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Clinically recognizable disease with negative result of routine gene panel — in search of genetic background with innovative whole genome sequencing

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Background:

Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is an autosomal recessive disease with early presentation and unfavorable clinical course. Pseudohypoparathyroidism type 1A (PHP1A) is an autosomal dominant disease characterized by end-organ resistance to PTH, a hormone responsible for the control of calcium, phosphorus, and vitamin D levels in blood. People with PHP1A likewise have resistance to other hormones, such as TSH and gonadotropins. In addition, it is also associated with an array of clinical features referred to as Albright hereditary osteodystrophy (AHO).

Case Presentation:

We present a 6-year-old girl on a mechanical ventilator due to respiratory insufficiency, with symmetrically diminished growth, multiple skeletal defects (cervicothoracic kyphosis, abnormally fused arches of the cervical vertebrae, equinus feet), liver lesion, dystonia, and delayed motor development. She developed necrotizing enterocolitis and was diagnosed with intraventricular hemorrhage grade 1, two weeks after birth. She has deviation in neurological status, dystonia, hypertonia, lags in acquisition of postural mechanisms, secondary osteoporosis due to malnutrition, chronic atelectasis of the left lung lobe, recurrent urinary bladder infections, and bilateral ureterolithiasis. Muscle biopsy excluded primary muscle disorder, while electromyoneurography indicated nerve disorder. Panel gene testing for the most frequent variants for SMA was negative, leaving the patient undiagnosed. A whole genome joint analysis was done under the "CroSeq-GenomeBank" project, yielding two causal variants in IGHMBP2 gene and one in GNAS gene. The patient was finally diagnosed with spinal muscular atrophy with respiratory distress type 1 and pseudohypoparathyroidism type 1A.

Conclusion:

Whole genome joint analysis provided new diagnostic findings, detected variants not previously identified on panel testing and allowed interrogation of newly found variants. Whole genome sequencing is superior to other gene testing tools currently in use. It is both cost- and time-effective due to its elimination of the steps in-between, leading to faster diagnosis and reducing complications.

Keywords:

CroSeq-GenomeBank, Personalized Medicine, Whole Genome Sequencing