

genotype–phenotype correlation difficult. As far as we know, this is one of the smallest duplications associated with BWS and is consistent with the independent regulation of ICR1 and ICR2. Our patient presented moderate developmental delay and craniofacial features typical of 11p15 duplication. Future studies exploiting this subtle 11p15.5 rearrangement will provide an important tool to further dissecting the genomics of BWS region and the pathogenesis of this imprinting disorder.

Keywords: Beckwith–Wiedemann syndrome, Imprinting control regions (ICR), Microduplication at 11p15.5

1.P89

Parental insertional balanced translocations are an important cause of apparently de novo CNVs in patients with developmental anomalies

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In several laboratories, genome-wide array analysis is already the first-tier diagnostic test for the identification of copy number changes in patients with mental retardation and/or congenital anomalies. The identification of a pathogenic copy number variant (CNV) is important not only to make a proper diagnosis but also to enable the accurate estimation of the recurrence risk to family members. Upon the identification of a de novo interstitial loss or gain, the recurrence risk is considered very low. Nevertheless, apparently,

de novo imbalances in a patient can be the consequence of the unbalanced transmission of a derivative chromosome involved in an insertional translocation (IT) in one of the parents. To determine the frequency with which insertional balanced translocations would be the origin of submicroscopic imbalances in a total of 10,459 patients with developmental abnormalities, we investigated the potential presence of an insertional translocation in a consecutive series of 419 de novo interstitial CNVs. We demonstrate that insertional translocations underlie approximately 1.5% of the apparently de novo CNVs, indicating that submicroscopic ITs are at least 40-fold more frequent than cytogenetically visible ITs (0.04%). This risk estimate should be taken into account during counselling and warrant parental testing in patients with a de novo interstitial aberration.

Keywords: De novo CNVs, Insertional balanced translocations

1.P90

Tricho-rhino-phalangeal syndrome type I as a “cis-ruption disorder” caused by a translocation

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Tricho-rhino-phalangeal syndrome type I (TRPS I; OMIM 190350) and type II (OMIM 150230) are two forms of the rare autosomal-dominant TRP malformation syndrome localised in 8q23.3–24.1. TRPS I is generally caused by point mutations or deletions of the *TRPS1* gene, whereas type II is characterised by the presence of multiple cartilage exostoses (EXT) and deletions comprising the *TRPS1* and *EXT1* genes. In the present study, we have mapped and sequenced the breakpoints of a balanced familial translocation [t(8;13)(q23.3;q21.32)] segregating with mild TRPS I and analysed the *TRPS1* candidate gene. The proband, in addition to features compatible with TRPS I, also presented developmental delay and severe mental

retardation. The pathogenic chromosome 8 breakpoint was localised within a transposon type I element at 116.768 Mb, 87 kb from the *TRPS1* 5' end. The breakpoint on chromosome 13 was localised within a gene-poor region at 65.101 Mb, and the nearest gene, 1.5 Mb distal from the breakpoint, is protocadherin 9 (*PCDH9*). Analysis of the three affected relatives by the 33K tiling BAC array and of the proband by 2.7-M high-resolution oligonucleotide array painting did not reveal additional genomic variation. Furthermore, mutation screening of the *TRPS1* also did not reveal any alteration. Finally, expression studies of *TRPS1* performed from LCLs indicate that inter-individual variation is higher than the expected gene expression changes induced by the translocation. Although the reason underlying the severe mental retardation observed in the proband is unknown, the available data indicate that this is not associated with the translocation. As far as we know, this is the first reported case of position effect or “*cis*-ruption” causing TRPS I. Finally, further studies are necessary to unveil the molecular pathogenic mechanisms of this “*cis*-ruption disorder” triggered by chromosome translocation.

Keywords: Balanced translocation, Tricho-rhino-phalangeal syndrome type I, Position effect, *cis*-ruption disorder

1.P91

A pathogenic breakpoint at 566.8 kb from the 3' end of the *SATB2* leads to a 2q33.1 microdeletion-like phenotype

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SATB2 is an AT-rich sequence-binding protein that binds to nuclear matrix attachment regions. It plays an important role in transcription regulation and chromatin loop remodelling. Deletions, chromosome translocations, as well as heterozygous nonsense mutations affecting this gene have been reported associated with overlapping conditions involving

craniofacial anomalies such as the isolated cleft palate (OMIM 119540), 2q33.1 microdeletion syndrome (OMIM 612313) and Toriello–Carey syndrome (OMIM 217980). The aim of this study was the identification of the breakpoint sequences and candidate gene/s of a de novo t(1;2)(q14.1;q35) associated with severe mental retardation, behaviour disturbance, dysmorphic facies, dental anomalies, convergent strabismus and high palate but without clefting. The chromosome 2 breakpoint is localised at position 199,567,382 of the current human genome assembly (hg19), within IVS1 of the processed transcript AC019330.1. This breakpoint disrupts an evolutionarily conserved non-coding genomic element localised 566.8 kb from the 3' end of the *SATB2* gene. The chromosome 1 breakpoint is localised within IVS13 of the zyg-11 homolog A (*Caenorhabditis elegans*) *ZYG11A* gene, at position 53,355,744 (assembly hg19). Although the chromosome 1 breakpoint disrupts the *ZYG11A*, we consider that the *SATB2* is the main candidate gene, which is substantiated by the overlap observed between the probands' phenotype with the pathologies associated with this gene. The characterization of the translocation breakpoints allowed us to establish an accurate clinical diagnosis. As pathogenic mechanism, we propose the disruption of the genomic architecture of evolutionary conserved long-range regulatory elements leading to a so-called *cis*-ruption disorder. The elucidation of the pathogenic mechanism by which disruption of such an evolutionarily conserved sequence element leads to the aforementioned condition will allow us to consider new therapeutic strategies that may hinder progressive deterioration of the clinical condition in such “*cis*-ruption disorders”.

Keywords: *SATB2*, Position effect, Microdeletion-like phenotype, Toriello–Carey syndrome

1.P92

Characterization of a familial case with complex chromosome rearrangement involving chromosomes 1, 10, 11, 13 and 18

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