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BOOK OF ABSTRACTS

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HYPERPHOSPHATASIA WITH SEIZURES, NEUROLOGIC DEFICIT AND CHARACTERISTIC FACIAL FEATURES: FIVE NEW CASES OF MABRY SYNDROME.

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In 1970, Mabry et al. described multiple cases of persistent hyperphosphatasia associated with developmental delay and seizures in a single consanguineous family (OMIM#239300). The nosology of this condition, however, is uncertain. We report five new cases that help delineate this disorder and provide further evidence favouring autosomal recessive inheritance, with sib recurrence in one instance (French non-consanguineous parents), and consanguinity (Lebanese parents) in another. Common to all five children is the Mabry triad of tonic-clonic seizures (usually beginning around one year of age), moderate to severe developmental delay, and persistently elevated alkaline phosphatase activity, without any indication of liver or metabolic bone disease. The degree of hyperphosphatasia varies considerably amongst cases (~1.3 to 20 times the upper age-adjusted reference limit). In addition, all five cases share show similar facial features, including hypertelorism, broad nasal bridge, and tented mouth. The three singleton cases were noted to have a distinctive brachytelephalangy recognized in early childhood, and there is radiographic evidence of distal phalangeal anomalies in the older French siblings. In the kindred first described by Mabry et al., at least one family member was noted to have intracellular inclusions on biopsy of rectal mucosa but not liver. In three of our cases, inclusions have been observed in cultured cells and in skin biopsy, but the cells are not uniformly affected and characterization is still in progress. There are similar cases in the literature which suggest genetic heterogeneity. However, the five cases we present provide further evidence for an autosomal recessive condition characterized by hyperphosphatasia, seizures, and neurologic deficit -- a disorder we call Mabry syndrome.



**HIGHLY VARIABLE PHENOTYPIC EXPRESSION OF THE MITOCHONDRIAL DNA MUTATION
3697G>A CAUSING COMPLEX I DEFICIENCY IN AN EXTENDED FAMILY**

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History: Over 20 years ago, a patient was diagnosed with Leigh disease presenting in early childhood, and isolated complex I deficiency was shown in muscle. No maternal family history of disease was evident at that time. Recently, however, a maternal cousin presented in infancy with Leigh disease, and several mildly affected relatives were then recognised.

Mutation analysis: Sequencing of the seven mtDNA genes encoding complex I subunits revealed a single pathogenic mutation, 3697G>A (substituting serine for glycine 131 in the ND1 subunit). We then performed targeted testing for this mutation on 8 family members with a wide spectrum of disease expression, ranging from asymptomatic to severely affected. A semi-quantitative PCR-RFLP assay was applied to various sample types (blood, muscle and/or urine).

Results: The 3697G>A mutation was detected in all 8 individuals. There appeared to be only a weak correlation between the mutant load in any sample type(s) and the clinical phenotypes. The mutant load (degree of heteroplasmy) was substantially higher in muscle than in blood (n = 4 patients), and likewise the mutant load was considerably higher in urine than in blood (n = 3 patients). In one asymptomatic patient, the mutation was not detected in blood but clearly present in urine.

Discussion: The 3697G>A mutation has been reported only twice before, in one patient with MELAS and in two siblings with LHON and spastic dystonia respectively. Our present report extends the range of associated clinical phenotypes. Testing for this mutation using urine is more sensitive than testing on blood and provides a non-invasive method for extended family investigation, to facilitate diagnosis and reproductive decision-making. However, the presence, diversity and severity of clinical symptoms are not simply predictable by assessment of mutant load in any accessible tissues. This may reflect tissue-specific variations in load and/or other genetic modifiers.



RAPID ANEUPLOIDY DETECTION FOR LOW RISK PREGNANCIES: A SUITABLE REPLACEMENT FOR G-BANDING?

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Rapid aneuploidy detection (RAD) is a molecular technique that uses microsatellite markers on chromosomes 13, 18, 21 and the sex chromosomes to evaluate DNA obtained from amniotic fluid or chorionic villi for the presence of aneuploidies. It is used extensively in England, but has not yet gained popularity in North America due to the reduced sensitivity in detecting all chromosome anomalies in comparison to G-banded analysis. However, it is not currently clear whether the limitations associated with RAD outweigh the disadvantages of G-banded analysis, which is costly, has a long turnaround time and may lead to results with low predictive value, such as supernumerary markers, *de novo* balanced rearrangements and mosaicism. To examine the feasibility of using RAD as the primary test for prenatal diagnosis of chromosome abnormalities, we decided to establish simplified risk criteria that can be used by our counseling staff to select patients with the highest likelihood of any kind of chromosome abnormality versus patients at low risk. Patients received RAD, with results available within 24-48 hours of the amniocentesis, plus G-banded analysis, which had a 9 to 21 day turnaround. We categorized our patients into risk groups and evaluated the detection rate of RAD only versus RAD plus G-banded analysis. Through this prospective study, we tested, in theory, the use of QF-PCR as the primary method of prenatal chromosome abnormality detection, with G-banded analysis reserved for a subset of cases deemed at higher risk. Data will be presented for >2500 patients that supports the use of RAD only in low risk pregnancies.



