

**P-10**

**AUTOSOME-AUTOSOME RECIPROCAL TRANSLOCATION: IMPLICATIONS IN THE FERTILITY**

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Chromosomal abnormalities have been described as important causes of male infertility. Structural rearrangements have been reported as 10 times more frequent among infertile men than in the general population.

The most common chromosomal abnormality is Klinefelter's syndrome, but translocations may also cause reduction in testicular volume and testosterone level, which may impact spermatogenesis, resulting in oligozoospermia or azoospermia and thus male infertility. The involvement of acrocentric chromosomes and the presence of translocation breakpoints in close proximity to the centromere are associated with the most destructive effects on spermatogenesis.

It has been suggested in some publications that the most likely reason for the development of azoospermia in patients with reciprocal translocations is a very high proportion of an association between XY bivalents and quadrivalent formations in prophase I; the instability in chromosome segregation during consecutive cell divisions might be a contributing factor inducing spermatogenic disruption.

The authors present a male patient, aged 41, with azoospermia and reduced testicular volume, without family history of infertility.

The karyotype revealed an autosome-autosome reciprocal translocation: 46,XY,t(20;22)(q11.21;q11.21). Chromosomal analysis has become increasingly important for characterizing possible causes of human infertility, and has shown that male infertility might be associated with autosomal chromosome abnormalities. Infertile men who have chromosomal abnormalities such as translocations but normal phenotypes have shown that these translocations may have a devastating impact on spermatogenesis during meiotic division. In addition, detailed meiotic analysis may be recommended for each translocation, to obtain better diagnosis, prognosis and genetic counselling to the patient.

The authors will establish the relationship between male infertility and chromosomal translocations and compare the findings of this patient with similar cases described in the literature.

**P-11**

**MOLECULAR PROFILE OF MYOTONIC DYSTROPHY TYPE 1 (DM1) IN PORTUGUESE FAMILIES**

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Myotonic Dystrophy type 1 (DM1), also known as Steinert disease, is the most common adult form of muscular dystrophy. It is an autosomal dominant disorder caused by the expansion of unstable [CTG] repeats in the 3' untranslated region (3'UTR) of the gene of myotonic dystrophy protein kinase (*DMPK*), located at 19q13.3. The expanded mRNA products are toxic to cells, affecting normal splicing of other proteins in different tissues.

Myotonia is the principal manifestation of DM1, but other organ systems are also affected (e.g. ocular, cardiac and respiratory). Clinically, DM1 may be phenotypically classified into four main subtypes: i) mild, ii) classical or adult-onset, iii) juvenile and iv) congenital. The age of onset and severity are variable and directly associated with the number of expanded [CTG] repeats: larger expansions usually result in earlier onset and a more severe phenotype. Due to the instability of the expanded [CTG] repeats during transmission, it is common to observe in affected families a decreasing in age at onset and an increasing degree of severity in successive generations (anticipation).

In this work we present the molecular profile of DM1 in affected families studied at our diagnostic service, on a national basis, since the implementation of the molecular genetic testing for this disorder in 1997.

All the cases were tested for the presence of expanded pathogenic alleles. Depending on the size of the expanded alleles, a combination of three different methods was used to determine the number of [CTG] repeats in 3'UTR of the *DMPK* gene: 1) conventional PCR amplification of the [CTG]-repeat region; 2) Triplet repeat-Primed (TP)-PCR and 3) Southern blotting (SB) technique. Larger expansions (about [CTG]<sub>15-100</sub> repeats) are only detected by the last two methods; moreover, the exact size of these larger expanded repeats can only be assessed by SB. In order to establish the most accurate molecular diagnosis, the SB technique is therefore essential, particularly in the prenatal diagnostic setting.

We also present both clinical and genotype heterogeneity in the DM1 families, thus demonstrating some of the characteristics associated with this triplet repeat disorder: somatic mosaicism, anticipation, influence of gender of the

transmitting parent and occurrence of inter-generational size reduction in the expanded repeats.

The aim of the present work is to establish the mutation profile in patients and their families, where detailed molecular characterization is fundamental, not only to confirm the clinical diagnosis and to establish genotype-phenotype correlations, but also for trial-readiness given the emergent mutation-based therapies for DM1.

## P-12

### HIGH PHENOTYPIC VARIABILITY IN TWO SIBLINGS WITH SPINAL MUSCULAR ATROPHY

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**Introduction:** Spinal muscular atrophy (SMA) is the second most common lethal autosomal recessive disease in caucasians after cystic fibrosis, with an estimated incidence in Portugal of 1 in 10.800 live births. SMA is a severe neuromuscular disease characterized by degeneration and loss of spinal and brain stem motor neurons (lower motor neurons), resulting in progressive proximal muscle weakness and atrophy. The disease-causing gene is the survival motor neuron 1 (*SMN1*) localized in 5q13. This gene has a highly homologous copy - *SMN2* - differing in only 5 base pairs. While the *SMN2* gene does not compensate entirely the loss of *SMN1* in SMA patients, the number of *SMN2* copies modulates the disease's severity.

About 95% of patients have a homozygous deletion of exons 7 and 8 of *SMN1*. The remaining cases are compound heterozygotes for the deletion of *SMN1* and an intragenic mutation in the other allele. Clinically SMA is classified into four subtypes (I – IV) on the basis of age of onset, the maximum motor function achieved and survivorship. This classification is useful for prognosis and clinical management. Intrafamilial phenotypic variability is quite rare, but different SMA subtypes within the same family have been previously reported.

**Case report:** We present a family with two siblings diagnosed with SMA. They demonstrate a remarkable clinical variability and were classified with different SMA subtypes. The first patient, a 25 year-old woman, was referred to our genetic consultation with proximal limb weakness and difficulty in walking which started at 22 years of age. Her brother, 32 years old, is also affected with SMA but remarkably more severe in weakness. His limb weakness started at 5 years of age and significantly deteriorated to lose independent ambulation at the age of 7 years. Molecular genetic investigations revealed that both sibs have the same *SMN1* genotype: compound heterozygosity for an *SMN1* deletion and a novel point mutation [c.460C>T, (p.Gln154\*)] in exon 3 of *SMN1*. MLPA technique revealed the presence of two *SMN2* copies in both patients.

**Conclusion:** In this report we demonstrated the presence of intrafamilial phenotypic variability in two siblings classified with different SMA subtypes. This variability cannot be