TYPE AND COUNTER-TYPE FROM SPECIFIC CHROMOSOMAL REGIONS

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[Tipi e controtipi in specifiche regioni cromosomiche]

ABSTRACT

Several studies have shown the importance of segmental deletions/duplications in the field of chromosome pathologies. Non allelic homologous recombination, NAHR, between chromosomes or sister chromatids, mediated by segmental duplications, is the foundation of frequent mechanisms for structural chromosome mutations such as micro-deletions, micro-duplications, translocations, inversions, and marker chromosomes. We analyzed three distinct genomic regions (22q11.2, 17p11.2, 16p11.2) and we discussed how the same chromosome region can be affected by deletion or by reciprocal duplication, respectively responsible for a syndrome or for a reciprocal counter-syndrome, with different phenotypic manifestations.

***Key words*:** *Type/countertype, a-CGH, genomic variants.*

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Introduction

Several studies, for quite a number of years now, have demonstrated the importance of the role of segmental duplications in the field of chromosome pathologies. Segmental duplications are blocks of few low copy repeats(LCRs) that recognize a reciprocal homology higher than 90% in non-homologous 200 to 400 kb chromosome segments. They account for about 6% of the human genome and are interspersed through the genome, but especially located in the pericentromeric, thelomeric and subthelomeric regions. They can include a large number of genes , but can also include broken non-processed pseudogenes. Segmental duplications are often duplicated in one chromosome region at a reciprocal distance of a few megabases (less than 10 Mb) and they mediate a possible non allelic homologous recombination, NAHR, between chromosomes or between sister chromatids: this may result in unequal crossing-over or in chromosome rearrangements and is, therefore, the basis of frequent and specific mechanisms of structural chromosome mutations such as micro-deletions or micro-duplications, but also translocations, inversions and marker chromosomes. Micro-deletions are more frequent than micro-duplication, as widely stated in scientific literature. Micro-deletions can in fact originate from a wide range of recombination mechanisms and can be intra-chromatid, inter-chromatid or intra-chromosomal, whereas micro-duplications can only originate from an inter-chromatid or intra-chromosomal recombinations[(1,2)].

The advent of array-CGH with its high image definition (it can detect chromosomal anomalies even lower than 50 kb) paves the way for an easier mapping of such submicroscopic genomic variants (micro-deletions or micro-duplications), increasing the possibility of a correct diagnosis. The introduction of array-CGH also represents a significant advancement in the diagnosis of individuals with a "chromosomal phenotype" (mental retardation, dysmorphic features, congenital anomalies)[(3-7)] and normal karyotype. All these conditions play a very important role in determining morbidity and mortality rates, especially in neonatal age, when many other

risk factors (prematurity[8,9], twinning, nosocomial infections[10,11,12,13], chemical mediators[14,15]) may add their cumulative effect influencing short- and long-term outcome. No less than 15-20 % of the patients with mental retardation, dysmorphic features, congenital anomalies, and normal karyotype are carriers of a cryptic chromosomal unbalance sometimes as extended as 100 kb, not detected by the classic cytogenetic techniques[16,17,18,19,20,21].

Undoubtedly array-CGH allows ever more accurate and precise analyses with greater simplicity and faster response[22,23,24,25,26,27,28]. In the present study we discuss how the same chromosomal region can be affected by deletion or by duplication, respectively responsible for a syndrome (type) and for a counter-syndrome (counter-type), with different phenotypic manifestations.

22q11.2

Region q 11.2 of chromosome 22 shows eight LCRs organized in clusters (4 thelomeric ones and 4 centromeric ones, called LCR 22s). Namely, a deletion of 3 Mb is the cause of a DiGeorge/velo-cardio-facial syndrome, while a reciprocal interstitial duplication characterizes both CES (cat eye syndrome) and dup22, precisely a tetrasomy in the first and a trisomy in the second[29,30]. Analyzing the phenotype features we can see how deletion and duplication occurring in the same region 22q11.2 (included TBX1 gene) can actually determine two distinct syndromes with different courses and prognoses, so that we can define the 22q11.2 micro-duplication syndrome as a "countersyndrome" or a "countertype" of the 22q11.2 micro-deletion syndrome(31,32). In fact, the clinical picture leading to or hinting at a micro-deletion syndrome diagnosis is more frequently an occurrence of multiple congenital anomalies (generally cardiac conotruncal defects, cleft palate, velopharingeal insufficiency, tonsillar hypertrophy, dental anomalies), convulsions and tremors due to neonatal hypocalcaemia, a typical facies, recurrent infections due to immune deficiency and thymus aplasia, and psychomotor and/or language retardation, hypothyroidism and behavioral disorder[33,34]. On the other hand, the most frequent features of a 22q11.2 micro-duplication syndrome are a varying degree of mental retardation/learning difficulties, attention defect and hyperactivity, hearing impairment, language disorder, psychomotor retardation, growth delay, low muscle tone, epileptic seizures[35,36,37,38,39]. Comparing the features in either syndrome we can notice that facial dysmorphic features variably present in 22q11.2 micro-duplication syndrome are different and often slighter than those of a 22q11.2 micro-deletion syndrome.