HYPERTELORISM-MICROTIA-CLEFTING (HMC) SYNDROME: EXPANSION OF THE PHENOTYPE

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Abstract: Hypertelorism, Microtia, Facial Clefting Syndrome (HMC syndrome) is a rare most likely autosomal recessive condition characterized by hypertelorism, microtia, and clefting of the lip, palate and nose. So far six reports with total number of 9 patients have been reported. We report a boy who was born to healthy, non-consanguineous parents; born with hypertelorism, bilateral anotia, right cleft lip and palate and absent right thumb. He has ventricular septal defect, and has normal kidneys and spine. Hearing test showed good bone conduction and normal cochlear function in both ears. Chromosome and microarray analysis were normal. Although hypoplasia of the thenar eminence and unilateral anotia were reported in the past, our patient expand the spectrum of the condition to include absent thumb and bilateral anotia not previously reported in this condition.



PATERNAL UNIPARENTAL ISODISOMY FOR CHROMOSOME 14 IN A CHILD WITH NORMAL KARYOTYPE, RESULTING FROM Malsegregation of Maternal Robertsonian Translocation

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Paternal uniparental disomy for chromosome 14 (patUPD14) is a rare abnormality associated with a recognizable phenotype of small thorax, hypoplastic ribs, short limbs, abdominal wall defects and characteristic facies. Most of the patUPD14 cases have been ascertained because of an abnormal phenotype. UPD14 can result from trisomy or monosomy rescue during fetal development. Some cases are associated with a familial Robertsonian translocation (ROB), where the affected children were shown to carry the translocation.

We report a 8 month old girl diagnosed with patUPD14 and normal karyotype 46,XX. Polyhydramnios, short limbs and small thorax were detected prenatally. Post natal clinical features included a narrow bell-shaped chest, short limbs, contractures of the thumbs, blepharophimosis, congenital heart defect and dysmorphic features (deep-set eyes, full cheeks, vertical chin crease and short neck). Molecular analysis confirmed complete paternal isodisomy of chromosome 14. Parental chromosome analyses showed that the mother is a carrier of der(13;14)(q10;q10). The proposed mechanism leading to patUPD14 in this patient is the duplication of paternal chromosome 14 in a monosomic conceptus resulting from maternal meiosis I nondisjunction and fertilization of a nullisomic gamete.

The majority of published UPD14 cases with normal karyotypes were not followed with parental karyotype analysis. As der(13;14) is the most common translocation in humans, we propose that chromosome analysis in parents of UPD14 patients with normal karyotype should be considered to better determine the frequency of ROB in these families.



ARRAY CGH ANALYSIS OF 4q TERMINAL DELETION DIAGNOSED IN A GIRL WITH MILD DYSMORPHIC FEATURES, DEVELOPMENTAL DELAY AND NO MAJOR CONGENITAL ANOMALIES

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The 4q deletion syndrome, comprising all cytogenetically visible deletions (interstitial or terminal) of the long arm of chromosome 4, is a well-recognized distinctive disorder, described in more than 100 patients. Common phenotypic features of 4q- syndrome are mild dysmorphic features, mild to severe mental retardation, growth deficiency, cleft palate, limb anomalies, cardiac and genitourinary defects. A unique finding consisting of a stiff, pointed 5th finger with a hypoplastic distal phalanx and either a hooked or a volar nail is observed in two thirds of patients. Patients with large terminal deletions, with breakpoints in 4q31, are most severely affected. More distal 4q deletions involving bands 4q33 to 4q35 have been found so far in about 25 cases. These patients present less characteristic dysmorphisms and less severe mental retardation. Some authors suggest that the region 4q31-q34 is critical for most of the clinical phenotype. *HAND2* in 4q33 has been proposed as a candidate gene for the cardiac defects, and a gene involved in limb deficiencies was tentatively assigned to 4q33. It is clear that phenotypes associated with 4q deletion are grossly related to the breakpoint location and the amount of genetic material lost.

