Facial Dysmorphism, Skeletal Abnormalities and Central Nervous System Abnormalities in Two Sibs Born to a Consanguineous Couple: A New Autosomal Recessive Condition

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We report two female fetuses born to a consanguineous Sri-Lankan couple with facial dysmorphism, central nervous system and skeletal abnormalities. To our best knowledge this is a hitherto new autosomal recessive condition.

The fetuses, both female, presented with thickened nuchal folds, echogenic bowel and kidneys, rocker-bottom feet, ventriculomegaly and intrauterine growth restriction. Detailed autopsies following termination of pregnancy at 23.4 and 22.3 weeks gestation respectively revealed short sloped forehead and hypertelorism with webbing of the neck, hydrocephalus with aqueduct stenosis as well as marked narrowing of the spinal canal and platyspondyly with delayed ossification and flattened acetabular roofs, broad hands with brachydactyly and narrow wrists. Microarray analysis was normal on both. These findings likely represent a new genetic syndrome with most probably autosomal recessive mode of inheritance. Whole genome sequencing is being done to try and identify the causative gene.

Global Developmental Delay And Characteristic Facial Features Associated With PACS1 Gene Mutation – Report Of Two Cases

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Intellectual disability (ID) affects 1%-3% of the population. While it has a strong genetic component, finding a genetic diagnosis remains challenging. Given the high rate of de novo events in ID, family-based sequencing may be an important tool. In 2012 Schuurs-Hoeijmakers et al., reported two children with ID and characteristic features associated with a heterozygote mutation in PACS1. We report the same mutation elucidated by whole exome sequencing (WES) in two additional children.

Patient 1 was born at term to a 30-year-old primigravida from Bangladesh. Her birth weight and length were 3-10th% and head circumference 50-75th%. ID presented in the first year of life. She had sparse hair, a high forehead, frontal bossing, hypertelorism, deep-set eyes, a broad nasal root, full lips and a wide mouth. She had marked hypotonia, decreased muscle bulk and hyperextensible joints. WES revealed a PACS1 mutation.

(NM_018026)exon4:c.C607T:p.R203W.
Patient 2 was born at term to a 34-year-old primigravida from China. Birth weight and length were 10-25th% and head circumference 25-50th%. At birth, an anoplasty was performed for an ectopic anus. A right duplex kidney and undescended testes were identified. ID presented before age one. He had a short forehead, bushy eyebrows, short nose, large mouth, uplifting earlobes, bilateral single palmar creases, widely spaced nipples and an umbilical hernia. WES revealed the same mutation.

Our two cases highlight the clinical utility of WES in helping establish a diagnosis of an unfamiliar clinical syndrome and supports the discovery of a now recognizable syndrome due to mutation in PACS1.

MG-107 - Clinical Genetics

Congenital Sucrase-Isomaltase Deficiency: Identification of the Common Inuit Founder Mutation

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Objective. Congenital sucrase-isomaltase deficiency (CSID) is a rare hereditary cause of chronic diarrhea in children. Persons with CSID lack the intestinal brush-border enzyme required for digestion of di- and oligosaccharides, including sucrose and isomaltose. Malabsorption results in abdominal pain, distention, copious diarrhea, and failure to thrive. If recognized, dietary avoidance of the offending carbohydrates is highly effective. Although CSID is known to be highly prevalent (~5-10%) in several Inuit populations, the genetic basis for this condition has not been described.

Methods. We sequenced the sucrase-isomaltase gene, SI, in a single Inuit CSID proband with severe fermentative diarrhea and failure to thrive. We then genotyped a further 128 anonymized Inuit control individuals from a variety of circumpolar locales to assess for a possible founder effect.

Results. We identified a novel, homozygous frameshift mutation, c.273_274delAG (p.Gly92Leufs*8) in exon 4 of SI in the proband, that is predicted to result in complete absence of functional protein product. This change is indeed very common among Inuit control specimens, with an observed allele frequency of 0.17 (95% confidence interval 0.13-0.22). The predicted Hardy-Weinberg prevalence of CSID in the Inuit, based on this single founder allele is ~3% (95% confidence interval 1.6-5.0%), comparable with previous estimates.

Interpretation. Targeted mutation testing for the c.273_274delAG allele should afford a simple and minimally invasive means of diagnosing CSID in persons of Inuit descent. Because CSID is a readily treatable disorder, such testing should be considered at an early stage in the assessment of Inuit patients with chronic diarrhea.

MG-108 - Molecular Genetics Clinical Genetics

Agenesis of the Corpus Callosum and Autism associated with ZEB1 gene deletion - A case report

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Background: Agenesis of the corpus callosum (ACC) is a rare congenital anomaly presenting with partial or complete absence of the corpus callosum (CC). ACC could present as an isolated finding or a part of a genetic syndrome. A recent publication reported two cases of mal-development of CC in two unrelated individuals with posterior polymorphous corneal dystrophy (PPCD), an autosomal dominant inherited disorder of the corneal endothelium. Both cases presented novel deletions of the ZEB1 gene. Of note, ZEB1 mutations are reported in approximately one third of PPCD patients (vision research 2014; 100:88-92).

Objective: to report a case of a child with ACC and de novo chromosome 10 deletion involving ZEB1 gene. Case report: a 12-year-old girl presented with facial dysmorphism, bilateral renal reflux, developmental delay, autism and ACC. She presented with normal growth parameters, continued to acquire new developmental skills with no regression episodes or seizures. Ophthalmological exam showed thinning of the retinal nerve fiber layer in the nasal aspect around the discs with relative sparing of the macular areas bilaterally. The rest of the ocular examination, including corneal exam was normal.

Results: Whole genome sequencing revealed heterozygous de novo deletion in chromosome 10p11.23- p11.22 (del:chr10:30814000-32892000) overlapping ZEB1 gene.

Conclusion: this is the third case reported of ZEB1 gene deletion in a patient with CC anomalies, and the first patient with no corneal anomalies but with autism. This finding might imply a broader phenotypic range for ZEB1 deletion than previously thought and add it to the possible causes of autism.
ABSTRACTS - CCMG

MG-111 - Molecular Genetics & Cytogenetics/Microarray

A Paternally Inherited Interstitial Deletion of 15q11.2 Causing Clinical Features of PWS: Refinement of the PWS-IC.

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Background. Imprinting occurs on chromosome 15q11.2-q12 by differential methylation of genes on each parental chromosome. Prader-Willi syndrome (PWS) is caused by the absence of paternally imprinted genes at chromosome 15q11.2, whether by deletion, uniparental disomy, or imprinting center (IC) defect. The PWS-IC is defined by the 4.1 kb shortest region of overlap (SRO) of reported deletions, which includes the promoter and exon 1 of the SNRPN gene. Mutation of the PWC-IC blocks the switch from maternal-to-paternal imprint within the male germ line. We describe a neonate with a classical clinical presentation of PWS.

Objective. To describe a patient with PWS whose clinical features were further delineated by demonstrating a de novo deletion occurring on the grand-maternal allele.

Conclusions. These analyses refine the PWS-IC to a 1.8 kb region of 15q11.2.

