poster presentations in clinical genetics

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Familial aortic aneurysms. D.N. Abuelo[1], D. Guo[2], A. Cantu[2], S. Carmical[2], D. Milewicz[2]. [1]Rhode Island Hospital and Brown University School of Medicine, Providence, [2]University of Texas-Houston Medical School.

Thoracic aortic aneurysms and dissections can occur in families with autosomal dominant inheritance. Mutations in the fibrillin-1 gene on chromosome 15 cause Marfan syndrome (MFS), a known cause of familial aortic aneurysms and dissections. Affected individuals have phenotypic stigmata involving the skeletal, ophthalmologic and other systems. Mutations in the type III procollagen gene cause the vascular type of Ehlers-Danlos syndrome (EDS IV), which can include aneurysms that involve the aorta and other arteries, but account for a small minority of aortic aneurysms. Affected individuals have characteristic skin and joint findings. Families with no external phenotypic stigmata of conneetive tissue disorders have been reported as cases of Erdheim disease or annuloaortic ectasia. The causative gene(s) have not yet been identified.

We report a family in which aortic aneurysms occurred in several family members who have no phenotypic findings suggestive of either MFS or EDS IV. None of the affected individuals have tall stature, dislocated ocular lenses, scoliosis or pectus deformities. The proband (II-1) was thought to be in good health until she developed chest pain at age 56 and died of a dissecting aneurysm of the ascending aorta that ruptured into the pericardial space. Microscopic examination of the aorta showed cystic medial necrosis. She had 5 children, 3 of whom also had thoracic aortic aneurysms. Her oldest son (III-1) and older daughter (III-4) have had prophylactic surgery at ages 60 and 49. The younger daughter (III-5) had emergency surgery after aortic rupture during catheterization at age 48.

A skin biopsy was obtained from the older daughter and dermal fibroblasts explanted. Metabolic labeling studies done in triplicate showed diminished amounts of fibrillin-1 deposited into the matrix by the patient's cells when compared with controls. A similar defect in fibrillin-1 incorporation is observed in cells from MFS patients. Linkage and mutation studies are in progress to determine if the phenotype is due to a FBN1 mutation or a mutation in another gene that disrupts fibrillin-1 deposition in the matrix.

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Clinical and Molecular diagnosis of Nager syndrome in a preterm Infant (27 week gestation) – A case report

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An 800-gram male baby was born as product of twin 27-week gestation by emergency C-section due to fetal distress. The first male baby was phenotypically normal and required little resuscitation. The second baby has multiple congenital anomalies including triangular face, down slanting palbebral fissures, cleft palate, small low set posterior rotated ears with preauricular and buccal skin tags, absent thumbs, elbow contractures and by X-ray showed radioulnar synostosis. Abdominal ultrasound showed horse-shoe kidney with grade I hydronephrosis, which later complicated by bilateral renal calculi. Echochardiogram showed PDA, which was treated medically. The baby required ventilatory support due to severe tracheomalacia and bronchomalacia, and tracheostomy was done before extubation. Due to gastro-oesphageal reflux, the baby was fed by D-tube feeding through the period of hospitalization till G-tube was placed with fundoplication. Pathology study of the placenta showed that it is diamniotic, dichorionic placenta. The baby did not pass BAER test, with suggestion of mild to moderate bilateral deafness. Karyotype showed normal 46,XY male for the proband and his twin brother. A chromosome breakage study was doneto rule out Fanconi syndrome and it was negative. A FISH study using ZFP37 probe, which has been mapped on 9q32 and is expressed in several human tissues including fetal cartilage and could be linked to Nager's syndrome, is in progress. DNA sequencing mutation study of that ZFP37 in our patient will also be explored.

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BRCA1 and BRCA2 Mutation Analysis in At-risk African-American Families: Results and Implications. L. Baumbach[1], L. Gayol[1], T. Scholl[2], H. Basterrechea[1], I. Pfeifer[1], J. Davies[1], E. Perera[1], S. Smith[1], and J. Fernando Arena[1]. 1)Univ. of Miami Sch. of Med, Miami, FL; 2) Myriad Genetics Laboratories, Salt Lake City, UT.

