The American Society of Human Genetics

Abstracts

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THE AMERICAN SOCIETY OF HUMAN GENETICS

58th Annual Meeting

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1079/W

Genotoxicity assessment of two mouthwashes by means of micronuclei assay in buccal mucosa cells. *A.L. Zamora-Perez[1], M. Fuentes-Lerma[1,2], C. Guerrero-Velázquez[1], R. Brihuega-Velázquez[1], B. Gómez-Meda[3], G. Zúñiga-González[4], R. Mariaud-Schmidt[1].* 1) Instituto de Investigación en Odontología, Departamento de Clínicas Odontológicas Integrales, División de Disciplinas Clínicas del Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; 2) Departamento de Ciencias de la Salud, División de Ciencias Biológicas e Ingenierías, Centro Universitario de los Altos, Universidad de Guadalajara; 3) Instituto de Biología Molecular en Medicina, CUCS, U de G; 4) Laboratorio de Mutagénesis, CIBO, IMSS.

Researchs in the dentistry fields has allowed the knowledge of the structure and biology of dental tissues, as well as technological development, resulted in new materials, tools and techniques which indicated the need to apply methods or models to evaluate the possible genotoxic properties of it. There are many different tests for the detection of genotoxic effects, as is the micronuclei assay (MN). Mouthwashes components may vary and some contain high levels of alcohol. This produces a burning sensation caused by the chelating action in the basal layer of the exfoliated cells and this direct stimulus to the epithelium, might causes increase in the rate of cell renewal. The aim of the present work was to assess the genotoxicity of two mouthwashes by means of the MN assay in buccal mucosa cells. Twenty healthy adults volunteered to participate in the study and were divided into two groups (10 each). Samples were taken from buccal mucosa before starting treatment and 30 days after treatment. A marked increased in MNC was seen in subjects that rinse their mouth with mouthwash with alcohol compared with those without that used mouthwash without alcohol (mean (SD) 2.6 (1.0) MNC/2000 cells vs 1.3 (0.6) MNC/2000 cells, respectively. Intragroup comparisons showed no differences in the MNC frequencies in group 1, whereas the MNC frequency in group 2 varied significantly (before: 1.0 (0.6) MNC/2000 cells; after: 2.6 (1.0) MNC/2000 cells. In the present study, the frequency of MNC from buccal mucosa increased significantly in those subjects who rinse their mouth with mouthwashes who contain alcohol compared with those without alcohol.

1080/W

Periventricular heterotopia, mental retardation and epilepsy associated with 5q14.3-q15 deletion. *C. Cardoso[1], A. Boys[2], E. Parrini[3], A. Carabalona[1], S. Khantane[1], C. Mignon-Ravix[4], J.M. McMahon[5], E. Bertini[6], F. Novara[8], O. Zuffardi[8], L. Villard[4], S. Giglio[3], B. Chabrol[7], H.R. Slater[2], A. Moncla[7], Y. Ben-Ari[1], I.E. Scheffer[5], A. Represa[1], R. Guerrini[3].* 1) INMED, INSERM U901, Université de la Méditerranée, Marseille, France; 2) Victorian Clinical Genetics Services, Melbourne, Australia; 3) Children's Hospital A. Meyer, University of Florence, Italy; 4) INSERM U910, Faculté de Medecine La Timone, Marseille, France; 5) Austin Health and Royal Children's Hospital, Melbourne, Australia; 6) Bambino Gesù Hospital, Rome, Italy; 7) Timone Children's Hospital, Marseille, France; 8) Genetica Medica, Università di Pavia, Italy.

Periventricular heterotopia (PH) is an etiologically heterogeneous disorder characterized by nodules of neurons ectopically placed along the lateral ventricles. Most affected patients have seizures and their cognitive level varies from normal to severely impaired. To date, two genes have been identified to cause PH. Mutations in FLNA (Xq28) and ARFGEF2 (20q13) are responsible for X-linked bilateral PH and a rare autosomal recessive form of PH with microcephaly. Eleven additional distinct anatomoclinical PH syndromes, including chromosomal rearrangements involving the 1p36, 5p15 and 7q11 regions, have also been reported but the genes implicated remain unknown. Here, we report the clinical and imaging features of three unrelated patients with epilepsy, mental retardation and bilateral PH in the walls of the temporal horns of the lateral ventricles, associated with a de novo deletion of the 5q14.3-q15 region. Using CGH arrays and FISH analysis, we defined the boundaries of the deletions. The three patients shared a common deleted region spanning 5.8 Mb and containing 14 candidate genes. To identify the PH-associated gene, we are currently screening these genes for mutations in sporadic cases with PH. We are also using the in utero RNA interference approach to identify if one of these candidate genes contributes to neuronal migration. This combined strategy should allow us to identify the gene that is implicated in the temporal PH and provide new insights into the genetic and developmental basis of this cortical malformation.