We present a 12-year old girl with mild dysmorphic features and developmental delay with learning difficulties. Karyotype analysis revealed a terminal deletion on chromosome 4q. Array CGH showed a deletion of over 17 Mb, with the breakpoint within the 4q34.2 band.

Literature review and genotype-phenotype correlations in 4q deletion syndrome will be discussed.



UNDERSTANDING THE MOLECULAR PATHOGENESIS OF MALFORMATION SYNDROMES IN AN ISOLATED POPULATION

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Clinics that see patients from unique populations are often enriched for novel and unreported phenotypes, providing resources for the identification of new genes associated with malformation syndromes. The Hutterites are an isolated population living on the North American prairies that originated from one of several Anabaptist groups formed during the Protestant reformation in the 16th century. The current population, numbering over 40,000, has descended from less than 89 common founders. Over 30 different autosomal recessive conditions have been described in the Hutterites. The gene and/or Hutterite-specific mutation remains to be identified for more than half of these conditions (Boycott et al, AJMG 2008, 146A:1088) and novel malformation syndromes continue to be identified.

We are systematically approaching the autosomal recessive disorders in this community to identify the molecular pathogenesis for each condition. For those disorders that are present in other populations and are genetically heterogeneous we have used a targeted identity-by-descent approach to prioritize analysis. With only one patient we identified a homozygous novel mutation in BBS2 as the cause of Bardet-Biedl syndrome in this population. For disorders unique to the Hutterite population we have used a genome-wide identity-by-descent approach to localize the gene. Three novel autosomal recessive Hutterite syndromes associated with congenital anomalies have recently been identified and mapped. JSRD (Joubert syndrome related disorder) is a mid-hindbrain malformation syndrome associated with occipital encephalocele and renal disease which maps to 2q37; FARR (Forehead, Abnormal heart, Renal, Rhino) syndrome is a microcephaly syndrome associated with congenital heart and renal malformations which maps to 16ptel; and CASS (Cerebellar Atrophy, Short Stature) syndrome is a cerebellar atrophy syndrome associated with short stature which maps to 4q24. Candidate genes are currently being analyzed. Identification and subsequent characterization of novel genes causing malformation syndromes in this population will enhance our understanding of potentially several developmental pathways.



MOLECULAR ETIOLOGY OF STARGARDT DISEASE IN NEWFOUNDLAND AND LABRADOR

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Objective: to identify mutations in the *ABCA4* gene in Newfoundland (NL) families with Stargardt disease (STGD) and related retinal dystrophies.

Patients and Methods: 31 families with STGD have been identified in NL since 1978 and members of 22 families were available for molecular analysis. DNA was collected from 37 affected and 27 unaffected consenting members of these families and sequenced on the ABI 3130 automated sequencer. Variants were reviewed manually and with Mutation Surveyor and compared with Asper Ophthalmics and Retina International mutation databases. Clinical records were reviewed for all affected individuals and phenotypes for each genotype compared. The study was approved by the Human Investigation Committee of Memorial University Faculty of Medicine.

Results: Ancestors of 13/22 families came from one bay in eastern NL. Both mutations have been identified in 28 patients, a single mutation in 4 individuals and no mutation for five individuals in five families. The common IVS40+5G>A mutation was homozygous in seven individuals and heterozygous in 11 others all from the eastern bay. A second mutation IVS38 -10T>C was present in 7 individuals from this same bay. Twelve other mutations were identified in fewer individuals.

Conclusions: Multiple mutations were identified in NL families with IVS40+5 G>A being the most common mutation. IVS40+5G>A homozygotes had less severe disease than compound heterozygotes with this mutation. The IVS38 -10T>C mutation was seen in two families with severe disease confirming the cone-rod dystrophy presentation previously reported. As with other hereditary eye diseases in NL, founder effect and diversity of mutations for STGD was found with 75% of individuals explained.



**DETECTION OF MUTATIONS IN BRCA1 AND BRCA2 GENES USING ENHANCED MISMATCH
MUTATION ANALYSIS (EMMA)**

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Mutation detection in inherited breast cancer is a labour intensive process associated with a high cost in both technologist time and supplies. A number of methods have been employed to detect mutations ranging from PTT to DHPLC and finally sequencing of all exons as well as MLPA to detect large gene rearrangements. Recently Claude Houdayer et. al. reported on a new technology for BRCA1 and BRCA2 mutation detection (10th International Symposium on Mutations in the Genome). This technique, referred to as Enhanced Mismatch Mutation Analysis (EMMA), uses heteroduplex analysis and capillary electrophoresis to screen for mutations in both genes. The improvement over traditional heteroduplex analysis involves the use of a proprietary matrix for electrophoresis and the addition of nucleosides in the buffer that enhance the discrimination between homoduplexes and heteroduplexes. In working with the company Fluigent they have developed and validated 24 multiplex PCR reactions that scan for mutations throughout both genes. In addition, by adding control PCR reactions large gene rearrangements can be detected simultaneously. They have validated this technique on 402 patients and have shown that it is at least as sensitive as DHPLC. By using this technique they claim to have reduced the cost of BRCA testing by 33% and increased the throughput by 4X.