MG-112 - Clinical Genetics Molecular Genetics

Ten new cases further delineate the syndromic intellectual disability phenotype caused by mutations in DYRK1A

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Background. The dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) gene on chromosome 21q22.13 within the Down syndrome critical region has been implicated in syndromic intellectual disability associated with Down syndrome and autism. DYRK1A plays a critical role in brain growth and development primarily by regulating cell proliferation, neurogenesis, neuronal plasticity and survival. Several patients with chromosome 21 aberrations, such as partial monosomy, involving multiple genes including DYRK1A have been reported. In addition, seven other individuals have been described with chromosomal rearrangements, intragenic deletions or truncating mutations that specifically disrupt DYRK1A. Most of these patients have microcephaly and all have significant intellectual disability.

Objectives. The purpose of this study was to further delineate the recurrent clinical features and types of mutations that disrupt DYRK1A in patients with ‘DYRK1A syndrome’.

Design/Method. Targeted or whole exome next-generation sequencing and array comparative genomic hybridization analysis were used to identify DNA sequence variations and copy number variants, respectively.

Results. We identified unique mutations in DYRK1A
in nine patients and a large chromosomal deletion that encompassed DYRK1A in one patient. These individuals had a recurrent pattern of clinical manifestations including primary or acquired microcephaly, intellectual disability ranging from mild to severe, 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.

**MG-114 - Clinical Genetics**

**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 specialized in adult congenital heart disease, heart surgeons specialized in aortic surgery) and a genetics team (medical geneticist, genetic counselor) 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), Loey-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 center. Genetic tests were ordered for 35 patients. Close links with the pediatric 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 specialized cardiac and genetic assessments and rapid management when required.

**MG-115 - Molecular Genetics & Clinical Genetics**

**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 recognized autosomal-recessive syndrome comprising severe congenital hypotonia with respiratory failure in a family of Punjabi descent, with 2 of 3 children affected.

Methods & 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 characterize 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.


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Background: Emberger syndrome is caused by mutation in GATA2 and predisposes to myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), lymphedema, warts, subtle dysmorphic features, and, rarely, congenital anomalies.

Objectives: To describe the heterogeneity associated with GATA2 mutation and highlight features that should prompt testing.

Design/Methods: Case report of 2 families with mutation confirmed Emberger syndrome.

Results: Family 1: The proband presented with warts and mouth ulcers. WHIM syndrome was considered when neutropenia and B-cell deficiency developed, despite negative CXCR4 testing. Years later, he developed AML with monosomy 7 and underwent chemotherapy and stem cell transplantation. Idiopathic leg lymphedema occurred. Family history was significant for warts. Re-examination identified subtle dysmorphisms. GATA2 sequencing detected a missense mutation.

Family 2: Sibling 1 had a history of warts, mouth ulcers, vesicoureteral reflux (VUR), ectopic anus, mild sensorineural hearing loss, and new-onset neutropenia. Bone marrow testing diagnosed MDS with monosomy 7. Sibling 2 had hypocellular, mildly dysplastic bone marrow. History included warts, VUR, and leg lymphedema. Sibling 3 had mild bone marrow hypopcellularity. Paternal history was significant for childhood warts and mouth ulcers. Siblings 1-3 had subtle dysmorphisms. GATA2 sequencing identified a nonsense mutation. Sibling 1 underwent stem cell transplantation. Siblings 2-3 are closely monitored.
Conclusions: The literature is biased towards individuals who present with overt hematological malignancies; however, Emberger syndrome can be recognized earlier. Suspicion should be high in patients with persistent hematologic/immunologic abnormalities, warts refractory to treatment, and/or lymphedema in the setting of subtle, but typical, dysmorphisms. Intervention before development of AML decreases morbidity/mortality.

MG-117 - Cytogenetics/Microarray

Chromosome Microarray and Non-coding DNA Copy Number Variants - A Case of Alveolar Capillary Dysplasia at FOXF1 Locus.

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Background. Chromosome microarray (CMA) analysis typically focuses on coding DNA (RefSeq and OMIM genes). Although non-coding intergenic and intronic variants may be critical in disease pathogenesis, copy number variants (CNV) in these regions are usually interpreted as variants of unknown clinical significance.

Objective. We present a case of a lethal neonatal condition in which the pathogenic CNV lies in a distant, upstream non-coding region.

Design/Method. Chromosome microarray was performed in a newborn female with a prenatal diagnosis of AVSD, who presented with severe neonatal respiratory distress out of keeping with her cardiac issues.

Results. CMA analysis revealed a de novo 1.5 Mb deletion at 16q24.1. None of the 16 RefSeq genes mapping within the deleted region appeared causative. However, this deletion is located 157 kb upstream of FOXF1, a gene responsible for congenital alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV). The observed deletion encompasses a recently characterized distant regulator/enhancer of the FOXF1 gene. The pathological diagnosis of ACDMPV was confirmed posthumously.

Conclusion. This case highlights the importance of relevant clinical information for CMA interpretation, and the importance of the analysis of flanking regions if an identified CNV does not initially appear pathogenic. As our knowledge of epigenetics and the genomic landscape improves, an increasing number of non-coding CNVs are poised to gain clinical relevance. We suggest that a database of well-characterized non-coding regulatory regions be developed and incorporated into CMA analysis.

MG-118 - Cytogenetics/Microarray Molecular Genetics

Towards understanding phenotypic variability using exome sequencing

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Background: The recurrent 1q21.1 CNV has been associated with considerable phenotypic variability ranging from normal to severe neurodevelopmental delay, noted even among members of the same family. The reason for this variability is unknown.

Objective: We screened for mutations within the 1q21.1 CNV or genome wide that could explain the phenotypic variability among ten 1q21.1 carriers from 4 families.

Methods: Whole exome sequencing (WES) was performed on 6 subjects with deletions, 4 subjects with duplications and their 4 unaffected family
members using an Illumina HiSeq 2000 sequencing platform. Golden Helix SVS v8.1.5 was used for raw data analysis. We assessed the de novo (MAF) results: We found no pathogenic mutations in the 1q21.1 CNV region in any of the subjects. One de novo, 2 autosomal recessive and 2 compound heterozygous pathogenic variants in 2 most affected probands were identified. All affected genes have a role in brain function, and 4/5 genes are associated with stress response pathways. Pathogenic mutations inherited from the affected parent were also enriched for genes in stress response pathways and for one of them (ATF6) we investigated the functional consequences in patient lymphoblasts.

Conclusions: Impaired stress response, due to pathogenic mutations, in carriers of 1q21.1 CNVs combined with more or less favourable environmental conditions during development could contribute to their phenotypic variability and severity.

MG-119 - Clinical Genetics
The Evolving Features Of Nicolaides-Baraister Syndrome - A Case Report of a Twenty-Year Follow-Up
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Background. Nicolaides-Baraister syndrome (NCBRS) is a rare genetic condition, with approximately 50 reported cases, characterized by dysmorphic facies, developmental delay, seizures, short stature, sparse hair and prominent interphalangeal joints. Limited cases have followed NCBRS features’ evolution. We report a twenty-year follow-up of a NCBRS patient to elucidate the syndrome’s natural history.

