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A comparison of the Berlin and Gent Nosologies in the diagnosis of Marfan syndrome : the NIH experience. P. Rose[1], H. Levy[1], N. Ahn[2], P. Sponseller[2], T. Magyari[1], J. Davis[1], C. Francomano[1]. [1]National Human Genome Research Institute, NIH, Bethesda, MD and [2]Department of Orthopaedic Surgery, Johns Hopkins Hospital, Baltimore, MD.

We reviewed clinical and radiographic data on 73 patients evaluated for possible Marfan syndrome (MFS) at the National Institutes of Health for the purpose of comparing the 1987 Berlin and 1996 Gent diagnostic criteria. All patients had a physical examination, all had echocardiograms or known aortic root dilatation, 64 (88%) had ophthalmologic exams or known ectopia lentis, and 35 (48%) have had MRI scans to screen for dural ectasia. Thirty-one had a first degree relative who had been diagnosed with MFS, and we directly confirmed this diagnosis in 22 cases. Forty-eight patients met diagnostic criteria under the Berlin criteria and 39 under the Gent criteria (kappa correlation coefficient K=0.75). No patient who met diagnostic criteria under the Gent criteria failed to meet the Berlin criteria. Of patients diagnosed under the Berlin criteria, all had skeletal features of MFS, 40 (83%) had aortic root dilatation, 19 of 27 examined (70%) had dural ectasia, 27 (56%) had an affected first degree relative, and 12 of 44 examined (27%) had ectopia lentis. Determination of dural ectasia established the diagnosis for 9 patients under the Gent criteria but had no effect on diagnoses made under the Berlin criteria (K=0.53 comparing Berlin to Gent without dural ectasia data). In summary, approximately 20 percent of patients diagnosed with Marfan syndrome using the Berlin criteria do not meet the Gent diagnostic standard. Long term follow-up or molecular diagnostic data are necessary to establish the relative sensitivity and specificity of these diagnostic tools.

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The molecular pathogenesis of Schmid metaphyseal chondrodysplasia. R Savarirayan[1], S Freddi[2], D.R. Keene[3], J.G.Rogers[1], J.F.Bateman[2]. [1] Victorian Clinical Genetics Services, [2] Department of Pediatrics, University of Melbourne, Royal Children's Hospital, Parkville, Victoria, Australia [3] Shriners Hospital Portland, Oregon.

Schmid metaphyseal chondrodysplasia (SMCD; MIM 156500) is an autosomal dominant skeletal dysplasia characterized clinically by short stature and genu varum and radiographically by metaphyseal irregularities and coxa vara. The condition results from heterozygous mutations in the gene for type X collagen, whose expression is restricted to the hypertrophic chondrocytes of growth plate cartilage. The molecular pathogenesis of SMCD is unresolved with haploinsufficient, dominant negative and dominant gain of function models being proposed. We present a large kindred with typical SMCD in which the type X collagen mutation was characterized at both the genomic and tissue (growth plate) level. The mutation was a single nucleotide substitution in the carboxyl-terminal NC1 domain, changing a Trp^{611} codon (TGG) to a stop codon (TAG). Analysis of expression of normal and mutant allele transcripts in growth plate cartilage by RT-PCR, sequencing and single nucleotide primer extension assay (SNuPE) revealed <1% mutant mRNA. The phenomenon of nonsense-mediated mRNA decay is most likely responsible for the lack of mutant mRNA transcripts in growth plate cartilage. In addition, electron microscopic analysis of affected growth plate cartilage revealed changes in the organization of type II collagen fibrils compared with control cartilage. These data support the findings in the only other patient with SCMD who has been studied by direct analysis of cartilage. These studies provide strong evidence to indicate that a functionally null allele, leading to haploinsufficiency of type X collagen, is the molecular basis of SMCD in at least a proportion of cases.

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Partial Monosomy of Chromosome 5 in 2 Male Siblings – Phenotypic Correlates

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We describe the phenotypes of two male siblings with partial monosomy of chromosome 5 [46XY,del(5q34q35.3)]; maternally derived from a balanced insertion of 1 and 5 [inv. ins (1:5) (p.32; q35.3:3q34)]. Sib #1, (8 yrs.) - microcephaly, cleft lip and palate, facial dysmorphism, atrial (ASD) and ventricular (VSD) septal defects, contractions of fingers, tight hamstrings, developmental delay. Sib #2, (2 months) – small stature, ASD, hypotonia, primary optic nerve hypoplasia. Only 4 patients with distal 5 q deletions have been reported and none showed the putative breakpoints identified in our 2 patients. All 6 showed developmental delay; 4 of 6 had defects of cardiac septation. Our 2 patients and 1 other were shown to have only one copy of the cardiac specific hCSX gene which defines in part the etiology of their ASD and VSD. Isolated mutations of the hCSX gene encoding homeobox transcription factor NKX2-5 have been shown to produce nonsyndromic septation defects (ASD) in 4 families. Deleted contiguous genes may account for other phenotypic features in our patients.

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BRCA testing uptake and participation in ovarian cancer prevention in women at risk for an inherited ovarian cancer susceptibility. Scheuner MT, Cheng LS-C, Hixon HEC, Rotter JI. Cedars-Sinai Medical Center, Los Angeles, CA.

The aim of this study was to assess BRCA testing uptake in women with a family history suggestive of an inherited ovarian cancer risk, and to evaluate their participation in preventive measures including bilateral salpingo-oophorectomy (BSO), screening with transvaginal ultrasound (TVUS) and serum CA125, and chemoprevention with oral contraceptives (OCPs). From January 1998 through June 1999, 112 women received genetic risk assessment and counseling regarding a possible inherited susceptibility to ovarian and related cancers. 62% were Jewish and 42% had a history of breast cancer. Of these 112 women, 72% elected to participate in BRCA testing; deleterious mutations were identified in 22% (18/81). Jewish patients represented 79% of the subjects who chose to undergo testing, and included 93% (64/69) of all Jewish patients. Only 40% (17/43) of non-Jewish patients chose testing. Almost all (89%) of the 18 deleterious mutations identified were in Jewish patients; 25% (16/64) of Jews who were tested had deleterious mutations compared to only 12% (2/17) of non-Jews. Jewish patients were more likely than non-Jews to have a personal history of breast cancer, 52% (33/69) compared to 26% (11/43), $p<0.03$. Follow-up regarding participation in preventive services was available for 18 of 22 women seen in the past 3 years who had both intact ovaries and deleterious BRCA mutations. 10 of the 18 women underwent BSO, and 7 are participating in TVUS and CA125 and/or are taking OCPs for ovarian cancer prevention. Only 3 women had been participating in ovarian cancer screening prior to their genetic consultation, and none were taking OCPs for chemoprevention. Age and personal history of breast cancer did not distinguish between those who did and did not elect BSO. 9 of the 13 Jewish women (69%) with a BRCA mutation had BSO, as did 1 of 2 non-Jewish women. These preliminary data suggest that women with BRCA mutations participate in appropriate preventive strategies for ovarian cancer; most choosing prophylactic BSO. Jewish patients were more likely to undergo BRCA testing than non-Jewish patients; this might be due to the increased mutation detection rate and reduced cost of testing. Thus at this time, genetic risk assessment and testing appears to be most beneficial for Jewish women at risk for an inherited susceptibility to ovarian cancer.