a new dominant mutation seemed possible, but a detailed family history revealed that the child's mother was born with ankyloblepharon. An IRF6 mutation was confirmed in the mother, reminding us that ankyloblepharon can be a feature of the VDWS, as well as of popliteal pterygium syndrome and non-penetrance in VDWS is relatively common.

As a final discussion topic we reviewed recently published and presented work on the use of microarray analysis pointing out in particular the difficulties of interpretation, particularly of duplications, which can have long range effects.

A study of the phenotypic characteristics of the patients who have undergone microarray analysis in Manchester for investigation of learning disability had shown that compared to the group where no array abnormality was identified, the group proven to have pathogenic imbalances were more likely to have behavioural features. Seizure and clefting were also seen at a higher frequency. Interestingly, microcephaly was no more common in the group with positive findings.

Feedback from the meeting was good and it gave us all a chance to network over lunch. The next meeting will be held on Friday January 15th 2010. Once more it will be at the Nowgen building in Manchester. The programme will be circulated nearer the time. Visitors are welcome, but please contact Jill.Clayton-Smith@cmft.nhs.uk if you are intending to come. In the meantime the M62 group will convene for the Northern skeletal dysplasia meeting in Leeds on the 14th October 2009.

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