Case description. This patient was born at term to a 28-year-old primigravida mother. His birth weight and head circumference were at the 50th percentile and length was at 10th percentile. Apgars were 9 at 1 and 5 minutes. He was assessed at 6 weeks for failure to thrive. Initial examination revealed left-sided torticollis, cryptorchidism, hypospadias and umbilical hernia. He had sparse hair, droopy eyelids with curly eyelashes, prominent nasal root, bulbous nose, malar hypoplasia and thin upper vermillion. Karyotype was 46, XY and basic metabolic work-up, brain MRI, abdominal ultrasound, and EEG were normal.

Over years, his mild dysmorphism became more prominent with coarsening of facial features. His lips became fuller with thicker lower vermillion. By age 2, he developed mild scoliosis and seizures. Distal phalangeal broadening was noted at 6-year. Puberty started at age 15-16, with increased self-aggression. Developmentally, there was global mild delays. Short stature and microcephaly persisted into adulthood. He was accepted into a college program with disability services.

Conclusions. Our case broadens the NCBRS phenotype, as this mild developmental delay has been rarely described in NCBRS before. It also highlights early recognition challenges since several diagnostic features may only become evident with long-term follow-up, as illustrated in our case.

MG-120 - Molecular Genetics Clinical Genetics
Next Generation Sequencing for the Diagnosis of Heterogeneous Diseases: Our Four Years’ Experience
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Background. Next Generation Sequencing (NGS) through the use of targeted re-sequencing panels has recently become a widely available tool for genetic diagnosis of heterogeneous diseases, being most useful for clinical entities with overlapping clinical symptoms. Different technical approaches for target enrichment, capture and sequencing are available, and flexibility of panels is necessary for an ever-
ABSTRACTS - CCMG

growing field as molecular genetics.

Objective. To summarize our 4 years’ experience in design, validation, and clinical application of re-sequencing panels for the diagnostics of complex diseases, from benchtop to laptop, and the reporting of nucleotide variants.

Method. Panels were designed for the study of cardiomyopathies (236 genes), neuropathies (201 genes), hearing-loss (83 genes), hereditary cancer (80 genes), and skeletal dysplasies (227 genes). Target regions were enriched and captured using the SureSelect system (Agilent) and sequenced with a SOLiD 5500 (Life Technologies) or MiSeq (Illumina) platform.

Results. A total of 864 clinical samples have been investigated by NGS. Out of them, 383 were tested for cardiomyopathies, 155 for neuropathies, 99 for hearing-loss, 206 for hereditary cancer, and 21 for skeletal dysplasies. Disease-causing mutations were identified among patients; however, a significant number of variants of unknown significance (VUS) were found. All pathogenic, likely-pathogenic, likely-benign and VUS were subjected to confirmation by Sanger sequencing.

Conclusions. Targeted gene panels represent a useful, cost-effective and faster alternative to Sanger sequencing for the genetic diagnosis of heterogeneous diseases. The interpretation of VUS however, comprises perhaps the greatest challenge that the use of NGS in the clinical diagnostics field may encounter.

MG-121 - Cytogenetics/Microarray & Clinical Genetics

Five New Patients With Pure Distal 1q Trisomy, Review of the Literature and Phenotype Redefinition

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Background. Pure distal 1q trisomy is rare and there is limited information on genotype-phenotype correlation. The common 1q trisomy phenotype attributed to the 1q42qter segment is based on a small number of patients and consists of small for gestational age, developmental delay, macrocephaly, dysmorphic features and heart defects.

Objective. To clarify the genotype-phenotype correlation of pure distal 1q trisomy.

Design/Method. We report five patients with pure distal 1q trisomy: 1q32.2qter (patient 1), 1q41q44 (patient 2), 1q43qter (patient 5) and 1q42.13qter in two siblings (patient 3 and 4). A PubMed search was done to identify patients with trisomies distal to 1q32. Patients with pure 1q trisomies that matched the duplications found in our patients were selected.

Results. Thirty-three patients have been reported with partial trisomy distal to 1q32. Only 17 patients with pure 1q trisomy matched our patients’: ten for 1q32qter, four for 1q41q44, two for 1q42qter and one for 1q43qter. Our patients presented additional features than the common 1q trisomy phenotype. Patients 1, 2, 3 and 4 have had frequent infections with normal immunological status. Patients 1, 3 and 4 had significant sleeping problems. Patients 3 and 4 have camptodactyly and patient 4 had hypertrophied cardiomyopathy. Patients 4 and 3 respectively have moderate and mild intellectual deficiency, a feature that was thought to be mostly normal distal to the 1q42 region.

Conclusions. The partial 1q trisomy phenotype is constantly expanding. An improved definition allows for the identification of critical regions and better genetic counseling and follow up.

MG-122 - Cytogenetics/Microarray Clinical Genetics

Cytogenetic characterization of 3 small supernumerary chromosomal markers in a 1 year-old girl

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Background. The frequency of small supernumerary chromosomal markers (sSCM) are estimated to be ~0.03-0.15% and are not necessarily always associated with clinical phenotypes. Their characterization is important since they can be helpful in establishing phenotype-genotype correlations, which is essential for genetic counseling.

Objectives. Cytogenetic and phenotype-genotype characterization of 3 sSCM in a 1 year-old girl exhibiting growth delay and complex cardiopathy.

Design/Method. Array-CGH and FISH analyses were performed. Literature review was also completed in order to find a genotype-phenotype relationship in this patient.

Results. We found three regions of duplication, all near the centromeric region from the short chromosome arm on band q12. The first duplication was localized on chromosome 4q12 and represented a region of 5.4 Mb consisting of 326 oligonucleotides with ~40 genes. The second duplication was on chromosome 11q12 and corresponded to a region of 1.6 Mb consisting of 84 oligonucleotides with also ~40 genes. However, this latter duplication was much weaker and therefore probably present in mosaic. The third duplication on 12q12 was characterized by a region of 0.8 Mb with 23 oligonucleotides and included only two genes. These results were further confirmed by FISH analyses on metaphases, which revealed three distinct sSCM in this patient. The markers der(4) and der(12) were found in all cells, whereas the der(11) was absent in most cells. FISH analyses on parents revealed that these anomalies were de novo.

Conclusions. Remarkably, the de novo character of these three sSCM reflects the complex nature of genomic imbalances possible during embryogenesis.

MG-123 - Cytogenetics/Microarray

Genomics of Early Pregnancy Loss

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Background: Chromosomal abnormalities are a frequent cause of miscarriage, however the etiology of karyotypically normal miscarriages remains unknown in many cases.

Objective: Our objective was to find new genetic causes of idiopathic miscarriages by evaluating miscarriage CNVs and sequence variants detected by whole exome sequencing (WES).

Methods: We used a)bioinformatics to assess genomic characteristics of CNVs (size, gene content) reported in 4 recent studies of 101 miscarriages b)RNA and protein expression to determine the function of their integral genes in miscarriage cells and c) exome sequencing to look for mutations associated with recurrent pregnancy loss.

