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Abstracts

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material (CBG banding). Spectral karyotyping identified its origin in chromosome 22 and chromosomal microarray showed a 3 MB partial tetrasomy 22q11.1-22q11.21 encompassing the cat eye critical region.
The above mentioned chromosomal conditions originating in 22q abnormalities have an overlapping spectrum and sometimes they are a difficult call for the geneticist; further cytogenetic investigations are protean in such cases. Cat eye syndrome without cat eye (coloboma) may be more frequent than we have thought.

P11.024
CDC42 as a new human disease gene associated with thrombocytopenia and intellectual disability

K. Kosaki[1], *T. Takenouchi*[1], *T. Uehara*[1], *S. Ida*[2], *R. Kosaki*[3], *N. Okamoto*[4];
[1]*Center for Medical Genetics, Keio University School of Medicine, Tokyo, Japan,* [2]*Department of Gastroenterology and Endocrinology, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan,* [3]*Division of Medical Genetics, National Center for Child Health and Development, Tokyo, Japan,* [4]*Department of Medical Genetics, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan.*

CDC42 encodes critical regulator for the cell cycle and actin cytoskeleton formation. More than 5000 articles have been published concerning Cdc42 in various organisms. The conditional homozygous knockout of Cdc42 in mice results in macro-thrombocytopenia and structural abnormality in the central nervous system. However, no human disorder associated with CDC42 mutations has been described until our identification of two patients with de novo CDC42 (p.Tyr64Cys) mutation [MIM 616737: Takenouchi-Kosaki syndrome]. The two patients shared macro-thrombocytopenia, developmental delay, lymphedema of the lower extremities, and contracture of the fingers as common features. Characteristic facial features included arched eyebrows, mild ptosis, eversion of the lateral portion of the lower eyelid, exotropia, midfacial hypoplasia, short philtrum, thin upper lip, and malocclusion. The present observation of the two unrelated patients with a strikingly similar phenotype and the same CDC42 mutation establishes that CDC42 is a new human disease gene and that a mutation in CDC42 causes a recognizable syndromic form of thrombocytopenia. Differential diagnosis of isolated thrombocytopenia and intellectual disability include Jacobsen syndrome (11q23 deletion), Braddock-Carey syndrome (21q22), and Takenouchi-Kosaki syndrome. Takenouch-Kosaki syndrome caused by CDC42 mutation is clinically recognizable in that the size of the platelets is large and lymphedema is a unique feature. Lymphedema could be ascribed to the CDC42 mutation, since Cdc42 directly interacts with Rac1, the defect of which leads to lymphedema in mice.

P11.025
Molecular characterization of the first Spanish case of Hypotrichosis with juvenile macular dystrophy (HJMD)

F. Blanco-Kelly, L. Rodriguez da Silva-Jacy, I. Sanchez-Navarro, R. Riveiro-Alvarez, M. Lopez Martinez, M. Corton, ***C. Ayuso****;*
Servicio de Genética, ISS-Fundación Jiménez Díaz, Madrid, Spain.

Introduction: The CDH3 gene on 16q2 is responsible for two ultrarare autosomal recessive disorders characterized by hypotrichosis and progressive macular dystrophy: Hypotrichosis with Juvenile Macular Dystrophy (HJMD) and Ectodermal Dysplasia, Ectrodactyly and Macular Dystrophy (EEM).
Patients and methods: A Spanish male born in 1998 from non-consanguineous healthy parents sent to the Genetic Department from University Hospital Fundación Jimenez Díaz, with a suspected diagnosis of decalvant spinulous follicular keratosis (probable Siemens Syndrome) and inverse retinitis pigmentosa. Neither limb nor dental abnormalities were observed. Sanger sequencing of coding exons of ABCA4 and CDH3 were performed. In addition, MLPA analysis using a commercial kit was used to study ABCA4 exonic deletions or duplications.
Results: First, differential diagnosis of isolated juvenile macular dystrophy was performed. Only a heterozygous missense p.Val2050Leu variant in ABCA4 was found after a comprehensive analysis of coding regions and gene rearrangements. A second allele was not found.
Further CDH3 sequencing allowed to detect compound heterozygous variants: a novel maternal missense change p.Val205Met, predicted as probably pathogenic by in silico analysis and a previously reported paternal frameshift c.830del p.Gly277Alafs*20. Clinical revision allowed reclassified this patient as HJMD.
Conclusions: This is the first report of a Spanish patient with HJMD and the first report of a patient carrying mutations in the CDH3 gene in Spain. A new mutation has been described in CDH3. This work reflects the importance of both the joint assessment of clinical signs and the evaluation of the pedigree for a correct genetic study approach and diagnostic.

