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New Variant of Unknown Significance found in ERCC6 gene -Cerebro-oculo-facio-skeletal syndrome

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Keywords: Cerebro-oculo-facio-skeletal syndrome, ERCC6, Whole Exome Sequencing

INTRODUCTION/OBJECTIVES: Cerebro-oculo-facio-skeletal syndrome (COFS) is a genetic disorder caused by a mutation of the DNA repair genes presenting with severe sensorineural involvement. The aim was to present a possible new pathogen mutation in the ERCC6 gene responsible for the clinical presentation of COFS.
CASE PRESENTATION: We present an 18 months old boy of healthy non-consanguine parents, born from the first pregnancy with perinatal risk factors in whom phenotypic dysmorphia has been observed at birth. Phenotypic features include microcephaly, left occipital plagiocephaly, deeply implanted small eyes, blepharophimosis, the tuberous tip of the nose, longer filter, gothic palate, left ear without cartilage, microretorgnancy, wide-set nipples, furrow 4 fingers right palm, clenched fists, and knee contracture. Clinically presenting with global psychomotor delay showed as possible gyration disorder on ultrasound of the brain, and cortical atrophy on magnetic resonance. Genetic processing was started with karyotyping, which excluded chromosomopathies and Chromosomal Microarray Analysis also didn't show changes. Whole Exome Sequencing shows a Variant of unknown significance (VOUS) in the ERCC6 (10-50708680-A G gene; c.1589T> C). Individuals with COFS and ERCC6 mutation are sometimes considered as having Cockayne Syndrome Type II.
CONCLUSION: This mutation hasn't been described yet, and the currently available database is not sufficient to link variation to COFS. Due to the clinical presentation of this patient, there is a clinically reasonable suspicion that hat it is a new mutation of the ERCC6 gene that could potentially be pathogenic. Parental testing should also be done to classify the variant and confirm the pattern of segregation.

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Nusinersen treatment in SMA type III: treating an adult patient

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Keywords: nusinersen, Revised Hammersmith Scale, spinal muscular atrophy

INTRODUCTION/OBJECTIVES: Spinal muscular atrophy (SMA) is a rare disorder which presents as a loss of (spinal) lower motor neuron with consequential muscular atrophy. It is caused by absence of SMN1 gene on chromosome 5 due to exon 7, or additionally exon 8, deletion. Presence or absence of SMN2 and NAIP genes determine the severity and time of onset of the disease. SMA is divided in 5 types ranging from 0 to 4 with 0 being the most severe with the earliest time of onset and 4 being the mildest with the latest time of onset.
CASE PRESENTATION: A 30-year-old female patient was admitted for nusinersen treatment. Patient was diagnosed with SMA type III at the age of 3 years with the exact chromosomal abnormalities confirmed via molecular genetic testing 2 years prior to the start of the treatment. Efficacy of the treatment was evaluated by Revised Hammersmith Scale (RHS) and Revised Upper Limb Module (RULM). The results before treatment were 29/69 RHS and RULM 43/43. Walking difficulties were the most prominent symptom prior to the therapy. After six primary doses, results were 39/69 RHS and RULM 43/43, with patient showing remarkable improvement especially regarding walking on her own.
CONCLUSION: Nusinersen can be effective at treating SMA type III in adult age. It modulates alternative splicing of the SMN2 gene, functionally converting it into an SMN1 gene. The patient has shown improvement and will continue the treatment with maintenance doses each 4 months should there be no stopping criteria met.