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.

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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.

Discussion and Conclusion: This clinical case highlights the difficulty that clinicians experience in GC when the index case is a pregnant and the fetus has similar features, but the clinical diagnosis is not yet confirmed by molecular testing. One should always keep in mind that the optimal time for determination of genetic risk and GC regarding prenatal testing is before pregnancy, even when the prognosis is likely good as in DA, as well as address associated psychological aspects.

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WHOLE-EXOME SEQUENCING ANALYSIS OF ADULT PATIENTS WITH RARE GENETIC DISEASES: WHAT HAVE WE LEARNED?

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Introduction: Next-generation sequencing (NGS) is accelerating clinical genetics research and diagnostics, given its capacity to generate genomic data in a faster and cheaper way. NGS may avoid the usual stepwise gene-by-gene analysis by performing targeted resequencing of several loci simultaneously (gene panels). Wider NGS applications, such as whole-exome sequencing (WES), may even enable the identification of new genes associated with human diseases. Nevertheless, WES applicability is challenging considering the large number of variants obtained which require specific analytical strategies and bioinformatic resources. The authors describe the use of WES in three adult patients, exemplifying its diagnostic potential but also difficulties encountered during analysis.

Materials and Methods: WES was performed using the Ion Proton system in five individuals: Case #1- a female patient with a childhood-onset progressive muscular dystrophy (35 years of clinical follow-up) and her parents; Case #2- an infertile male with situs-inversus and total sperm immotility; Case #3- a male patient presenting limb-girdle muscular dystrophy with onset during early adulthood. Bioinformatic analysis was performed using several algorithms for variant annotation, filtering and to identify autozygosity through runs of homozygosity.

Results and discussion: In case #1, analysis assumed an autosomal recessive (AR) disease model and focused on genes implicated in hereditary myopathies. This analysis suggested the choline kinase beta (*CHKB*) gene as a possible candidate, where the detailed scrutiny of sequence alignments revealed the causal variant (c.1031+3G>C). Although the mutation was successfully detected its zygosity was incorrectly called suggesting a possible pitfall in WES.