We have evaluated this technique for BRCA1 and BRCA2 testing in our laboratory. A total of 35 previously analyzed samples were selected for analysis. The selected samples were chosen based on the presence of common polymorphisms in both genes as well as different types of mutations and variants and whole exon deletions and duplications. The samples were blinded and the results were compared with previous results obtained by DHPLC/MLPA testing. The questions asked were 1) Is EMMA able to identify all variants, mutations and polymorphisms 2) Does EMMA discriminate between mutations / unknown variants and common polymorphisms 3) Does EMMA reliably detect large gene rearrangements. The results from these analyses will be presented as well as a comparison between the costs associated with this technique and other commonly used techniques.



Abstract withdrawn by author.



REARRANGEMENTS OF THE CIZ(ZNF384) GENE IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA WITH CD-10-LOW/NEGATIVE IMMUNOPHENOTYPE

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The CIZ (ZNF384) gene, a putative zinc finger transcription factor located distal to the TEL (ETV6) gene on the chromosome 12 short arm, is recurrently rearranged in acute leukemia. To date, twenty-two patients with CIZ rearrangements have been reported. Most of the patients with CIZ rearrangements are children or young adults with B-precursor acute lymphoblastic leukemia (ALL). The CIZ gene has three known partners: TAF15 (17p13; 16 cases), EWSR1 (22q12; 4 cases) and E2A (19p13; 2 cases). We present seven additional pediatric ALL patients with CIZ gene rearrangements. Four of the patients had E2A-CIZ rearrangements and one had an EWSR1-CIZ rearrangement. The remaining two patients had CIZ gene rearrangement involving novel regions on chromosome 6 and chromosome 22, suggestive of a two additional CIZ partner genes. As with ETV6(TEL)-RUNX(AML1) rearrangement, the t(12:19)(p13;p13.3) and t(12:22)(p13;q12) mediating the E2A-CIZ and EWSR1-CIZ translocations are cryptic by traditional karyotyping analysis. Identification of the rearrangements was facilitated using dual colour breakapart probes for the E2A, CIZ and EWSR1 loci. The patients, five females and two males, ranged in age at diagnosis from 2 to 15 years. All of the patients presented with a CD10-negative or CD10-low immunophenotype with concurrent expression of myeloid antigens CD13 and CD33, similar to the antigenic profile seen in MLL gene-rearranged ALLs. Follow up on the patients ranges from 3 to 33 months, and none of the patients have relapsed. Since CIZ gene rearrangement may be associated with a more favorable prognosis than MLL rearrangement, FISH analysis with probes to detect CIZ gene rearrangements is recommended in patients with CD10-low/negative ALL.



BCCGN - A MODEL FOR CLINICAL INVOLVEMENT IN GENOMIC RESEARCH

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A survey of BC doctors has shown they are interested in participating in genomic research and have patients for whom genomic studies might be informative but lack the knowledge, funding and translational research framework needed to carry out such research. The BC Clinical Genomics Network (BCCGN) aims to increase clinical and translational research through programs that educate physicians in genomics and provide an infrastructure that supports them as they design, carry out and analyze clinical research studies. The Network is in its second year of operations and has successfully assisted 28 physicians to address genetic questions and discover new answers for their patients.

BCCGN staff work together with BC's state-of-the-art high-throughput sequencing, high-throughput genotyping, copy number analysis and bioinformatics platforms in providing access to genomic technologies for clinical research studies. BCCGN also provides consultation in genetic epidemiology, biostatistics, database design, health technology assessment, and clinical ethics to facilitate clinical genomics studies by general practitioners and specialist physicians. This will in turn advance knowledge in the field of genomics, improve patient care and result in increased research in the province.

Some examples of projects conducted with the assistance of the BCCGN include a study of comparative genomic hybridization of children with intractable cryptogenic epilepsy, the identification of a gene responsible for a new X-linked mental retardation syndrome and a study using metagenomics to identify pathogens that cause Crohn's Disease.