Results: The majority of reported rare CNVs with a known origin are familial, and small (median 0.5Mb), with ~5 genes/Mb. For 3/14 genes integral to CNVs the RNA and protein expression was abnormal in miscarriages. These genes have a role in processes required for successful pregnancy development; TIMP2 and TRAPPC2 in tissue remodelling, cell adhesion and migration and OFD1 in cilia function. WES of recurrent miscarriages from 3 couples (2 miscarriages each) revealed a total of 8 rare and putatively pathogenic compound heterozygous variants present in both miscarriages affecting genes involved in ciliogenesis (4), and neovascularization (4).

Conclusion: CNVs in miscarriages tend to be small (0.5Mb), based on the 4 recent reports. However, they impact the function of genes relevant for pregnancy development. Exome sequencing has the potential to identify genetic causes and pathways associated with recurrent pregnancy loss.
ABSTRACTS - CCMG

MG-124 - Molecular Genetics Clinical Genetics
Zebrafish as an emerging model for human disease
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Background: The advance of next generation sequencing has resulted in the identification of many new disease associated gene mutations. However, validating the function of these variants, particularly in rare diseases, is still a challenge. Recent advances in targeted mutagenesis technology have led to the development of zebrafish models of human disease. Zebrafish have rapid early development, transparent embryos, and large clutch sizes making them suitable for high throughput drug screening and quick, in vivo testing of the consequences of newly identified gene mutations.

Objectives: Our goal is to use the expertise and infrastructure at the Hospital for Sick Children to establish a Zebrafish Genetics and Disease Model Core Facility, accessible to researchers worldwide, that provides all the services required to generate and analyze zebrafish models of human disease at the highest quality, most affordable prices and most efficient time frame.

Design/Methods: Our facility provides targeted mutant generation and phenotype analysis services for a reasonable fee as part of our cost-recovery business plan.

Results: The core facility leadership has exemplary experience in zebrafish mutant generation and characterization as well as the use of zebrafish for drug discovery. Examples of our initial zebrafish mutants created to model and study human diseases will be presented.

Conclusions: Our facility provides high quality, cost efficient services for generating and analyzing zebrafish models of human disease. These models can be used both as a validation tool to complement human disease studies using next generation sequencing and to identify new disease treatments via high throughput drug screening.

MG-126 - Clinical Genetics & Molecular Genetics
A De Novo Truncating Mutation in the Chromatin Remodeler CHD8 in a Patient with Autism, Macrocephaly and Overgrowth.

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Background: CHD8 is one of a few genes in which de novo loss of function mutations have been identified in multiple cases across multiple autism cohorts in recent extensive exome sequencing studies. CHD8 is an ATP-dependent chromodomain helicase involved in chromatin remodeling and regulation of Wnt/beta-catenin and p53 pathways, which are pathways that have been implicated in non-syndromic and syndromic autism and intellectual disability.

Objectives: We will describe a patient with autism and intellectual disability with a novel CHD8 mutation. We also review the phenotype of previously reported patients with CHD8 loss of function mutations.

Methods. Exome sequencing of the proband and parents was used to identify de novo variants using the trio approach. A PubMed-based literature search identified other reported patients.

Results. Our patient has a de novo truncating CHD8 mutation (c.4342C>T, NM_020920). He is macrocephalic (>+3SD), and has extremely tall stature with proportionate weight (>+7SD), suggestive of an overgrowth phenotype. Other patients with CHD8 mutations that have been reported in the literature also have macrocephaly and a tendency to taller stature.

Conclusions. CHD8 mutations may cause syndromic autism. Further delineation of this phenotype will be helpful for diagnostic and prognostic guidance in the future. The association of a truncating CHD8 mutation with macrocephaly and overgrowth is particularly
ABSTRACTS - CCMG

interesting since other disorders of chromatin remodeling implicated in the Wnt/beta-catenin pathway, such as Coffin-Siris and Weaver syndromes, also have abnormal neurodevelopment associated with altered head size and in some instances generalized overgrowth.

MG-127 - Cytogenetics/Microarray Clinical Genetics

Diagnostic accuracy of chromosome microarray in children with epilepsy and neurological abnormalities of unknown etiology

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Background Chromosome MicroArray-based genomic copy-number analysis (CMA) has an important role in the discovery of both novel and recurrent epilepsy-associated copy number variants (CNVs) in patients with epilepsy. In case of an additional neuro-developmental disorder the diagnostic accuracy may be as high as 15%.

Objectives. The purpose of this study is to describe the results of performed CMA on 706 children with unexplained epilepsy associated with developmental delay/intellectual disability, autism spectrum disorders and/or multiple congenital anomalies ('epilepsy plus').

Design/Method. Retrospective chart review on clinical and genetic aspects of CNVs identified in 706 patients with epilepsy plus, seen at the Vancouver BC Children’s Hospital from 2009 to 2014. All patients had CMA performed using Affymetrix Genome-Wide Human SNP Array 6.0 or CytoScanHD®.

Results: Abnormal CMA results were identified in 191 out of 706 children with ‘epilepsy plus’. 122/706 (17.3%) patients had variants of unknown significance (VUS), and 80/706 (11.3%) patients had pathogenic CNVs. This group included 33 patients that had CNVs in genomic “hotspots” predisposing to epilepsy, including deletions at 1q21.1 (n=1), 15q11.2 (n=7), 15q13.3 (n=4), 15q11-q13 (n=4), 16p11.2 (n=7), and 16p13.11 (n=10). Another recurring CNV identified was 22q13.3 deletion (Phelan-McDermid Syndrome) (n=4). One of the four 22q13.3 deletion patients had treatment resistant epilepsy and a small deletion (47kb) of the SHANK3 gene.

Conclusions: CMA revealed pathogenic CNVs in epilepsy “hotspots”, and known microdeletion syndromes like Phelan-McDermid syndrome in 11.3% of children with ‘epilepsy plus’. Examination of CNVs also plays an important role in the identification of possible epilepsy genes i.e. SHANK3 mutations in patients with 22q13.3 deletions.

MG-128 - Clinical Genetics & Cytogenetics/Microarray

Use of Prenatal Array Comparative Genomic Hybridization in Cases of Fetal Structural Cardiac Anomalies: New Cases and Review of the Literature

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Background: Array comparative genomic hybridization (aCGH) has been used to provide genome-wide screening for small chromosome imbalances in the prenatal setting, however use is not uniform across Canada. Many studies have looked at overall yield of aCGH, however, there has been less literature examining utility of array in the case of specific congenital anomalies.

Objectives: To determine the utility of aCGH in cases of prenatal cardiac anomalies.

Methods: A literature review was conducted using PubMed for all studies reporting results from prenatal aCGH, and those reporting cardiac anomalies as a distinct category were selected. Results of aCGH testing for cases prospectively recruited for this indication at our centre were also included. Outcome measures included detection rate, number of variants of uncertain significance (VOUS), and number of incidental findings.

Results: Eleven published studies and 22 patients at our centre were included. Most studies did not report cardiac anomaly-specific results for all categories of
array results. Overall detection rate over karyotype for pathogenic anomalies was 6.6%. Incidental findings were found in 7.69% of cases. VOUS occurred in 1.47% of cases.

