

### CR47 Innovative Genome Joint Analysis for identification of novel deep-intronic de novo pathogenic variants in KMT2A gene - Wiedemann-Steiner Syndrome

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**KEYWORDS:** Hypertrichosis cubiti; KMT2A protein, human; Rare Disease; Whole Genome Sequencing

**INTRODUCTION/OBJECTIVES:** Heterozygous mutations in KMT2A gene are known to cause Wiedemann-Steiner Syndrome (WDSTS), a rare, autosomal dominant disease characterized by facial dysmorphism, intellectual disability, hypertrichosis cubiti, and psychomotor developmental delay. Whole genome sequencing (WGS) is a promising method to both identify pathogenic gene variants and facilitate personalized medical management.

**CASE PRESENTATION:** We present an 8-year-old boy with WDSTS caused by four de novo mutations in KMT2A gene, encoding a transcriptional coactivator that plays an essential role in regulating gene expression during early development. Born at term with birth weight 2460 g, Apgar 6/8, pregnancy was associated with intra-uterine growth retardation. Growth and psychomotor development were delayed during the first 4.5 years of life. Dysmorphic facial features include hypertelorism, antimongoloid eyes and epicanthus. Hypertrichosis, growth hormone deficit, chronic tonsil inflammation, gastroesophageal reflux, convergent strabismus, allergic diathesis, ADHD, and hypovitaminosis D3 with hypercalcemia are present. Intelligence is below average. He is obese (BMI 24.1 kg/m<sup>2</sup>). Bender-Gestalt Test demonstrated difficulties in visuomotor coordination and visuomotor perception. Under the "CroSeq-GenomeBank" project, an analysis of the child's entire genome was performed and four de novo pathogenic variants in the KMT2A gene on 11q23 in the heterozygous composition were identified.

**CONCLUSION:** A patient with four de novo pathogenic variants in the KMT2A gene not previously reported in the literature was described. A multidisciplinary approach with an emphasis on neurodevelopment and diet therapy is key to the treatment of WDSTS. "CroSeq-GenomeBank" Project has brought the opportunity for personalized approach to a rare disease, keeping Croatia in step with highly developed countries.

### CR48 Innovative Whole Genome Joint Analysis – case report of early diagnosis and preventive approach to HFE Hemochromatosis

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**KEYWORDS:** Genetic Variations; Primary Hemochromatosis; Whole Genome Sequencing

**INTRODUCTION/OBJECTIVES:** Whole Genome Joint Analysis is an innovative method to elucidate the full spectrum of genome complexities and alterations in the family members, comprehensively and unbiasedly. Once identified in the preclinical phase of the disease, causative variants can anticipate a personalized preventive approach and medical treatment.

**CASE PRESENTATION:** We present a patient who is the mother of our index child whom we evaluated for a rare disease. Therefore, the mother was a „healthy“ participant in this research. The biallelic variants of the HFE gene have been identified: p.Cys282Tyr and p.His63Asp which makes the patient compound heterozygous for the HFE gene, therefore having hemochromatosis type 1b. Often the first signs are arthropathy, an increase in skin pigmentation, cardiomyopathy, hepatomegaly, and common nonspecific symptoms. Women are affected less frequently than men. However, our patient is female and has a low to moderate genotype but has developed symptoms at the age of 40. Screening using transferrin saturation, noninvasive liver, and quantitative cardiac MRI may be considered to support the diagnosis. Periodic phlebotomy is a simple and effective treatment. Results of the deferasirox (Exjade®) trial suggest that the oral iron chelator is effective at reducing iron burdens within an acceptable safety profile.

**CONCLUSION:** The "CroSeq-GenomeBank" project which enabled us to diagnose our patient with primary hemochromatosis, acts as an innovative and precise basis for personalized medicine using artificial intelligence. It is an expensive and insufficiently accessible approach that would mean a lot to us as a society if we were to maintain our profession at the highest level.