

## CR79 Whole Genome Joint Analysis for identification of rare non-coding causative variants - case report of a child with mitochondrial disease

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**KEYWORDS:** Mitochondrial Diseases; Mutation; Whole Genome Sequencing

**INTRODUCTION/OBJECTIVES:** Pediatric genetic conditions are caused by a spectrum of genomic alterations, including non-coding variants, which often fail to be identified using low throughput methods. Whole genome sequencing (WGS) can detect the full spectrum of genome alterations simultaneously, comprehensively, and unbiasedly.

**CASE PRESENTATION:** We present a 3-year-old girl with a Mitochondrial complex I deficiency, nuclear type 3 (MC1DN3), caused by a biallelic mutation in the NDUFS7 gene, encoding a subunit protein of a complex forming the mitochondrial respiratory chain. As a newborn, she presented with progressive multiorgan deterioration, hypoglycemia, hypocalcemia, hypokalemia, lactatemia, metabolic alkalosis, hypernatremia, hypomagnesemia, hyperphosphatemia, and signs of mitochondrial dysfunction in organic acids. She was stabilized and started habilitation. Currently, she is uncoordinated, fatigued, and has impaired speech. A joint analysis of the child's and her family's entire genome was done under the "CroSeq-GenomeBank" project. As a result, a rare non-coding causative variant in the NDUFS7 gene in the homozygous composition was identified, and she was diagnosed with MC1DN3. This autosomal recessive disease causes dysfunction of energy production in the mitochondria with a heterogenous and unpredictable clinical course with symptomatic treatment.

**CONCLUSION:** With the evolution of diagnostic methods, more non-coding variants are being discovered and connected to various pathological conditions. Although diagnosing is challenging given the unspecific clinical presentation, early detection is possible using innovative and precise techniques such as Joint-WGS. The infrastructure of the "CroSeq-GenomeBank" has brought this foundation of personalized medicine to Croatia, keeping us in step with highly developed countries.

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## CR80 USE OF IMMUNOTHERAPY IN THE TREATMENT OF A PATIENT WITH TWO SIMULTANEOUS METASTATIC DISEASES

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**KEYWORDS:** Immunotherapy; Metastatic disease; Nivolumab

**INTRODUCTION/OBJECTIVES:** Immunotherapy is an evolving and promising cancer treatment proven to significantly prolong survival in a multitude of oncological diseases. Nivolumab, a monoclonal antibody to the PD-1 receptor, is an immunotherapy used in the treatment of several cancers, including melanoma and renal cell carcinoma (RCC). **CASE PRESENTATION:** Initially, 44-year-old patient underwent nephrectomy due to RCC and two years later an excision of melanoma on the lower leg. 23-years later, he reported with fatigue, weight loss and anemia. PET/CT detected metabolically active mass in the pancreas and subcutaneous accumulation on the left leg. Biopsy confirmed RCC metastasis in the pancreas while the excision of leg lesion revealed melanoma metastasis with BRAF mutation. As melanoma metastasis was removed, and the only confirmed active malignancy was RCC metastasis, treatment with sunitinib was started. After four months, the patient was admitted to emergency room due to small intestine obstruction which was surgically treated and PHD revealed melanoma metastasis. Sunitinib therapy was continued due to good response for five months when new melanoma metastases occurred, and instead of sunitinib, nivolumab immunotherapy was started. Follow-up PET/CTs showed lower metabolic activity in all metastases. Patient is still receiving the same treatment – nivolumab for more than three years, without any major side effects. The latest PET/CT evaluation showed no pathological uptake and reduction in size of the metastases.

**CONCLUSION:** Both the RCC and melanoma are highly immune mediated diseases which could explain the concurrent reactivation and metastatic spread of both diseases as well as positive and lasting therapeutic response to immunotherapy.