The incidence of *BRCA1* germ-line mutations in at-risk individuals is controversial. In Caucasians, the detection of *BRCA1* mutations varies from 5-40%. Even more controversial is the incidence of *BRCA1* mutations and genetic variants in at-risk African-Americans (AA), which has been reported as ranging from very low to incidences equaling those in Caucasians. We report our results of completed BRCA1 and *BRCA2* analyses in 20 AA families at-risk for breast/ovarian cancer. Families were ascertained based on a history of breast cancer or breast/ovarian cancer and further subdivided into the following categories: high-risk (HR; three affected 1st degree relatives; 10 families), moderate-risk (MR; two affected 1st degree relatives, 7 families) and undetermined risk (UR; single affected with medical information being updated).

Germ-line alterations in *BRCA1* and *BRCA2* coding sequences were first detected using a series of exon-specific PCR primers in SSCP analysis to visualize regions of genetic variation. These experiments were followed by DNA sequencing of SSCP variants, using either DNA extracted and purified from SSCP variant bands, or the corresponding PCR product generated from genomic DNA. A limited number of *BRCA1* polymorphic intronic variants detected as a result of these studies were analyzed for their effect on *BRCA1* mRNA splicing using DNA and RNA extracted from patients' peripheral blood in a splicing assay developed by Myriad Genetics.

We have identified only one deleterious mutation (3875 del GTCT, *BRCA1*, a MR family), in either *BRCA1* or *BRCA2* in this patient cohort. However, a number of exonic and intronic polymorphic variants in *BRCA2* have been detected, as well as two different AA-specific *BRCA1* intronic polymorphisms detected in two HR unrelated families in which a disease-causing mutation was not otherwise detected. In addition, two missense mutations (one in *BRCA1* and one in *BRCA2*) were detected in two unrelated families, again in the absence of any apparent disease-causing mutation. The novel *BRCA1* missense mutation [exon 19 (W1718C)] in the second HR family appears to co-segregate with breast cancer. The relative frequencies of these *BRCA1* and *BRCA2* variants in Caucasian and AA control populations is being evaluated. In conclusion, our data support other recent reports concerning low germ-line *BRCA1* and *BRCA2* mutation rates in AA patients, and suggest a possible role for AA-specific *BRCA1* and *BRCA2* variants in modulating breast cancer risk.

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Mitochondrial disease and disorders of energy metabolism: A recognizable pattern of systemic disease. C.A. Bay [1,2], G.L. Matika [1], M.A. Del Vecchio [1]. [1]Children's Hospital of Pittsburgh, Pittsburgh, PA, and [2]University of Pittsburgh, School of Medicine, Pittsburgh, PA

Symptoms of mitochondrial diseases and disorders of energy availability are a consequence of abnormalities in the general function of mitochondria, the electron transport chain and related transport and assembly proteins to generate available energy in the form of ATP, and to act as an effector of apoptosis. Despite the popular notion that mitochondrial diseases are always maternally inherited, disorders of energy production and/or availability can be inherited following maternal mtDNA inheritance patterns as well as Mendelian patterns. The vast majority of electron transport chain and related proteins are encoded by nuclear DNA. Thus, the majority of disorders of energy availability are predicted to be consistent with Mendelian inheritance patterns. Previously recognized diseases with symptomatology typical of a mitochondrial disorder or deficient energy availability should be reevaluated. Additionally, chromosomal deletion disorders whose deletions encompass genes involved in energy metabolism, could result in lactic acidosis or reduced ATP availability, which could contribute to the pathogenetic mechanism of disease.

By summing all symptoms present in individual family members and considering the symptoms as if in one individual, we have been more effective in recognizing the typical systemic pattern of illness. A complete review of systems of family members is necessary to truly exclude this class of disorders.

Cross referencing, especially against a rare feature as well as the inheritance pattern significantly decreased the number of disorders in the differential diagnosis and the cost of diagnostic testing. The cross referencing system can also be used to predict those known disorders with Mendelian inheritance patterns that may be due to abnormal mitochondrial function or deficient energy availability. Examples of the cross referencing system in evaluation of patients will be presented.