Conclusions: Array CGH increases the yield of chromosomal findings over karyotype alone in cases of prenatal cardiac anomalies, and has a place in clinical use. In addition, VOUS and incidental findings are as common as pathogenic anomalies in this cohort. Prenatal clinics must be prepared to deal with these findings in this setting. More studies are needed to determine the incidence of pathogenic, VOUS and incidental findings in cardiac-specific cases.

MG-129 - Molecular Genetics

The development of a genetic newborn screening assay for permanent hearing loss using blood spots - a collaboration between Newborn Screening Ontario (NSO) and the Infant Hearing Program (IHP)

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Background. The Ontario Infant Hearing Program identifies babies born with, or at risk for, permanent hearing impairment. The current method of audiometric screening may be limited in detecting forms of hearing impairment, which are clinically silent in the newborn but may become apparent in the preschool period.

Objectives. To determine the prevalence of detectable CMV genomes and determine the disease allele frequencies for selected mutations in GJB2, GJB6, SLC26A and MT-RNR1 in Ontario Newborns.

Methods. 10,000 historical blood spots were screened to determine the first Ontario population-based data regarding the prevalence of congenital CMV and the allele frequencies of the common mutations in GJB2, GJB6, SLC26A and MT-RNR1 which are associated with hearing impairment. A 2-part assay was developed to screen newborn dry blood spots – 1) a multiplex genotyping assay based on Sequenom® iPlex technology and 2) a multiplex qPCR assay to detect and quantify CMV, as well as to detect a known deletion in GJB6.

Results. We detected CMV genomes in 0.6% of blood spots screened. Disease allele frequencies were determined and those for GJB2/GJB6 as well as SLC26A were found not to be in Hardy-Weinberg equilibrium (HWE), with non-assortative mating postulated to be the major contributing factor. Lastly, the population frequency of MT-RNR1 alleles responsible for sensitivity to aminoglycoside antibiotics was 1.7%.

Conclusions. In the future, possible implementation of newborn blood spot screening for hearing impairment would enhance the current ascertainment of infants at risk for hearing impairment and introduce an etiologic component to hearing screening in Ontario.

MG-130 - Clinical Genetics & Cytogenetics/Microarray

Pure Duplication of 1q42.11-Q44(Qter): Further Clinical Delineation of a Rare Terminal Duplication Syndrome.

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Background: Pure partial trisomy of 1q42 to 1q44 (terminal end) is an extremely rare chromosomal abnormality reported in only 5 patients to date (Am J Med Genet A 2007;143A(19):2339-42). We present one additional case with the breakpoints molecularly characterized by array CGH. Clinical features are similar to those previously described with 1q42
terminal duplication syndrome.

Objective: To contribute to the growing clinical knowledge of pure 1q42 terminal duplications.

Design/Method: A G-banded karyotype with subsequent FISH to confirm the location of the breakpoints was performed. The breakpoints were further refined with an array Comparative Genomic Hybridization (CGH) using the oligoarray platform CytoChip™ ISCA 8x60K v2.0.

Results: Our case has a pure partial duplication of chromosome 1q42.11 to the terminal end, resulting from a one-way translocation of this segment to the distal long arm of chromosome 2. Array CGH identified this to be 24.8 Mb in size (nucleotides 222,299,920 – 247,179,262; NCBI36/hg 18). Array CGH did not identify a deletion on chromosome 2.

Conclusions: We describe a 12-year-old male with the distinctive appearance similar to those previously described with 1q42 duplication syndrome including macrocephaly, down-slanting palpebral fissures, a high arched palate, low-set, abnormal ears and cryptorchidism. Height measured 138.5 cm (just below the 3rd percentile) and weight measured 34.9 kg (3rd – 10th percentile), while head circumference measured 53.8 cm (50th percentile). Additional features not previously reported include two conjoined teeth, mild pectus carinatum and microphallus. He has a history of developmental delay and intellectual disability, aggressive and self-injurious behavior and obstructive sleep apnea.

Incidential germline findings in tumor molecular profiling by Next Generation Sequencing

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Objectives. Molecular profiling of solid tumors using Next Generation Sequencing (NGS) aims to detect tumor-specific somatic mutations for targeted drug treatments. Parallel testing of tumor and blood samples can enable identification and verification of of tumor-specific somatic mutations. However testing blood may also reveal incidental germline variants in cancer predisposition genes. The objective of this study was to determine type and frequency of clinically relevant incidental germline variants from molecular profiling of paired tumor/blood samples.

Design/Methods. NGS molecular profiling data of tumor/blood pairs from 786 patients with metastatic solid tumors enrolled in the Princess Margaret IMPACT clinical trial were reviewed. NGS testing used Illumina TruSeq Cancer Amplicon Panel (TSCAP) on the MiSeq. The TSCAP targets regions of 48 genes including 8 genes on the ACMG germline incidental list (APC, PTEN, MLH1, RET, RB1, STK11, TP53, VHL).

Results. Data review revealed 277 patients with germline variants including 2 previously reported pathogenic cancer predisposition mutations: TP53 c.817C>T in a breast cancer patient, and RET c.1900T>A in a thyroid cancer patient. Three other patients had acquired mutations of JAK2 or TP53 in blood, confirmed by serial testing that likely represented secondary changes related to previous cancer treatments. In addition 105 germline variants of uncertain significance were identified; 12/105 were recurrent and may represent benign germline changes.

Conclusions. Solid tumor NGS molecular profiling using paired tumor/blood samples can incidentally identify pathogenic germline mutations in cancer predisposition genes. Appropriate consent and genetic counseling support is crucial for NGS tumor molecular profiling using blood/tumor pairs
MG-133 - Biochemical/Metabolic Genetics Clinical Genetics

**ABSTRACTS - CCMG**

**Background:** Rare disease can present in the first days and weeks of life and is associated with significant morbidity and mortality. The genetic and clinical heterogeneity of these conditions can pose a significant challenge for diagnosis.

**Objective:** To evaluate the diagnostic utility of the Illumina TruSightTM One panel, we performed NGS for a series of 20 newborns presenting with features suggestive of a Mendelian disease in the Neonatal Intensive Care Unit (NICU).

**Design/Methods:** Twenty patients were recruited from the NICU at the Children’s Hospital of Eastern Ontario. Inclusion criteria required a complex medical presentation (congenital anomalies, abnormalities in growth and/or neurological features). We used a family-based trio approach. Target enrichment was performed with the Illumina TruSightTM One Sequencing Panel kit. This panel targets 4,813 genes that are deemed clinically-relevant and referred to as the “clinome”. Sequencing was performed on the Illumina MiSeq. NextGene software (v2.3.4.4) was used for analyses. Time from sample acquisition to data analysis was possible in 7 working days.

**Results/Conclusion:** To date, 12 trios were sequenced and analyzed. A molecular diagnosis was made in 4 of 12 patients, comparable to the rate obtained by whole-exome sequencing from the literature. Positive cases included bi-allelic mutations in WDR19 and ACE, an X-linked mutation in MTM1 and a de novo mutation in SCN1A. Clinome sequencing has the potential to improve our ability to efficiently diagnose rare diseases in the NICU providing a cost-effective tool to evaluate the clinically relevant portion of the genome in a week’s time.

