Genetics

CHALLENGING VARIANT INTERPRETATION IN CARDIAC GENETICS

Edwin Kirk^{1,2}

¹Department of Medical Genetics, Sydney Children's Hospital, and ²Genetics Laboratory, South Eastern Area Laboratory Services, Randwick, NSW, Australia

The field of cardiac genetics spans congenital heart disease, cardiomyopathies, disorders of cardiac rhythm, aortopathies and the numerous and varied syndromes in which cardiac disease can be a feature. A common theme is that for many phenotypes, numerous genes are implicated, and as a result, screening of panels of multiple genes has been standard practice for some years. Correct classification of variants identified on genetic testing is of critical importance. A variant incorrectly classified as pathogenic or likely pathogenic may be used for predictive testing, leading to incorrect decisions to continue or discontinue screening, and to treatment (lifestyle modification, medications and even insertion of implantable devices) in individuals who are not at increased risk of cardiac complications. The reverse situation—in which a pathogenic variant is classified as being of uncertain significance or even benign—can also have negative consequences, with family members losing the chance to be tested and either cleared of risk or managed appropriately. The aim of this talk is to present key issues which may be encountered, with specific examples from relevant cardiac conditions.

COMPLEX GENETIC TEST REQUESTS IN SA: AN MDT APPROACH

Peter A. Kaub, Karin S. Kassahn, Janice M. Fletcher
Genetics and Molecular Pathology, SA Pathology, Adelaide, SA, Australia

New genetic testing platforms offer much promise, but are still a relatively limited resource in clinical diagnostic settings. Embedding medical scientists in an active clinical conversation is essential to maximising the utility of diagnostic services and assisting best clinical outcome for patients.

For complex requests, we have developed a systematic multi-disciplinary team (MDT) approach for case presentation, plus decision criteria to assist determination of the most appropriate testing, based on both clinical and laboratory information. Consideration is given to management implications, evidence supporting genetic testing indication and utility, test availability, service capacity and in-house expertise, as well as expected turnaround time. At regular formal meetings, a recommendation is formed after open and robust discussion between clinicians, scientists and bioinformaticians. Outcomes include recommendations for phenotype-targeted next generation sequencing (NGS) gene panels, clinical exome, whole exome or whole-genome sequencing, array-based testing and MLPA.

In just over one year, this consensus-based, open discussion platform has reviewed more than 75 complex clinical cases. The

majority have been paediatric patients, with the greatest number referred from clinical geneticists, however a diversity of clinical specialties have been represented. A summary of the MDT system used, with range of outcomes, phenotypes and results encountered will be presented.

MATERNAL CARNITINE UPTAKE DEFICIENCY DETECTED BY NEWBORN SCREENING

Beena Devanapalli, Kevin Carpenter
NSW Biochemical Genetics, Sydney Childrens Hospital Network, Westmead, NSW, Australia

Carnitine is an essential cofactor in the transport of long chain fatty acids across the inner mitochondrial membrane. A defect in the carnitine transporter occurs due to defects in OCTN2 which is a high affinity sodium dependent carnitine transporter. Patients may present with cardiomyopathy and/or repeated hypoketotic hypoglycaemic episodes and have extremely low blood carnitine concentration. Carnitine is also transported across the placenta and thus mothers with carnitine uptake deficiency (CUD) can be detected if their normal baby has decreased carnitine. Babies with low free carnitine on newborn screening (NBS) and their mothers are further evaluated to identify CUD. Plasma total and free carnitine are measured in babies and their mothers. Specific enzyme studies on skin samples are performed on mothers with persistent low total and free carnitine. Since 1998, 32 babies have been identified with decreased free carnitine on NBS. CUD was diagnosed in 12 babies and confirmed by enzyme assay in 16 mothers. Four babies and mothers had normal level on follow-up testing. The symptoms of CUD can be reversed with oral carnitine supplementation. Diagnosis of CUD in otherwise asymptomatic patients can help prevent potential serious complications.

SKELETAL DYSPLASIA AS THE PRESENTING FEATURE OF A CONGENITAL DISORDER OF GLYCOSYLATION

Francesca Moore¹, Andreas Zenkl², Kevin Carpenter¹
¹Biochemical Genetics Service, and ²The Department of Clinical Genetics, The Children's Hospital at Westmead, Sydney, NSW, Australia

Congenital disorders of glycosylation (CDG) form a rapidly growing group of inherited metabolic diseases caused by hypoglycosylation of proteins and lipids. Patients present with a clinical spectrum of defects involving multiple systems including the central nervous system, muscle function, endocrine system, transport, regulation and coagulation. Skeletal abnormalities are a predominant feature in only about 20% of the known CDG.

We present a case of CDG, presenting at birth with skeletal dysplasia. Following abnormal transferrin isoform and APO CIII