DEPARTMENT OF GENOMICS AND MOLECULAR DIAGNOSTICS

SPINAL MUSCULAR ATROPHY DELETION & DUPLICATION ANALYSIS (SMN_MLPA)

Referral Reason

Genetic testing for SPINAL MUSCULAR ATROPHY (SMA).

Test Result

- **NO DELETION OR DUPLICATION DETECTED IN SMN1 GENE.**
- **NO DELETION OR DUPLICATION DETECTED IN SMN2 GENE.**

Interpretation

The MLPA data analysis using coffalyser showed no deletion or duplication of exon 7 and 8 in SMN1 and SMN2 genes in the tested Sample. (SMN1 Exon 7 copy number: 2, Exon 8 copy number: 2, SMN2 Exon 7 copy number: 2).

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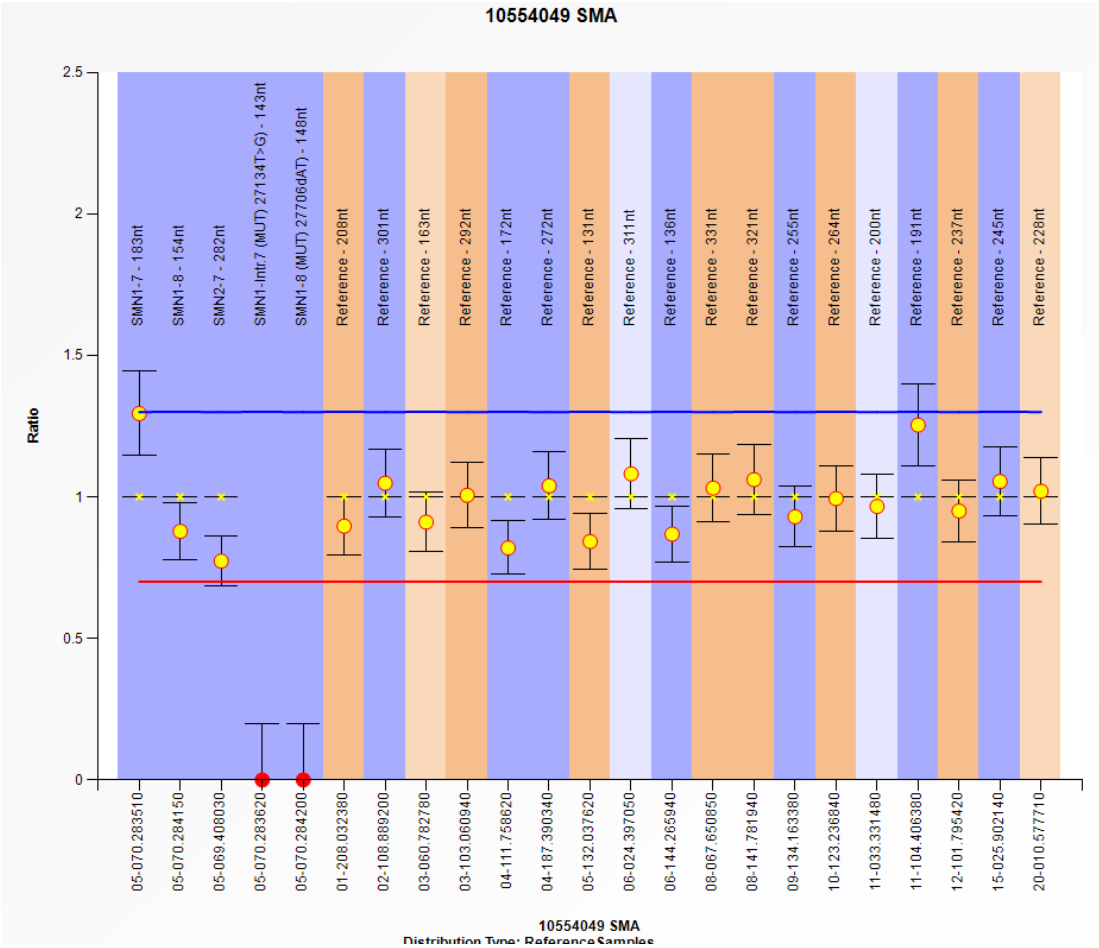

Recommendations

- Genetic Counselling is recommended

Methodology

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Multiplex Ligation-dependent probe amplification (MLPA) method is used for the detection of copy number changes of Exons 7 and 8 of SMN1 and SMN2. Coffalyser software is used for data analysis. DNA was isolated from the provided sample using commercial kit according to manufacturer's instructions and was subjected for MLPA analysis.