1081/W

Autistic features with speech delay in a girl with an ~1.5 Mb deletion in 6q16.1, including *GPR63* and *FUT9*. *E. Bocian[1], K. Derwinska[1,2], J. Bernaciak[1], E. Obersztyn[1], P. Stankiewicz[1,2].* 1) Dept. of Medical Genetics, Institute of Mother and Child, Warsaw, Poland; 2) Dept. of Molecular & Human Genetics, Baylor College of Medicine, Houston TX, USA.

Recent studies have shown that up to 40% of the apparently balanced reciprocal chromosome translocations in patients with abnormal phenotype can be accompanied by a chromosome imbalance. We present a 10-year-old girl with mild mental retardation, language delay, and autistic behavior. She had no dysmorphic features and her brain MRI was normal. Karyotype analysis revealed a de novo apparently balanced translocation t(6;14)(q16;q22). Interestingly, autism, schizophrenia, and bipolar disorder have been linked previously to chromosome 6q16q21. Whole genome array CGH analysis with ~385,000 oligonucleotide probes (NimbleGen) identified an ~1.5 Mb deletion in 6q16.1. FISH with BAC clones mapping within and directly flanking the deleted segment showed that the deletion arose at the translocation breakpoint. The deleted segment harbors *FUT9, GPR63, FHL5, KLHL32, c6orf66*, and *AK091365*, but does not involve *GRIK2*, previously linked and associated with autism and schizophrenia. *GPR63* (*G-protein-coupled receptor 63*) is expressed in the frontal cortex, with lower levels in the thalamus, caudate, hypothalamus and midbrain and encodes a G-protein-coupled receptor for sphingosine 1-phosphate. The *fucosyltransferase 9* (*FUT9*) gene, is highly conserved among humans, mice, rats, and hamsters and is strongly expressed in brain during embryogenesis. *FUT9* is considered to be involved in cell-cell interactions, differentiation, and neurodevelopmental processes. We propose that haploinsufficiency of *GPR63* or *FUT9* may be responsible for the austistic spectrum features present in our patient. Our data confirm previous observations that copy-number variation is a significant factor responsible for autistic spectrum behavior and speech delay.

1082/W

Efficacy of clinical diagnosis of chromosome disorders in cases with dysmorphic features and the cytogenetic findings: A study of 438 cases with dysmorphic features. *F.M. Badr[1,2], K. AlSaidi[2], K. AlMuteri[2], M.M. AlSamman[2], S.S. Binhassan[2].* 1) Faculty of Medicine, King Fahad Medical City, Riyadh, KSA; 2) Cytogenetics and Molecular Cytogenetics Laboratory, King Fahad Medical City, Riyadh, KSA.

Objectives : To report the incidence and distribution of chromosome disorders confirmed by different cytogenetic techniques among cases with dysmorphic features clinically diagnosed as genetic disorders. Subjects and Methods : A total of 438 newborn babies and infants up to 4 years old were referred by clinicians for cytogenetic analysis. Indications for referral were multiple congenital anomalies, and a wide spectrum of dysmorphic features. All cases were karyotyped by conventional G-banding technique and fluorescence insitu hybridization (FISH) was done on interphase cells or on metaphase chromosomes. Results : 137 cases were diagnosed clinically as specific chromosome disorders. All cases referred as Edward, Patu's syndromes (trisomy 13 & 18) and Klinefelter were positively confirmed by cytogenetic testing. Only 57 cases out of 100 clinically diagnosed as Down's syndrome (trisomy 21) were confirmed cytogenetically. Concordance between clinical diagnosis of cases as Turner syndrome with karyotype analysis was very low (5%). Non specified dysmorphic feature cases revealed an incidence of 10.7%; with structural chromosomal aberrations. Of the latter, deletions were the most frequent (37%), translocation (7%), isodicentric ((7%), duplication (21%), marker chromosome (7%), and complex rearrangements (21%). Conclusion: The highest concordance ratio between clinically diagnosed cases and positive cytogenetic findings included chromosome disorders with well recognizable symptoms as the case with trisomies 13, 18 & 21. The low concordance ratio between referral cases and chromosomal abnormalities could be due to the inclusion of cases which mimic phenotypic description of clinically recognizable chromosome syndromes. Other factors which lead to suspicion of chromosome aberration are increased maternal age, consanguinity and familial history.

