## 031 ACTIVATING MUTATIONS IN STIM1 AND ORAI1 CAUSE OVERLAPPING SYNDROMES OF TUBULAR AGGREGATE MYOPATHY AND CONGENITAL MIOSIS

DJ Nicholl, G Sadalage, N Shahrizaila, A Wills, MR Rose, F Bremner, K Wierenga.
*City Hospital, Birmingham*

10.1136/jnnp-2014-309236.31

We describe the clinical phenotype in five members of an English family (three female), with tubular aggregate myopathy and congenital miosis who were previously described at this meeting 10 years ago (Nicholl DJ *et al JNNP* 2004;75:1213) and are genealogically linked to other UK families (Shahrizaila *et al* 2004 Familial myopathy with tubular aggregates associated with abnormal pupils. *Neurology* 63:1111–13).

The phenotype is similar to the previously described Stormorken syndrome (MIM 185070) but without associated thrombocytopathy, asplenia, dyslexia, icthyosis, or migraine. Patients, ranging in age from 22 years to 79 years first manifested slowly progressive symptoms in the lower limbs but progressed later to involve the upper limbs, and in one member also the respiratory musculature. All had congenital miosis. Detailed pupillometry was performed on three members of the family which were suggestive of intrinsic and highly specific myopathy or hypoplasia of the iris dilator muscle. In one family member (who also had GCH1 related dopa-responsive dystonia), the only clinical abnormality was detected via pupillometry- indicating how mild the phenotype can appear.

Four members of the family underwent biopsies from either quadriceps or biceps brachii muscle revealing myopathic features, and tubular aggregates on electron microscopy. All patients were found to have a heterozygous missense mutation (p.P245L) in ORAI1. The resulting protein has recently been shown to suppress the slow Ca2+-dependent inactivation of the store-operated Ca2+ release-activated Ca2+ (CRAC) channel, functioning as a gain-of-function mutation. Whereas those families with the more classical Stormorken syndrome phenotype were found to have mutations in the STIM1 gene. Our work identifies the first activating mutation in ORAI1 associated with a clinical pathology in humans. Functional studies show that the p.P245L in ORAI1 does not cause constitutive activation of the CRAC channel, but rather makes a channel that cannot be completely turned off.

These data suggest that therapeutic options aimed at attenuating store-operated Ca2+-entry may be beneficial.

### REFERENCE

1 Nesin V, *et al*. Activating mutations in STIM1 and ORAI1 cause overlapping syndromes of tubular myopathy and congenital miosis. *PNAS* 2014 (in press).