**INTRODUCTION:** Intellectual disability (ID) is a lifelong, debilitating condition affecting 2.5% of the population worldwide. Our TIDEX project aimed to identify novel (potentially treatable) inborn errors of metabolism (IEM-genes) employing the utility of the metabolic phenotype.

**Methods:** Criteria were applied to select patients for whole exome sequencing (WES) with customized bioinformatics and subsequent validation: patients with unexplained, Mendelian ID plus biochemical abnormalities.

**Results:** In 45 families meeting selection criteria, the diagnostic rate was >80%. We discovered 15 new gene defects (various phases of functional validation), including carbonic anhydrase VA deficiency (siblings with hyperammonemia -lactatemia, amenable to treatment with carglumic acid), Rabosyn5 deficiency (early endosomal recycling defect in female with intractable epilepsy), FAAH2 deficiency (in male with adolescent onset psychiatric disease), SORL1 deficiency (in boy with dementia and gaze palsy); as well as biotin responsive gene and neurotransmitter homeostasis genes. New phenotypes were detected.
in 11, including PIGA deficiency in a boy with MSUD-like brain lesions and progressive multi-organ involvement.  

Conclusions: Our success rate emphasizes the advantages of the biochemical phenotype: facilitation of candidate gene hypothesis, validation of causality, and targets for improved management with direct translation into patient care. We will now integrate metabolomics into an integrated program approach called Omics2TreatID.  

MG-134 - Biochemical/Metabolic Genetics & Clinical Genetics  

Update on Novel Treatments for Pyridoxine-Dependent Epilepsy Due to Antiquitin Deficiency  

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Background & Objectives: Seventy-five percent of patients with pyridoxine-dependent epilepsy (PDE) due to Antiquitin (ATQ) deficiency suffer developmental delay and/or intellectual disability (IQ).  

Methods: In two open-label observational studies, seven children with confirmed ATQ deficiency were started on dietary lysine restriction with regular nutritional monitoring. Biochemical outcomes were evaluated using piperolic acid and AASA levels in body fluids; developmental/cognitive outcomes were evaluated using age-appropriate tests and parental observations. Two other patients received additional arginine supplementation to reduce cerebral lysine flux.  

Results: Lysine-restriction was well tolerated and diet is safe, resulted in partial normalization of lysine intermediates in all body fluids in all patients (up to 80% reduction AASA in cerebrospinal fluid), with beneficial effects on seizure control and psychomotor development. Additional arginine fortification resulted in dramatic improvement of psychomotor development in 2 patients. Early intervention seems most effective.  

Discussion: To disseminate these novel strategies, and generate more evidence our PDE Consortium published Recommendations, developed a Digital Diet App and established a RedCap study database (www.pdeonline.org).  

MG-135 - Biochemical/Metabolic Genetics Clinical Genetics  

METABOLIC DIET APP SUITE: DIGITAL MEDICINE TO SUPPORT FAMILIES WITH INBORN ERRORS OF METABOLISM  

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Background: Diets for inborn errors of metabolism (IEMs) are known to be burdensome, with lack of nutrient information often leading to compliancy issues, one-sided nutrition and frustration for children and families. Digital technologies provide the opportunity to develop Metabolic Diet Applications for handheld devices which can help families overcome these problems.  

Objective: We aimed to develop Applications comprising nutrient information with options for tracking and exporting food records, to facilitate therapeutic compliance for IEM patients on diets.  

Methods & Results: Using Metabolic Pro Database we designed the 1st ever Metabolic Diet Apps Suite tailored to more than 15 different IEMs. Login to the App is personal. Features of each App include:
relevant nutrient listing per food item, calculation tracking of food / nutrient intake, summary of food records with graphs, own recipes, and the possibility to export the food records as PDFs. We have performed a study on user friendliness; data was used to improve the Apps, to be launched summer 2014.

Discussion: The Metabolic Diet App suite enhances personalized treatment of IEMs via digital medicine. Especially for adolescents the Apps will be attractive tools, allowing them to better understand and control their disease. Change in adherence will be evaluated.

MG-136 - Biochemical/Metabolic Genetics & Clinical Genetics
Tide Systematic Screening for Treatable Inborn Errors of Metabolism in 410 Intellectual Developmental Disability Patients

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Background: Intellectual developmental disorders (IDD), characterized by significant impairment of cognitive functions and behavior, affects 2.5% of the population with significant morbidity and associated healthcare costs. Inborn errors of metabolism (IEM) currently constitute the largest of genetic defects amenable to causal therapy. Early diagnosis prevents or minimizes brain damage.

Methods: Our literature review identified 91 such treatable IEM; although evidence is limited, therapies are often effective, safe, accessible. We translated this knowledge into the TIDE diagnostic protocol and App (www.treatable-id.org): The 1st tier comprises metabolic screening tests in blood/urine, the 2nd tier requires specific tests based on phenotype. The protocol was implemented during 2 years in 3 divisions in our tertiary care centre.

Results: Treatable IEMs were identified in > 5% (n=23) of 410 IDD patients, including creatine deficiencies, amino-acidopathies, metal/vitamin responsive disorders, lysosomal storage/neurotransmitter diseases (majority detected via 1st tier tests). Compared to previous clinical practice, the TIDE protocol reduced ‘time to diagnosis’ by 6 months (range 1-50months) as well as costs of unnecessary testing (>1500- per patient).

Conclusions: Our protocol for treatable forms of ID has proven effective in terms diagnostic yield, speed, costs. Better outcomes can be achieved via standard screening for treatable conditions in IDD patients.

MG-137 - Clinical Genetics Molecular Genetics
Autosomal recessive disorders are common in the Old Order Amish population of southwestern Ontario.

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Background. The Old Order Amish in Milverton, Ontario, represent a genetically isolated group which originated with 12 founding families in 1824. Due to inbreeding and founder effect, certain genetic disorders have become highly prevalent in Ontario Amish.

Objective. This study aims to describe the spectrum of genetic disorders observed in the Old Order Amish of Southwestern Ontario (population size ~ 2500).

Design and Method. Over the past 25 years, we have documented the clinical phenotype, and molecular etiology of genetic disorders in Old Order Amish children.
**Results.** A disorder characterized by acute encephalopathy with fever, visual hallucinations, hearing loss, and retinal dystrophy was observed in 7 out of about 220 families, caused by mutation in the histidyl t-RNA synthetase (HARS) gene. Acute respiratory distress syndrome may lead to sudden death. This disorder was first reported in the Amish in Pennsylvania. Other disorders observed in the Ontario Amish but not in American Amish include endocrine-osteodysplasia syndrome (ICK), cerebral atrophy (TMPRSS4), cystinosis (CTNS), sodium diarrhea (SPINT2), juvenile-onset glaucoma (CYP1B1), epidermolysis bullosa simplex, and Fraser syndrome (FRAS1). Lethal disorders include a central hypoventilation syndrome, a disorder with oligohydramnios and renal hypoplasia, and ichthyosis-microcephaly. In total, the causative mutations have been found for 8 disorders, while another 5 disorders are presumed autosomal recessive. Knowledge of these disorders enabled molecular diagnosis of a child affected concurrently with two conditions within 5 days of birth.

