speech delay or absence, seizures, autism, motor delay, deep-set eyes, poor feeding and poor weight gain.
Conclusions Based on the increasing identification of mutations in DYRK1A, we suggest this gene be considered as potentially causative in patients presenting with intellectual disability, primary or acquired microcephaly, feeding problems and absent or delayed speech with or without seizures.

Clinical Genetics

MG-114 FIRST 2 YEARS OF EXPERIENCE OF AN INTEGRATED MULTIDISCIPLINARY CLINIC FOR ADULTS WITH AORTOPATHIES IN A CANADIAN CONTEXT

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Background In 2012, the Montreal Heart Institute started an integrated multidisciplinary clinic for adults referred for suspicion of Marfan syndrome or other connective tissue disorders at risk of aortic disease. A heart team (cardiologist specialised in adult congenital heart disease, heart surgeons specialised in aortic surgery) and a genetics team (medical geneticist, genetic counsellor) work side-by-side. Both teams see patients with a family history of aortic disease or systemic features of Marfan syndrome. The heart team sees patients with presumed isolated aortic disease and determines if evaluation by the genetics team is needed.
Objective Assess first two years of clinic activities.
Methods Review of clinic database and patient charts for period between May 2012 and May 2014.
Results 183 new patients were assessed, from 146 different families. Reasons for referral included suspicion of Marfan (72), Loeys-Dietz (15), or Ehlers-Danlos syndrome (8); TAAD (56); and sudden death in the family (6). All were seen by the heart team; 70 were seen by the geneticist for a dysmorphological exam. All had dedicated cardiovascular imaging in our centre. Genetic tests were ordered for 35 patients. Close links with the paediatric and prenatal genetic clinics have facilitated efficient cross-referrals: we referred eight children of our adult patients. Most importantly, we rapidly assessed three pregnant women at risk of aortic disease and eight affected parents (identified through their child) who had no active follow-up.
Conclusions Our integrated multidisciplinary approach results in efficient access to specialised cardiac and genetic assessments and rapid management when required.

Molecular Genetics and Clinical Genetics

MG-115 COMPOUND HETEROZYGOUS SCN4A MUTATION UNDERLIES SEVERE CONGENITAL HYPOTONIA AND BIOPHYSICAL ALTERATION IN THE ENCODED VOLTAGE-GATED NAV1.4 SODIUM CHANNEL

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Introduction Mutations in the family of SCN genes encoding sodium channels are responsible for several disorders affecting the central and peripheral nervous systems and muscle. Disease arising from sodium channel mutants range from the relatively benign (e.g. mild myotonia) to the fatal (e.g. long-QT syndrome), with a wide variety of disorders spanning the spectrum of severity. Identified SCN4a mutations to date have been consistently autosomal dominant and associated with paramyotonia congenita, potassium-mediated periodic paralysis or aggravated myotonia due to defects altering the biophysical properties of sodium channels that mediate membrane hyper- or hypo-excitability. Here we describe a newly recognised autosomal-recessive syndrome comprising severe congenital hypotonia with respiratory failure in a family of Punjabi descent, with 2 of 3 children affected.
Methods and results Using whole exome sequencing we identified two new mutations (g. 62025363 C >T, D1069N and g. 62025425 T >G, splice site) in the SCN4A gene, confirmed via Sanger sequencing. Reverse transcriptase polymerase chain reaction shows that the splice-site mutation in SCN4A leads to altered RNA. To investigate the impact of the missense mutation, c.3205G >A, Chinese hamster ovary (CHOk1) cells transfected with either a WT or D1069N SCN4A were examined for their biophysical properties. A set of depolarizing test pulses was used to measure the voltage dependence of activation and indicated biophysical changes in the encoded voltage-gated sodium channel (NaV1.4).
Conclusions Together, our findings characterise the first reported evidence of an autosomal recessive SCN4a sodium channelopathy comprising severe congenital neuromuscular hypotonia and respiratory failure with biophysical dysfunction of NaV1.4 attributable to SCN4a compound heterozygous gene mutation.