BCCGN is currently taking part in consultations with organizations in other provinces who are interested in setting up similar networks.

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**GENETIC STUDY OF A FAMILY WITH SPLIT HAND/FOOT MALFORMATION
WITH LONG BONE DEFICIENCY**

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Split Hand Foot Malformation with Long Bone Deficiency (SHFLD) is a relatively rare autosomal dominant malformation with extremely variable presentation ranging from hypoplastic halluces to monodactyly with tibial aplasia. Typically the upper limbs are more affected than the lower limbs.

Overall the genetics of the SHFM malformations, including the SHFLD groups, are poorly understood. To date no genes have been specifically implicated in SHFLD however, at least three loci have been reported; 1q42.2-q43 (SHFLD1), 6q14.1 (SHFLD2) ¹ and 17p13.3-p13.1 ². Studies have not suggested any overlap in the genetic positions of the isolated SHFM loci or those for SHFLD.

We describe a three-generation Canadian -Mennonite family with 5 affected members and at least three unaffected obligate carriers. The inheritance pattern is in keeping with autosomal dominant inheritance with decreased penetrance. The proband has a moderate phenotype with characteristic split hand foot malformation, while two other individuals have a more severe phenotype with either isolated tibial aplasia, or unilateral monodactyly with tibial aplasia. The other two affected individuals have an intermediate phenotype.

Molecular investigations have revealed an intriguing 300 kb duplication involving three genes on chromosome 17 and overlapping the locus described by Lezirovitz in 2008 ². The 5'- and 3'- breakpoints of the duplication each disrupt a gene and the third gene is duplicated in its entirety. We will present the clinical features and results of additional genetic investigations in this family.

References

1. Naveed et al. *Am. J. Hum. Genet.* 80: 105-111, 2007.
2. Lezirovitz et al. *Hum Genet* 123: 625-631, 2008.



ADIPOCYTOKINES RESPOND TO CARDIAC STATUS IN MULTIPLE SYMMETRIC LIPOMATOSIS

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Multiple Symmetric Lipomatosis (OMIM No. 151800, also known as Cephalothoracic Lipodystrophy, Familial Benign Cervical Lipomatosis, Launois-Bensaude syndrome, and Madelung's Disease) is a poorly-understood late-onset disorder that features accumulation of adipose tissue in the proximal limb segments, upper thorax and neck. Many etiologies have also been proposed, including toxic (alcoholism), genetic and neoplastic. Here we report an elderly European lady who presented with signs and symptoms of MSL, and was discovered to be in atrial fibrillation. Coronary angiography revealed no stenosis or obstruction, and there was no thyrotoxicosis or ischemic heart disease. Circulating adiponectin was paradoxically elevated and leptin levels were paradoxically low. Surprisingly, treatment of cardiac failure normalized circulating leptin and adiponectin. Microarray analysis using the Affymetrix 6.0 array found a previously-unreported duplication of 150 kbp including a gene known to be critical for accumulation of subcutaneous fat. These findings suggest a link between cardiac failure, adiponectin and leptin levels, possibly indicating the presence of an "adipocardiac axis."



IS THERE EVIDENCE FOR AN AUTOSOMAL RECESSIVE VARIANT OF RUBINSTEIN-TAYBI SYNDROME IN THE HUTTERITE POPULATION?

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Rubinstein-Taybi Syndrome (RTS) is a rare autosomal dominant, multiple congenital anomaly syndrome, characterized by distinctive facial gestalt, broad thumbs and halluces, and mental retardation. RTS is genetically heterogeneous, with approximately 50% of patients having mutations in the CREB binding protein (CREBBP) or EP300 genes.

The Hutterites are an endogamous Anabaptist population. Over 30 autosomal recessive conditions-many novel- have been identified in this community.

We present two related Hutterite individuals born to unaffected parents, both with a clinical diagnosis of RTS. Patient 1 was born to double second cousin parents. By 5 weeks growth parameters were below the 3rd centile and dysmorphic features were noted including downslanting palpebral fissures, prominent long nose, and slightly broad halluces. Diagnosis of RTS was made at 6 months. By 6 years of age he had relative microcephaly and global developmental delay. Patient and parental karyotypes were normal. Patient 2 was a female whose father is a 2nd cousin to the mother of patient 1. She was referred because of dysmorphic features. Her phenotype was typical for RTS with head circumference and height below the 3% and weight at the 50%, broad/angulated thumbs and duplicated halluces. She had global developmental delay and normal karyotype. At 3 years of age, she developed medulloblastoma (a known RTS related malignancy) and died at age 4.