**Conclusion.** Awareness of genetic disorders common in this population will aid in early diagnosis and management, and avoid the diagnostic odyssey.

**MG-138 - Cytogenetics/Microarray & Molecular Genetics**

**Co-Occurrence of Cohen Syndrome with 16p11.2 Duplication: the Exome Sequencing Approach**

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**Background:** The recurrent duplication of 16p11.2 (dup16p11.2) is associated with a broad spectrum of neurocognitive phenotypes with incomplete penetrance and variable expressivity.

**Objective:** To explore the possibility of co-occurrence of other genetic alterations in the genome that could explain the variability in the clinical phenotypes of dup16p11.2 cases.

**Methods:** We used whole exome sequencing with Illumina HiSeq 2000 to screen the mutational load of a trio family involving a boy with idiopathic ID/ASD who inherited dup16p11.2 from his healthy mother. Golden Helix SVS v8.1.5 software was used for data analysis. We excluded all variants outside the exonic regions (except variants at canonical splice sites), synonymous and common autosomal dominant or X-linked variants (>1% MAF), or autosomal recessive variants (>5% MAF). Seven bioinformatics tools predicted functional damaging and conservation scores of remaining variants. Their expression pattern and role in disease based in literature were also considered.

**Result:** After filtering, two compound heterozygous variants of VPS13B (8q22.2) at canonical splice sites were detected in the proband, confirmed by Sanger sequencing. Nucleotide changes c.1426-1 and c.4157+1 were inherited from the mother and father, respectively. VPS13B protein is required for Golgi integrity and function and involved in vesicle-mediated sorting and intracellular protein transport. Mutations and/or CNVs in VPS13B cause the autosomal recessive Cohen syndrome with which the proband’s phenotype is consistent (ID, ASD, postnatal microcephaly, facial gestalt, retinal dystrophy, body habitus, joint hypermobility and episodic neutropenia).

**Conclusion:** Our study showed that variable expressivity among cases with 16p11.2 duplication may be due to the presence of other disease causing variants.

**MG-139 - Clinical Genetics Molecular Genetics**

**Non-penetrance, variable expressivity or non pathogenicity of ABCC9 dilated cardiomyopathy (DCM) mutation in 3 generation kindred**

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Mutations in ABCC9 have been implicated in the development of Cantu syndrome, Brugada syndrome, and isolated dilated cardiomyopathy (DCM). ABCC9 codes for the SUR2A subunit of the cardiac K(ATP) channel. Missense mutations are implicated in the development of Cantu as gain of function effects, but a null mutation has been reported in the literature as causing isolated DCM. We report a large family with an ABCC9 mutation. The female proband presented at age 63 with severe bradycardia requiring a pacemaker, and was diagnosed at age 67 with DCM. A heterozygous null mutation in ABCC9, c.169C>T (p.Gln57X) in exon 2 was discovered and was reported in 2009 as presumed pathogenic. Her obligate carrier brother had severe DCM in his mid-50’s requiring cardiac transplantation. Her obligate carrier sister is reported to have a pacemaker in her 60’s with no DCM. In the subsequent generation, a male with the mutation at age 46 had a normal LV size and function, with a reported mild concentric LVH. Four other mutation carriers (ages 32, 40, 42 and 59) have no echocardiographic evidence of DCM. Although non-penetrance and variable expressivity could explain the large number of unaffected mutation carriers in the family, it remains unclear if this ABCC9 mutation is responsible for the DCM in this family. Despite mutations in this gene being reported in 2004 as causing DCM, there are few subsequent reports of affected families, and no reports of familial segregation. This family illustrates the difficulty in interpreting molecular results when literature is limited and published before more stringent criteria for pathogenicity were established. The importance of careful family follow up of purported genetic mutations cannot be overstated. A critical literature review and correlating familial genotype and phenotype information should be performed when interpreting molecular genetic test results.
MG-141 - Clinical Genetics

A further report of pediatric cancer and cleidocranial dysplasia raises the possibility of a causative association of weak effect

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**Background.** RUNX2 can act as both oncogene and tumor suppressor. In cleidocranial dysplasia (CCD), RUNX2 mutations cause haploinsufficiency of the protein. We encountered a young man with CCD who developed lymphoma at age 16 years and melanoma in his early 20s. Sequencing of RUNX2 identified a novel, damaging and conserved missense mutation (p.Arg186Ile) not present in either parent.

**Objectives.** We sought evidence to support or refute a greater than expected cumulative incidence of pediatric cancer in CCD.

**Design/Method.** We reviewed English language descriptions of individuals with CCD to identify the proportion with pediatric cancer. We compared this frequency to the expected background frequency of cancer in the pediatric age range. We also performed a sensitivity analysis to determine a reporting bias threshold at which a perceived association would be spurious.

**Results.** Six of 1242 individuals with CCD had pediatric cancer. One would expect only 1 in 6250 individuals to have cancer prior to age 20 (SEER CDC data). The estimated relative risk is 30-fold based on this data. If, however, a co-occurrence of CCD and pediatric cancer is 15 times more likely to be reported in the literature than an occurrence without cancer, then the observation of increased relative risk is spurious.

**Conclusions.** Our data suggests a role for RUNX2 in some pediatric cancers and a possible increased relative risk, but low absolute risk, for cancer in CCD. A CCD registry with prospective data collection may be the best means to determine actual risk of pediatric cancer in CCD.

MG-142 - Biochemical/Metabolic Genetics

Improved Motor Function With 5-Hydroxytryptophan in a Family With Systemic Serotonin Deficiency, Hemiplegic Migraines and Neurodegenerative Course

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**Background:** Serotonin’s role is multiple: controlling mood and sleep, modifying vascular resistance, modulating spinal segmental reflexes and nociception amongst others.

**Case report:** We present a family with three affected siblings, presenting with hemiplegic migraines, spinal cord atrophy, progressive lower limb weakness and spasticity, who were found to have profoundly low CSF 5HIAA levels (25, 14, 18 nmol/L, ref 87-189) and low platelet serotonin levels. Their motor function and strength greatly improved with 5-hydroxytryptophan (5HTP)/carbidopa treatment.

Platelet serotonin transporter function was diminished, and cytoskeletal aggregates were proven to keep membrane proteins in the non-soluble fractions. Whole exome sequencing revealed a novel variant in SRRM2 gene, supporting alternative splicing of many target genes. This protein is a component of the spliceosome and has multiple functions in the splicing process. It also plays an important role in pre-mRNA splicing and has a role in cell migration. Alternative splicing increases the complexity of mammalian transcriptomes since nearly all mammalian genes express multiple pre-mRNA isoforms. Full transcriptome analysis comparing RNA expression in two affected and one unaffected sibling revealed multiple differences in levels of RNA expression and splicing.

**Conclusion:** Improvement of motor function with 5HTP/carbidopa proves yet another important role of
serotonin as a signaling molecule probably through its action on G-protein coupled receptors.