17 p11.2

Region 11.2 of arm p of chromosome 17 is sided with three "proximal" "middle" and "distal" copies of "low copy repeats (LCR)" also known as "SMS-REPs" (Smith-Magenis repeats). In particular, an interstitial deletion of about 3.7 Mb determines a Smith-Magenis syndrome, whereas an interstitial reciprocal duplication is the cause of a Potocky-Lupsky syndrome[40]. Analyzing the phenotype described in literature we can observe that the Potocky-Lupsky syndrome shows different, slighter and less severe clinic and phenotypic features than the Smith-Magenis syndrome. Such phenotypic diversity allows us to define the Potocky-Lupsky syndrome as a "counter-syndrome" or a "counter-type" of the Smith-Magenis syndrome, even if they both share the same genomic region and also several genes, among which the RAI-1 gene (retinoic acid 1 inductor) mainly responsible for the phenotypic manifestations in both syndromes. We can in fact, observe that, apart from delayed growth, cognitive and language deficiency, hyperactive or attention defects, EEG alterations, variably present though with different degrees of severity in both syndromes the most important features of the Potocky-Lupsky syndrome are: low muscle tone, scarce feeding and delayed growth in infancy, oropharyngeal dysphagia, dental issues, autistic disorders, central and obstructive sleep apnoea, cardiac anomalies, EEG alterations, hypermetropia, lower blood cholesterol, obsessive compulsive disorders. In addition, in the Potocki-Lupski syndrome, variable dysmorphic features may be variably present, including triangular face, frontal bossing, microcephaly, hypertelorism, wide nasal bridge, epicantal folds, flat philtrum[41].

On the contrary, in the Smith-Magenis syndrome, we can variably and frequently observe: cerebral malformations, peripheral neuropathy, epileptic seizures, markedly dysmorphic features, hypercholesterolemia, self-destructive or aggressive behaviors, important sleep disturbances, obesity, otorhinolaryngologic auditory and ophthalmologic anomalies, renal and genitourinary anomalies, skeletal and digital anomalies.

16 p11.2

It has been noticed in a recent study that 9.89% (7.8 Mb) of chromosome 16 shows segmental duplications. Analyzing the phenotype described in literature[42,43] we can see that a 16p11.2 micro-duplication syndrome shows less serious clinical and phenotypic features with respect to a 16p11.2 micro-deletion syndrome. It is therefore possible to point out that both a 16p11.2 micro-duplication syndrome and a 16p11.2 micro-deletion syndrome share phenotypic features such as delayed growth, delayed language development, learning difficulties, cognitive disability, low muscle tone. While the micro-deletion syndrome provokes an increased tendency to overweight and obesity, a possible association between 16p11.2 micro-duplication and reduced weight and reduced body mass index has been argued.

In fact, deletion of the region 16p11.2 seems to be associated with overweight and obesity liability, due to haploinsufficiency of SH2B1 gene, which is involved in leptin and insulin signaling. Micro-deletion is more frequently associated with macrocephaly while microduplication with microcephaly. It is argued, besides, that micro-deletion might more often be associated with delayed linguistic and cognitive development, with minor dysmorphic facial features without a consistent pattern, with autistic disorders, and with minor cardiac malformations, hemivertebrae and syringoyelia, while micro-duplication is associated with psychiatric problems such as bipolar disorder, depression, psychotic disturbance , schizophrenia.

Discussion

It is possible to highlight the differences between the phenotypic and neuro-behavioural manifestations of deletions and those of the reciprocal and complementary duplications in the same chromosomal region, especially as regards severity, frequency and recurrence. It must be noticed that the phenotypical appearance of both syndromes is often extremely variable with several degrees of severity.

Therefore micro-duplications, with respect to micro-deletion, show a slighter and milder clinical picture, sometimes even near normality, so that it is not always easy to recognize and identify such an anomaly. The identification of cryptic chromosome anomalies by means of modern molecular techniques, in particular array-CGH, has enabled physicians to devise follow-up programs intended to prevent the associated clinical problems.

We can conclude that array-CGH might become a means to fill the present gap between the knowledge of the human genome and the function of its genes: it is evident that any "de novo" deletion/duplication associated with a specific malformation or syndrome suggests that, among the genes located in the region studied, at least one is responsible for that malformation and for that syndrome, either due to aplo-insufficiency (deletion or type or syndrome) or to an excessive dosage (duplication or counter-type or counter-syndrome).

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