CREBBP gene sequencing in patient 1 was undertaken and no mutation was found. While several explanations could remain for the presence of RTS in 2 relatives born to consanguineous unaffected parents, an autosomal recessive RTS-like condition in this population cannot be excluded. In addition we have recently ascertained a 3rd Hutterite child with a similar phenotype. Further investigations are planned including homozygosity mapping. Genes with histone acetyltransferase activity would be compelling candidates if a shared region of interest is identified.



A MOSAIC SUPERNUMERARY RING CHROMOSOME 19 RED HERRING: DE NOVO DUPLICATION OF 7p22.1 AND DELETION OF 7q36.2

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Supernumerary ring chromosomes are rare cytogenetic findings. They are most often *de novo*, but occasional familial ring chromosomes have been reported. Herein, we report a 26-year old female with severe intellectual handicap, microcephaly, short stature and dysmorphic facial features. Cytogenetic studies revealed an apparently balanced paracentric inversion in the long arm of chromosome 7, inv(7)(q22.3q36.1), and a small supernumerary ring chromosome derived entirely of material from chromosome 19. While the inversion was detected in all cells, mosaicism was observed for the supernumerary ring chromosome 19. Interestingly, the same two cytogenetic abnormalities were detected in the patient's mother, who presented with normal stature, few dysmorphic features, and normal cognition without microcephaly. To investigate the mother-daughter phenotypic discordance we assessed the level of ring chromosome 19 mosaicism in both lymphocytes and skin fibroblasts and performed array comparative genome hybridization (CGH) on DNA from lymphocytes to uncover additional genomic imbalances. While the level of ring chromosome 19 mosaicism could not adequately explain the discordance, array-CGH revealed a *de novo* 4.6 Mb terminal duplication of the short arm of chromosome 7, dup(7)(p22.1), and a 4.6 Mb terminal deletion of the long arm of chromosome 7, del(7)(q36.2) in the daughter. The patient's distinctive features are consistent with the wide phenotypic spectrum reported in 7pter duplication and 7qter deletion syndromes. These chromosomal regions, in particular 7qter, contain several candidate genes of clinical significance, including SHH (developmental field defects) and HLXB9 (Currarino syndrome), that may contribute to our patient's phenotype. To our knowledge, this is the second reported case describing the occurrence of a 7pter duplication with a 7qter deletion. In conclusion, our findings strongly suggest that our patient's phenotype is largely attributable to partial 7pter trisomy and partial 7qter monosomy rather than mosaic supernumerary ring chromosome 19.



**IDENTIFICATION OF THE MOLECULAR BASIS OF RESTRICTIVE DERMOPATHY IN HUTTERITE
AND OLD COLONY MENNONITE FAMILIES**

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Restrictive dermopathy (RD, OMIM 275210) is a lethal disorder characterized by growth retardation, tight and rigid skin, and joint contractures. After the first publication (Toriello et al 1983), Lowry and colleagues (1985) reported on 3 Alberta kindreds (2 Hutterite and 1 Old Colony Mennonite (OCM)) with RD. Recently RD has been determined to be a 'laminopathy' with either dominant mutations in *LMNA*, or autosomal recessive mutations in *ZMPSTE24*. Moulson et al (2005) identified a homozygous mutation-c.54dupT-in *ZMPSTE24* in a "Mennonite" family with RD. We speculated this was a founder mutation in OCM, and possibly Hutterite families. While the Hutterites and OCMs are distinct genetic groups, we have observed an identical mutation causing hypophosphatasia in both populations, and some Mennonites joined the Hutterites in Russia in 1783.

We studied an infant with classic RD, born to non-consanguineous OCM parents. She did not carry the c.54dupT mutation. We learned that the c.54dupT mutation had been identified in Old Order Mennonites- a different genetic isolate. Therefore full sequencing of *ZMPSTE24* was undertaken. We also investigated 2 Hutterite families- the obligate carrier parents of a deceased child, and an affected child from another family. In the OCM and Hutterite patient we identified a homozygous mutation c.1085_1086insT. This same mutation was found in both carrier parents in the other family. This mutation has been reported frequently in the literature as a cause of RD. Some data suggests this is a result of a mutation hotspot, and not a single ancestral mutation.

We assumed that the mutation c.1085_1086insT was a common founder mutation in OCM and Hutterite families. To confirm this we initiated haplotype studies, using microsatellite markers. In the Hutterite parents there was evidence of a shared haplotype around *ZMPSTE24*, however in the OCM patient there was no evidence of homozygosity, nor evidence of shared markers with the Hutterite family. It appears as if this mutation has occurred on at least 2 founder chromosomes in the OCM. While the mutation c.1085_1086insT causes RD in Hutterite and OCM families, it is not a single shared founder mutation.