P11.026
The face of the developmental disorders of chromatin remodeling

S. Douzgou[1,2], *S. Banka*[2,1];
[1]*Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom,* [2]*Institute of Human Development, University of Manchester, Manchester, United Kingdom.*

Developments in technology led to increased understanding of the genetic basis of the Chromatin Disorders, a group of developmental disorders caused by disruption of chromatin remodelling (DDCRs). We used Facial Dysmorphology Analysis technology (FDNA®) to objectively evaluate the craniofacial dysmorphic features of DDCRs. We propose that a condition should be recognizable by gestalt if it fulfills the following criteria: (i) the 'syndromic face' is significantly different from the average, general population face (denoted as 'severity'); (ii) the syndromic face is significantly different from typical faces of other syndromes (denoted as 'distinctiveness'); (iii) the variability between faces of patients with the same syndromic diagnosis is minimal.
As variability is difficult to assess without knowing the full spectrum of the conditions, we focused our analysis on the severity and distinctiveness of DDCRs by using published, 2D facial photographs of patients with 20 distinct, molecularly confirmed DDCRs to create a common 'facial photo crop' for DDCRs. This was proven to be distinct to the 'average, normal face'. To evaluate the severity and distinctiveness of the DDCR faces, we compared each of the 20 syndromes' facial photo crops (n=5) to 1) other syndromes in the DDCR group (19 syndromes); 2) other dysmorphic syndromes not in the DDCR group (100 other syndromes); 3) normal (1000 photographs). Methods included the mean area under the curve (AUC) to compare between samples and ROC curve plotting the true positive rate as function of false positive rates. We report the results of this analysis and discuss its implications.

P11.027
Early results of next-gen cytogenetics implementation in Portugal

D. David[1], *J. Freixo*[2], *B. Marques*[1], *I. Carvalho*[2], *N. Tkachenko*[3], *N. Oliva Teles*[3,4], *M. Marques*[1], *M. Cardoso*[1], *J. Fino*[1], *A. Alves*[1], *A. Fortuna*[3,4], *S. Dória*[5], *C. Pinto de Moura*[5], *H. Correia*[1], *I. Marques Carreira*[6], *J. Sá*[7], *R. Gonçalves*[2], *J. Lavinha*[1], *T. Kay*[2], *M. Talkowski*[8,9,10], *C. Morton*[9,10,11];
[1]*National Health Institute ''Doutor Ricardo Jorge'', Lisbon, Portugal,* [2]*Centro Hospitalar de Lisboa Central, Lisbon, Portugal,* [3]*Centro de Genética Médica Doutor Jacinto Magalhães, Centro Hospitalar do Porto, Porto, Portugal,* [4]*Unit for Multidisciplinary Research in Biomedicine (UMIB/ICBAS), Porto, Portugal,* [5]*Faculdade de Medicina, Universidade do Porto, Porto, Portugal,* [6]*Faculdade de Medicina, Universidade de Coimbra, Coimbra, Portugal,* [7]*Centro Hospitalar de Coimbra, Universidade de Coimbra, Coimbra, Portugal,* [8]*Massachusetts General Hospital, Boston, MA, United States,* [9]*Harvard Medical School, Boston, MA, United States,* [10]*Broad Institute of MIT and Harvard, Cambridge, MA, United States,* [11]*Brigham and Women 's Hospital, Boston, MA, United States.*

Background: Most approaches are insensitive to the full mutational spectrum of chromosome rearrangements associated with human developmental abnormalities. Therefore, our aim is to introduce next-generation sequencing (NGS) into clinical cytogenetics, creating a sequence-based Next-Gen Cytogenetics to catalyze a dramatic advancement in clinical diagnostics.
Methods: Twenty families with chromosome rearrangement-associated diseases, including two prenatal (PN) cases, have been enrolled. Fourteen of these were also analyzed by NGS using large-insert paired-end libraries.
Results: The majority of these cases were confirmed to be balanced reciprocal rearrangements, whereas 4 were complex chromosomal rearrangements including 1 of chromothripsis. Thus far, over 50 breakpoints were identified disrupting protein coding genes, lncRNAs, or intergenic regions, thus revealing candidate genes or genomic loci. These cases are further assessed for pathogenicity from positional effects on genes located within topological domains (TADs) containing the breakpoints using DECIPHER predictions of haploinsufficiency. In one PN case, the 16q24 breakpoint disrupts ANKRD11, etiologic in the autosomal dominant KBG syndrome (OMIM #148050), predicting an abnormal phenotype. The chromothripsis case, submitted as 46,XY,t(7;14)(q22;q32.1),inv(15)(q21.2q26.1), proved by NGS to carry two further deletions, at 3p12 (5.3 Mb) and 15q14 (488 kb), as well as an insertion of 644.4 kb from 15q14 into 3p14. The inv(15) is in fact a complex rearrangement of 15q with eight breakpoints.
Conclusions: We demonstrate that NGS-based chromosomal rearrangement characterization leads to major improvements in identification of chromosomal aberrations and in prediction of clinical outcomes of postnatally and prenatally detected genomic rearrangements, and to contributions to human genome annotation.
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