BLM Gene Analysis in Bloom Syndrome

Clinical Features:
Bloom syndrome (BS) is a rare disorder characterized by severe prenatal and postnatal growth retardation, sun-sensitive facial erythema and predisposition to multiple cancers. The development of cancer is the most frequent complication and involves cancers of the skin, leukocytes, lymphoid tissues, connective tissues, germ cells, nervous system and kidneys. Other common findings in individuals with BS include learning disabilities, recurrent infections, chronic pulmonary disease and diabetes mellitus. Infertility is common in males with Bloom sydrome. While most females do not experience infertility, they may experience premature menopause. Affected individuals of different ethnic groups share a similar phenotype.[1] Although BS is rare, it is more common in the Ashkenazi Jewish population due to a founder effect.[2] Bloom syndrome is often in the differential diagnosis when there is unexplained severe intrauterine and postnatal growth retardation and/or a cancer in a very young individual.

Inheritance Pattern/Genetics:
Bloom syndrome is an autosomal recessive disorder caused by pathogenic variants in the BLM gene, which is located on chromosome 15q26.1. The BLM gene is composed of 22 exons and encodes the 1,416-amino-acid protein, RECQL3. This protein belongs to a family of DNA helicases that plays an important role in maintaining genome stability. Somatic cells from individuals with BS experience an abnormally high rate of variants and undergo increased recombination, which is evident by increased chromosome breakage and sister chromatid exchange. For this reason, initial testing for Bloom syndrome involves cytogenetic evaluation of chromosomes after exposure to BrdU. This somatic hypermutability and hyper-recombination provide an explanation of the increased cancer risks associated with Bloom syndrome.[3]

Test Sensitivity:
In a study of individuals with BS from the Bloom Syndrome Registry, 93% (125/134) of patients had at least one pathogenic variant in the BLM gene. Of the 125 affected individuals, 87% (117/134) of patients were found to have two variants in the BLM gene, while only one variant was identified in 8 other individuals.[4]

Many different pathogenic variants have been reported in the BLM gene. The BLMAsh variant is a 6-base pair deletion and 7-base pair insertion in exon 10. This variant is a common founder mutation in the Ashekenazi Jewish population but is also common in individuals of other ethnicities.[4-6] The carrier frequency of BLMAsh is approximately 1 in 104 in the Ashkenazi Jewish population[6] and unknown in other populations. Most other pathogenic variants associated with Bloom syndrome are small deletions/insertions leading to frameshifts

or nonsense variants, although splice site and missense variants can occur. Large deletions of one or more exons have also been reported, but the overall clinical sensitivity of deletion/duplication testing is unknown.[4] A registry of variants identified in individuals with Bloom syndrome is available online (http://structure.bmc.lu.se/idbase/) .[7]

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

References:

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