**DEFINING THE PHENOTYPIC SPECIFICITY AND VARIABILITY OF
SCHIMKE IMMUNO-OSSEOUS DYSPLASIA: A HYPOTHESIS**

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Objective: Schimke immuno-osseous dysplasia (SIOD), an autosomal recessive multisystem disorder, is caused by mutations in the *SMARCAL1* gene. Although the SMARCAL1 enzyme binds open chromatin diffusely and affects global transcription, we hypothesize that its deficiency gives rise to the pathognomic features of renal failure, skeletal dysplasia, and immunodeficiency by differentially affects some genes or signaling pathways.

Methods: We assessed this using an F1 genetic screen in *Drosophila melanogaster* to measure suppression or enhancement of ectopic wing veins induced by the overexpression of SMARCAL1 or Marcal1, the *Drosophila* homologue, reviewing dental anomalies among SIOD patients, and analyzing gene expression in cultured SIOD kidney tubule epithelial cells.

Results: In the *Drosophila* model, mutations in the wingless and epidermal growth factor pathways strongly suppressed, mutations of the notch pathway strongly enhanced, and mutations in the decapentaplegic and hedgehog pathways had no effect or weakly suppressed the ectopic wing veins. The dental findings ranged from normal to varying severity of oligodontia, microdontia, and misshapen teeth. Gene expression analysis in the kidney tubule cells identified expression changes in morphogenic genes and in FSGS-associated genes.

Conclusion: Similar to mutations of RNA polymerase II and general transcription factors, dysfunction of SMARCAL1 alters the expression of some genes more than others and in turn affects tissue development and maintenance. We hypothesize that this arises because some regions of the genome are more sensitive to SMARCAL1 dysfunction than are others.



INTRAUTERINE GROWTH RETARDATION AND COMPLEX HEART DEFECTS IN ASSOCIATION WITH A der(15)t(13;15)(q12;q26.3) CHROMOSOME REARRANGEMENT; FURTHER SUPPORT OF A 15q26 DELETION SYNDROME

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The introduction of array genomic hybridization (AGH) technology to Medical Genetics has led to an explosion of new syndromes that had not been previously recognized. Among these is the recent characterization of a chromosome 15q26 deletion syndrome. Although the number of cases described are limited, the primary associated features include intrauterine growth retardation (IUGR), congenital heart defects, and congenital diaphragmatic hernia. Myriad other features are described in some of those affected, but the involvement of other chromosome regions and variability in deletion size makes it difficult to decipher which of these features are attributable to monosomy for the 15q26 region. In the current case report we describe the prenatal diagnosis of a fetus with a genotype and phenotype consistent with 15q26 deletion syndrome. A fetal echocardiogram and a level II ultrasound performed at 21 weeks gestation showed evidence of intrauterine growth retardation (IUGR) and a variant of hypoplastic left heart syndrome. There were no further fetal abnormalities observed by ultrasound. Cytogenetic studies of cultured amniocytes revealed an unbalanced female karyotype with 45 chromosomes, including loss of one chromosome 13, and a derivative chromosome 15, derived from a translocation between the long arms of one chromosome 13 and one chromosome 15. The translocation breakpoints were interpreted as bands 13q12 and 15q26.3, suggesting a normal disomic complement for most of chromosomes 13 and 15. This was supported by quantitative fluorescent PCR which showed diallelic inheritance of multiple microsatellite loci between bands 13q12.21-q32. Further characterization of the derivative chromosome using a subtelomeric FISH probe specific for the long arm of chromosome 15 was consistent with deletion of the 15q subtelomeric region. The genotypic and phenotypic fetal findings in this case provide support for a direct association between 15q26, IUGR and congenital heart anomalies. There was no evidence of congenital diaphragmatic hernia, suggesting that the gene(s) contributing to this genotype may not be included in the current deletion. Further characterization of the deleted region is ongoing in this case, in order to better define candidate genes within the 15q26 critical region that may contribute to normal intrauterine/ postnatal growth and heart development.



