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The 15q11-q13 region is characterized by high instability, mainly caused by the presence of several homologous segmental duplications. Although most of the mechanisms dealing with cryptic deletions and amplifications, including inv dup(15)s, have been partly characterized, less is known about the rare translocations involving this region. We characterized at the molecular level five unbalanced translocations having most of 15q transposed to the distal region of another chromosome, whereas the der(15)(pter→q11-q13) was missing. Imbalances were associated with Prader–Willi syndrome in four patients and Angelman syndrome in one. Array-CGH analysis demonstrated that the recipient chromosome was unbroken in three cases, carried a cryptic terminal deletion in one case, and a large terminal deletion, already diagnosed by classical cytogenetics, in another one. We were able to clone the breakpoint junctions in two cases, whereas cloning was impaired by the complex genomic architecture of the region in two other cases and by mosaicism in the last case. The results demonstrate the occurrence of different breakpoints in the region and highlight some unexpected findings, suggesting, in some cases, complex mechanism of formation at the basis of this type of rearrangement.

Keywords: Translocation breakpoint cloning, Prader–Willi syndrome, Angelman syndrome, Inverted duplication deletions, Translocations mechanism of formation

1.P88

A rare case of Beckwith–Wiedemann syndrome caused by a de novo microduplication at 11p15.5 of paternal origin

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Beckwith–Wiedemann syndrome (BWS) is a disorder of growth regulation exhibiting somatic overgrowth and predisposition to paediatric tumours. With an incidence estimated at 1 in 13,700, it is caused by various epigenetic and/or genetic alterations associated with disturbances within two different 11p15 domains that are controlled by distinct imprinting control regions (ICR), ICR1 and ICR2. The majority of patients have abnormalities within ICR2 presenting hypomethylation, while less frequent aetiologies include mosaic paternal 11p uniparental disomy (11patUPD), maternally inherited mutations of the CDKN1C gene, and hypermethylation of ICR1. A few patients have cytogenetic abnormalities involving 11p15.5. Since the subgroups are associated with different recurrence risks, the identification of the molecular cause of BWS is particularly important for the follow-up of the patient and the genetic counselling of both the patient and the family.

Here, we report a 13-year-old girl with clinical diagnosis of BWS presenting macrosomia, umbilical hernia, kidney abnormalities, hydramnius, prematurity, typical face, advanced bone age, moderate developmental delay, prominent occiput and forehead, round face, epicanthus, short nasal bridge, and micro-retrognathia. Cytogenetic analysis with high-resolution banding showed an apparently normal karyotype. Microsatellite analysis and methylation-specific multiplex ligation-dependent probe amplification revealed a de novo microduplication at 11p15.5 of paternal origin. Duplication has a minimum size of 600 kb, covering only ICR1, not affecting ICR2.

This sporadic case with a de novo duplication without other chromosomal abnormalities makes

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