Clinical Sensitivity - MLPA

SMN1 deletions will be detected in over 99% of individuals with Spinal Muscular Atrophy in either the homozygous state (95% to 98% of affected individuals) or in the compound heterozygous state with another pathogenic variant (2% to 5% of affected individuals) (Rudnik- Schoneborn et al. 2012. PubMed ID: 22510849).

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder with variable age at onset and severity, characterized by progressive degeneration of the lower motor neurons in the spinal cord and brain stem, leading to muscle weakness, and in its most common form, respiratory failure by age two. Complications of SMA may include poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint deformities. In severely affected individuals, abnormal fetal ultrasound findings may include congenital joint contractures, polyhydramnios, and decreased fetal movement.3 Treatment is supportive. Targeted therapies may be available for some individuals. Approximately 94% of affected individuals have 0 copies of the SMN1 gene; in these individuals an increase in the number of copies of the SMN2 gene correlates with reduced disease severity.[4]

Genetics

Two nearly identical genes SMN1 and SMN2 located on complex region of chromosome 5 at band q13.2 plays crucial role in SMA. Most individuals have two copies of each gene. SMN1 gene codes the survival of motor neuron protein (SMN) and plays a crucial role in survival of motor neurons. SMN2, is a complicated inverted repeat area displaying high instability, leading to frequent deletions and gene conversions. SMN1 and SMN2 can only be distinguished by two single nucleotide differences: one in exon 7 and one in exon 8. The single nucleotide difference in exon 7 of SMN2 affects mRNA splicing resulting in an altered SMN protein with a limited half-life and function. The majority 95-98% of SMA patients show homozygous deletion of exon 7 in SMN1 gene which encodes the full-length survival motor neuron protein (Prior and Finanger. 2016. PubMed ID: 20301526) and SMA carriers can be identified by the presence of only one single SMN1 exon 7 copy. Determining the SMN2 copy number is important in SMA patients because more the copy number of SMN2 gene, less severe is the disease

Limitations of the test

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This test cannot detect copy number neutral inversions, translocations, and methylation changes. All possible causes of the syndromes included cannot be detected as the probe mix has limited number of probes for eachchromosomal region. The detection rate may vary between syndromes, depending on the heterogeneity of the disorder. Even when MLPA does not detect any aberrations, the possibility remains that biological changes in that gene or chromosomal region do exist but remain undetected.Sequence changes (e.g.SNPs, point mutations, small indels) in the target sequence or even when >20nt from the probe ligation site detected by a probe can affect the results. Sensitivity &specificity of the assay may be influenced by the quality of the specimen. The given test result should be interpreted in context of all available clinical findings. This method cannot detect point mutation in the SMN1/SMN2 gene. Some individuals have two copies of SMN1 on just one chromosome and no copies of SMN1 on the second chromosome, this individual will be a carrier but this will not be detected by this test.

* It is presumed that the specimen used to perform the test belongs to the patient specified above, such verification having been carried out at the collection level of the sample. This test does not report any other mutations other than SMN as it is a targeted test.

Although all precautions are taken while conducting these tests, there is a standard error rate of approximate 1% in all genetic tests and this should be taken into consideration before any clinical decision.

False-positive or false-negative results may occur for reasons that include genetic variants, technical handling, blood transfusions, bone marrow transplantation, mislabelling of samples, or erroneous representation of family relationships.

References

1. Katharina J Hoff (2009): The effect of sequencing errors on metagenomic gene prediction. BMCGenomics, 10:520.
2. Alias L et al. (2014). Improving detection and genetic counselling in carriers of spinal muscular atrophy with twocopies of the SMN1 gene. Clin Genet. 85:470-475
3. Ben-Sachar S et al. (2011). Large-scale population screening for spinal muscular atrophy: clinical implications.Genet Med. 13:110-114
4. Feldkötter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time light Cycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet. 2002 Feb;70(2):358-368.

***** End Of Report *****

Suggested clinical correlation & follow up

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