**MG-143 - Molecular Genetics**

**Molecular Genetics**

**MG-143 - Molecular Genetics**

**Age is significantly associated with the bone marrow engraftment in patients with allogeneic stem cell transplantation**

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**Objectives:** Allogeneic stem cell transplantation is a curative therapy for patients with hematological malignancies and nonmalignant hematological disorders. Measuring the bone marrow engraftment via donor chimerism following transplantation is often used as a predictor for the overall survival. However, prognostic factors associated with bone marrow engraftment are poorly understood. The objective of this study is to evaluate the effect of age, gender and the recipient-donor relationship on the extent of bone marrow engraftment following transplantation and thereby provide more precise counseling to patients.

**Methods:** The bone marrow engraftment was routinely monitored using the multiplex fluorescent short tandem repeat analysis. Complete engraftment is defined as ≥95% of both donor-derived white blood cells and T cells. Data from a cohort of 194 patients with various conditions and up to 10 years of follow up was retrospectively analyzed. Logistic regression and survival analyses were performed using the R statistic software.

**Results:** 64.9% of patients reached complete engraftment, ~70% out of which achieved this milestone within 2 years post-transplantation; but 6.3% of these patients relapsed. Gender and recipient-donor relationship (related or not, same sex or not) did not have significant effect on the probability and the time for reaching complete engraftment. Age was inversely related to the probability of complete engraftment. The older the patient was, the less likely he/she achieved complete engraftment (p value 0.0015), and the longer time took for reaching complete engraftment (p value 0.0009).

**Conclusion:** Age is significantly associated with the likelihood and time for reaching complete engraftment.

**MG-144 - Molecular Genetics**

**When Rare Happens: Characterizing Atypical Breakpoints in CML**

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Chronic Myeloid Leukemia (CML) is a hematopoietic disorder characterized by an increased proliferation of predominantly the myeloid lineage in the bone marrow and consequently the accumulation of these cells in the blood. It is caused by a translocation between the q arms of chromosome 9 and 22 resulting in the fusion of the proximal portion of BCR (on chromosome 22) to the distal portion of ABL1 gene (chromosome 9). In most cases of CML, the translocation breakpoint occurs either downstream of BCR exon 13 or 14 and upstream of ABL1 exon 2 (major breakpoint). In a small proportion of CML patients, the breakpoint occurs downstream of BCR exon 1 (minor breakpoint). Patients with either the major or minor breakpoint are monitored in our laboratory using quantitative RT-PCR (Q-RTPCR) from peripheral blood derived RNA in order to assess response to tyrosine kinase inhibitor (TKI) therapy. Here we describe two cases of CML from Saskatchewan with rare, atypical breakpoints. In each case, peripheral blood derived RNA obtained at diagnosis was subjected to Q-RTPCR. Results revealed an estimated molecular burden far inferior to what would be expected of such a specimen. This discordance was investigated using conventional
ABSTRACTS - CCMG

RTPCR using exon specific forward primers targeting BCR exons 1 through 12. For patient #1, the results revealed that the fusion point on BCR occurred downstream of BCR exon 8 and upstream of BCR exon 9 (i.e. in intron 8). Investigational sequencing studies on the PCR products seen in the RTPCR reaction revealed the presence of an atypical breakpoint involving BCR exon 8, SNRPD3 exon 3, and ABL1 exon 3 (b8s3a2 fusion variant). The second case was also subjected to exon-specific forward PCR which revealed the fusion point on BCR occurred downstream of BCR exon 6 and upstream of BCR exon 7. Sequencing analysis revealed that the patient had an in-frame b6a2 fusion variant. In addition, we describe a third Saskatchewan case in which the patient had developed resistance to treatment with imatinib. Sequential kinase domain sequencing studies revealed, in turn, that the patient evolved an imatinib resistant clone harbouring ABL1:p.Met244Val, followed by a clone in which ABL1 exon 04 encompassing codon 244 was deleted, followed by loss of the latter clone and re-emergence of ABL1:p.Met244Val.

MG-145 - Clinical Genetics

Importance of Fetal Fraction Analysis for cfDNA Testing in the General Pregnancy Population

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MG-146 - Clinical Genetics

Potential Biological Explanations for No Results for Sex Chromosome Aneuploidy Assessment Using Directed Cell-Free DNA Analysis: A Summary of Three Cases.

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Background: Analysis of cell-free DNA (cfDNA) isolated from maternal plasma for fetal trisomy 21, 18, and 13 risk assessment has been introduced into prenatal care across the globe. This technology also screens for sex chromosome aneuploidy (SCA). Regardless of the cfDNA test methodology used, small validation studies demonstrate lower test performance than for autosomal trisomy. The focus in scientific literature has been on predictive capabilities of cfDNA testing in successful analyses. Less attention has been given to analyses for which results cannot be provided. For SCA assessment, there are instances where sex chromosome copy number cannot be determined and a statistical likelihood of a disomic (XX, XY) or non-disomic (X, XXX, XXY, XYY, and XXYY) genotype cannot be established. Although infrequent, results may be due to technical or biological factors and represent a counseling challenge.
Objective: We present three cases using directed cfDNA analysis that resulted in trisomy risk assessment but no results for SCA. Further evaluation identified a potential explanation.

Results: Case #1: the patient opted to pursue diagnostic testing by amniocentesis, which revealed a 45,X[4]/46,XY[14] fetal karyotype. Case #2: peripheral blood chromosome analysis identified a 45,X[8]/46,XX[54] maternal karyotype. Case #3: a previously unreported twin gestation was revealed. Since extensive further evaluation is rarely indicated or pursued, the frequencies of these biological explanations are unknown.

Conclusion: Qualitatively, these cases underscore the importance of inclusion of the possibility of no results into pre-test counseling and add to the base of knowledge for use in post-test counseling in these situations.

MG-147 - Clinical Genetics & Molecular Genetics

Canadian Open Genetics Repository (COGR): a unified clinical genome database as a community resource for standardizing and sharing genetic interpretations

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Background: The utility of DNA variant databases created by Canadian laboratories is compromised by the many differences between them and data has become increasingly difficult to share. There is a critical need for collaborative measures between institutions to better facilitate variant analysis and information transfer.

Objectives: The Canadian Open Genetics Repository (COGR) is a collaborative effort for the collection, sharing and analysis of variants reported by medical diagnostics laboratories across Canada. Using a commonly shared platform, a large repository will be constructed consisting of information related to human gene DNA variants and their relationship to disease.

Design/Method: COGR uses GenelInsight™, a database featuring full versioning of variant assessments and interpretations, security, and role-based editing of variant information. COGR provides each participating lab with an instance of the application as well as a Variant Assessment Tool.

Results: The COGR network currently contains over 3,000 variants across 52 genes associated with 7 diseases. In total, 396 variants have been identified in more than one lab including 50 that have been identified by three labs. Around half of commonly identified variants have concordant classifications across labs.

Conclusions: As an ongoing endeavor and a permanent resource, COGR will facilitate collaboration between Canadian laboratories and with the international efforts to develop tools and methods for taking full advantage of clinical laboratory data. We expect as more labs begin sharing data, this resource will lead to more consistent reporting, generation of knowledge rings and ultimately improve patient care.