APPLICATION OF OLIGONUCLEOTIDE ARRAY CGH TO THE SIMULTANEOUS DETECTION OF A DELETION IN THE NUCLEAR *TK2* GENE AND MTDNA DEPLETION

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Thymidine kinase 2 (TK2), encoded by the *TK2* gene on chromosome 16q22, is one of the deoxyribonucleoside kinases responsible for the maintenance of mitochondrial deoxyribonucleotide pools. Defects in TK2 mainly cause a myopathic form of the mitochondrial DNA depletion syndrome (MDDS). Currently, only point mutations and small insertions and deletions have been reported in *TK2* gene; gross rearrangements of *TK2* gene and possible hepatic involvement in patients with *TK2* mutations have not been described. We report a non-consanguineous Jordanian family with three deceased siblings due to mtDNA depletion. Sequence analysis of the father detected a heterozygous c.761T>A (p.I254N) mutation in his *TK2* gene; however, point mutations in the mother were not detected. Subsequent gene dosage analysis using oligonucleotide array CGH identified an intragenic approximately 5.8-kb deletion encompassing the 5'UTR to intron 2 of her *TK2* gene. Sequence analysis confirmed that the deletion spans c.1-495 to c.283-2899 of the *TK2* gene (nucleotide 65,136,256 to 65,142,086 of chromosome 16). Analysis of liver and muscle specimens from one of the deceased infants in this family revealed compound heterozygosity for the paternal point mutation and maternal intragenic deletion. In addition, a significant reduction of the mtDNA content in liver and muscle was detected (10% and 20% of age- and tissue-matched controls, respectively). Prenatal diagnosis was performed in the third pregnancy. The fetus was found to carry both the point mutation and the deletion. This child died 6 months after birth due to myopathy. A serum specimen demonstrated elevated liver transaminases in two of the infants from whom results were available. This report expands the mutation spectrum associated with *TK2* deficiency. While the myopathic form of MDDS appears to be the main phenotype of *TK2* mutations, liver dysfunction may also be a part of the mitochondrial depletion syndrome caused by *TK2* gene defects.



SCHIMKE IMMUNO-OSSEOUS DYSPLASIA: A MENDELIAN COMPLEX TRAIT

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Schimke immuno-osseous dysplasia (SIOD, MIM 242900) is a highly pleiotropic incompletely penetrant multisystem childhood disorder associated with mutations of the SNF2 homolog SMARCAL1. Using phenotypic, genetic and molecular analyses of the *Drosophila*, mouse and human SMARCAL1 homologues, we found that loss of functional SMARCAL1 is insufficient to cause disease and that manifestation of disease requires the interaction of SMARCAL1 deficiency with environmental or other genetic factors. SMARCAL1, a chromatin binding DNA-dependent ATPase, is member of the trithorax group of SNF2 chromatin remodeling factor that modulates gene expression. These observations suggest that SIOD arises as a multifactorial trait when SMARCAL1 deficiency permits crossing of a gene expression threshold. Such a model explains the pleiotropism and incomplete penetrance of SIOD.



**A CRYPTIC FAMILIAL REARRANGEMENT OF 11P15, INVOLVING BOTH IMPRINTING CENTERS,
IN A FAMILY WITH A HISTORY OF SHORT STATURE**

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Silver-Russell syndrome (SRS) is a heterogeneous disorder characterized by intrauterine and postnatal growth retardation, dysmorphic facial features and body asymmetry. Both hypomethylation of the imprinting control region 1 (ICR1) in 11p15 and maternal duplication of 11p15 have been implicated in the etiology of this disorder. Here, we present a 14 year old girl with delayed fine motor and gross motor skills, expressive language delay, short stature, dysmorphic features, ADHD and anxiety. Cytogenetic analysis revealed a normal female karyotype. Array CGH was then performed and revealed a 1.98 Mb duplication of 11p15.4p15.5, containing ~28 genes and both imprinting centers (ICR1 and ICR2). FISH confirmed the duplication and showed that the duplicated material had been inserted into the long arm of chromosome 11 (at 11q23). Further FISH studies showed this duplication to be maternally inherited as the mother and half-sister had the same rearrangement; both were of short stature and had learning disabilities. The 11p15 rearrangement was also observed in the maternal first cousin who was also of short stature and the maternal grandmother who was of normal height. The 11p15 rearrangement was not seen in the maternal aunt and cousin who were of normal stature. The fact that the maternal grandmother had the 11p15 rearrangement and was of normal height could be explained by a paternally derived duplication and when passed on to her children would result in overexpression of maternally expressed genes, such as CDKN1C and H19. SRS is clinically heterogeneous and could explain both the family history of short stature and the learning disabilities and dysmorphic features seen in the proband. This study illustrates the importance of obtaining a detailed family history as this rearrangement may have been classified as an inherited CNV if pertinent family history was not included. In addition, this study demonstrates the importance of FISH in not only validating array findings, but also in detecting additional rearrangements not identified by array CGH.