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Genome-wide linkage study for ossification of the posterior longitudinal ligament of the spine reveals a major susceptibility locus on chromosome 21q. K. Furushima[1,3], K. Ikari[1,3], S. Maeda[2], H. Koga[2], J. Takeda[3], S. Harata[1] and I. Inoue[3]. [1]Hirosaki Univ., Aomori, Japan, [2]Kagoshima Univ., Kagoshima, Japan and [3]Gunma Univ., Gunma, Japan.

Ossification of the posterior longitudinal ligament of the spine (OPLL) is characterized by ectopic ossification in the spinal ligaments leading to a various degree of myelopathy by a compression of the spinal cord. OPLL is commonly observed among Japanese and throughout other Asian populations. The incidence of OPLL in the general Japanese population was reported to be 1.9 - 4.3% over 30 years of age. Although its etiology is thought to involve a multiplicity of factors, epidemiological and family studies strongly implicate genetic susceptibility in the pathogenesis of OPLL. The disease has a substantial genetic component, a risk in siblings compared to general population risk (λs) of 10. Previously, we have reported of suggestive evidence of linkage to a candidate gene, collagen 11A2, where only a candidate region (HLA region at 6p21.3) was tested for linkage. To define the genetic causalities of OPLL in more extensive manner, we performed a genome-wide scan with 138 affected sib-pairs. Non-parametric linkage analysis was performed with affected sib-pairs by the use of two different programs. Identical by descent (IBD) was tested for possible linkage with SIBPAL from S.A.G.E. package (single point analysis). Multipoint affected sib-pairs linkage analysis was performed using GENEHUNTER. We found that five principal loci of possible linkage were identified on chromosome 1, 6, 13, 16, 21 ($p < 0.01$). And the most significant evidence of linkage was observed with D21S263 at chromosome 21q ($P=0.000009$). Multipoint linkage analysis revealed that the peak linkage was also located close to D21S263 (maximum lod score = 3.4). These mapping results could be an important step towards identifying susceptible genes for OPLL.

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A novel nonsense mutation of the GTP cyclohydrolase I gene in a family with dopa-responsive dystonia. K.M. Hong, Y.S. Kim[1], M.K. Paik. Department of Biochmistry and [1]Neurology, Wonkwang University College of Medicine, Iksan, Korea

We report a new mutation in the GTP cyclohydrolase gene in a family with dopa-responsive dystonia. A patient and his sister and two children of the patient are affected among people of the three generations with 15 members. The exons of the GTP cyclohydrolase gene were amplified by PCR and sequenced. A novel nonsense mutation (C^{142} AG to TAG) in exon 1 was identified in all of the four affected patients.

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Molecular analysis of chromosome 6p rearrangement in retinoblastoma. I. Imbert[1,2], L.J.A. Coignet[2], F. Pellestor[1]. [1]Institut de Genetique Humaine, CNRS-UPR 1142, Montpellier, France. [2]Institute of Cancer Research/Royal Marsden Hospital, Sutton, Surrey, UK.

Recurrent cytogenetic abnormalities are the hallmark of all malignant tumors. Classification of malignancies depends on the location of the chromosomic disruption/deletion, which relates to prognosis of the disease and therapeutic choices. Molecular genetics and cytogenetics techniques are used to identify oncogenes localized near the chromosomic breakpoints, and oncogenes activation seem to be dependent on translocation mechanism. Recurrent atypical cytogenetic abnormalities of chromosome 6p have been reported in a few cases of translocations implicated in Retinoblastoma. The translocation der t(4;6)(p15;p21.2) was studied in the Y79 cell line established from the primary tumor (right eye) of a 2-year-old Caucasian girl in1971. To determine the site of the breakpoint on 6p, yeast artificial chromosome (YAC) clones from p21 to p22 bands were used. The breakpoint has been localised by FISH on 6p21.3 and the TNF-alpha gene has been shown to be involved in this rearrangement. TNF-alpha is a cytokine, a specialized hormone-like protein that can influence cellular development and function. Flow cytometric analysis has been shown to be useful to measure the expression of both cytoplasmic and cell surface proteins in retinoblastoma cells. To measure the expression of TNF-alpha gene in retinoblastoma cells, flow cytometric analysis and cytospins were performed using an anti-TNF-alpha antibody. This study has shown an enhancement of the expression of TNF-alpha gene in Y79 cells. Further cloning, sequencing and characterisation of the gene(s) involved in this rearrangement from patient samples with this reccurent breakpoint will allow us to study the possible consequences of disruption/deletion of this gene in the development or progression into low to high grade disease.

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Williams Syndrome: on the genetic basis of human cognition. J. R. Korenberg[1], X-N. Chen[1], H. Hirota[1], Z. Lai[2], U. Bellugi[2], D. Burian[3], B. Roe[3] and R. Matsuoka[4]. [1]Medical Genetics, Cedars-Sinai Medical Center, Los Angeles, UCLA, CA, [2]Laboratory for Cognitive Neuroscience, The Salk Institute, La Jolla, CA, [3]Dept of Chemistry and Biochemistry, Univ of Oklahoma, Norman, OK, and [4]Dept of Pediatric Cardiology, The Heart Institute of Japan, Tokyo Women's Medical University, Tokyo, Japan.

Williams syndrome (WMS) is a most compelling model of human cognition, of human genome organization and of evolution. Due to a deletion in chromosome band 7q11.23, subjects have cardiovascular, connective tissue, and neurodevelopmental deficits. Given the striking peaks and valleys in neurocognition including deficits in visual-spatial and global processing, preserved language and face processing, hypersociability, and heightened affect, the goal of this work has been to identify the genes responsible. To do this, we have generated an integrated physical, genetic and transcriptional map of the WMS and flanking regions using multi-color metaphase and interphase FISH of BACs and PACs, BAC end sequencing, PCR gene marker and microsatellite, large scale sequencing, cDNA library and database analyses.

The results indicate the genomic organization of the WMS region as a complex of duplicated regions flanking a largely single copy region. There are at least two common deletion breakpoints, one in the centromeric and at least two in the telomeric repeated regions. Primate studies indicate an evolutionary hot-spot for chromosomal inversion in the WMS region. A cognitive phenotypic map of WMS has been generated that combines previous data with five further WMS subjects and atypical deletions; two larger (deleted for D7S489L) and three smaller, deleted for only subsets of genes. The results establish regions and consequent gene candidates for characteristic WMS features including visual-spatial defidits, global processing. The approach provides the basis for defining pathways linking genetic underpinnings with the neuroanatomical, functional and behavioural consequences that result in human cognition.