

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.

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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

explained by the number of *SMN2* copies, since the siblings show an identical *SMN2* copy number. These results are suggestive that other modifying factors may influence the phenotypic variability of SMA, such as gender-related factors, variants in other loci or modifier genes involved in regulating alternative splicing. Phenotypic discrepancies in SMA among siblings are major resources to identify such modifying factors, which may represent additional therapeutic targets and contribute towards a better understanding of SMA's pathophysiology.

P-13**PREGNANCY IN A PATIENT WITH DISTAL ARTHROGRYPOSIS TYPE 2B - CLINICAL DIAGNOSIS, PRENATAL DIAGNOSIS AND GENETIC COUNSELING**

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Introduction: Arthrogryposis comprises nonprogressive conditions, which are characterized by multiple joint contractures. These include a group of autosomal dominant disorders that mainly involve the distal parts of the limbs without a primary neurological and/or muscle disease – the distal arthrogryposis (DA). The various phenotypic forms of DA are designated DA1 through DA10 and present genetic heterogeneity. DA type 2B (DA2B) or Sheldon-Hall Syndrome (SHS, OMIM 601680) is similar to DA1, but affected individuals tend to have typical craniofacial dysmorphisms. DA2B is thought to be the most common of the distal arthrogryposis disorders, with approximately 100 cases described so far.

Aims: We report a clinical case of a young woman with suspected DA and an ongoing pregnancy with fetal anomalies also suggestive of arthrogryposis. We hope to provide evidence that underlines the importance of establishing a definitive genetic diagnosis in patients with DA, in order to provide adequate Genetic Counseling (GC) and offer Prenatal Diagnosis (PND) / Preimplantation Genetic Diagnosis (PGD) in future pregnancies.

Clinical Case: At 21w+2d of gestational age, the fetal ultrasound revealed increased nuchal translucency, club foot and camptodactyly. The 23-year-old patient was then referred to our outpatient clinic for GC. Amniocentesis was performed to rule out chromosomal abnormalities: QF-PCR aneuploidy test and fetal karyotype (46,XX) were both normal. She had a personal history of multiple distal contractures suggestive of DA with extensive physiotherapy in childhood and of renal duplication with recurrent urinary tract infections. No definitive diagnosis had been established. Because of the uncertainty of diagnosis and of potential risk of developmental delay, the couple decided to terminate the pregnancy at 24w. The fetus was observed by an experienced clinical dysmorphologist. By combining the clinical features both of the index case and the fetus, we suspected of DA2B. The molecular testing of *TNNI2* gene revealed the heterozygous mutation c.527_529del (p.K175del), confirming the clinical diagnosis of DA2B. After terminating this pregnancy, the patient experienced great psychological distress, with depressive humor and guilt feelings, and she was referred to Psychiatry. GC was offered to the couple and they peremptorily refused PND in future pregnancies, opting for PGD.