1083/W

Duplications in the 17p13.3 Miller-Dieker syndrome region: Increased expression of *LIS1* affects human and mouse brain development. *W. Bi[1], T. Sapir[3], O.A. Shchelochkov[1,2], F. Zhang[1], M. Withers[1], J.V. Hunter[2], T. Levy[3], V. Shinder[4], D.A. Peiffer[5], K.L. Gunderson[5], X. Lu[1], T. Sahoo[1], Y. Yanagawa[6], A.L. Beaudet[1,2], S.W. Cheung[1], S. Martinez[7], J.R. Lupski[1,2], O. Reiner[3].* 1) Dept Molec & Human Genetics, Baylor Col Medicine, Houston, TX; 2) Texas Children's Hospital, Houston, TX; 3) Dept. Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel; 4) Dept. Chemical Research Support, The Weizmann Institute of Science, Rehovot, Israel; 5) Illumina, Inc., San Diego, CA; 6) Dept. of Genetic and Behavioral Neuroscience, Gunma University Graduate School of Medicine, Maebashi, Japan; 7) Instituto de Neurociencias, UMH-CSIC, San Juan de Alicante, Alicante, Spain.

Deletions of the *LIS1* gene in human chromosome 17p13.3 result in isolated lissencephaly sequence and the extended deletions including the *14-3-3ε* gene cause Miller-Dieker syndrome (MDS). By array CGH we identified seven unrelated cases with duplication ranging from 240 kb to 3.6 Mb in 17p13.3 involving the *LIS1* and/or the *14-3-3ε* genes. Duplications in three cases are complex and may represent the autosomal rearrangements generated by the DNA replication FoSTeS mechanism. Real-time RT-PCR showed that the expression levels of the *LIS1*, *14-3-3ε*, and *CRK* genes were increased when these genes are duplicated. Using a "forward genomics" approach we characterized the clinical consequences of duplications. Increased *LIS1* dosage causes smaller brains, mild brain structural abnormalities, moderate to severe developmental delay, and failure to thrive. Duplication of *14-3-3ε* and surrounding genes increases the risk for macrosomia, mild developmental delay, pervasive developmental disorder, and results in shared facial dysmorphologies. Transgenic mice conditionally over-expressing LIS1 in the developing brain exhibited a decrease in brain size, an increase in apoptotic cells, and a distorted cellular organization in the ventricular zone including reduced cellular polarity. Collectively, our results show that an increase in LIS1 expression in the developing brain results in smaller brains and neuronal migration abnormalities in mice and human patients.

1084/W

Delineating Williams-Beuren Syndrome Chromosomal Region Using High-density Targeted Array CGH. *X. Hu[1,2], D. Mercer[2], T. Narumanchi[2,3], H. Andersson[2,3], M. Li[1,2,3].* 1) Louisiana Cancer Research Cons, Tulane Univ Sch Medicine, New Orleans, LA; 2) Hayward Genetics Center,Tulane Univ Sch Medicine, New Orleans, LA; 3) Dept. of Pediatrics; Tulane Univ. Sch. Med, New Orleans, LA.

Williams-Beuren syndrome (WBS) is caused by a heterozygous deletion of contiguous genes at 7q11.2. Three large region-specific low copy repeat elements (LCRs A, B, and C) located in the proximal region of chromosome 7q are thought to be responsible for the high frequency of deletions in this region. These LCRs also hinder the molecular characterization of deletions in different WBS patients and the phenotype/genotype correlation of the syndrome. We attempt to use a novel technology, high density targeted array CGH, to delineate the deletions in 6 patients with WBS. In this study, we constructed a custom designed targeted array that covers the commonly deleted chromosomal region and flanking regions of WBS. A total of 36,400 genomic probes spanning a 10 Mb region with 200 bp - 500 bp intervals were selected for the Agilent 4x44K array format. Patients were initially diagnosed with standard Agilent 4x44K arrays and confirmed by FISH. The detailed deletion breakpoint junctions were determined by the high density targeted array CGH study. Five out of six patients showed a deletion of approximately 1,398 Kb with only 100 bp differences at distal and/or proximal breakpoints, indicating non-random recombination between LCRs. One case that showed a ~4,000 Kb deletion from 7q11.22 to 7q11.23 with the standard array displayed two adjacent deletions of 1,693 Kb and 1,390 Kb separated by an 897 Kb undeleted region. The 1,390 Kb deletion corresponds well with the WBS commonly deleted region and shares the same distal breakpoint as in the deletions of the other 5 cases. The 1,696 Kb deletion is centromeric to the common WBS deletion. The deletions in most of our cases occurred between centromeric and medial B block LCRs (Bc and Bm).The detailed mapping of WBS deletion breakpoints has not been possible before the use of the high density targeted arrays and the mapping data is of great significance in exploring the pathogenesis and phenotype/genotype correlations of the disease.

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