MISSING HERITABILITY IN BLOOM SYNDROME: FIRST REPORT OF A DEEP-INTRONIC VARIANT LEADING TO PSEUDO-EXON ACTIVATION IN THE BLM GENE

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Background Pathogenic biallelic variants in the BLM/RECQL3 gene cause Bloom Syndrome (BS), a rare autosomal recessive disorder. This syndrome is characterized by severe growth delay, immunodeficiency, genomic instability and a predisposition to a wide variety of cancers early in life. Literature shows that the main mode of BLM inactivation is protein translation termination. Here we expand the molecular spectrum of Bloom Syndrome by reporting the first deep intronic variant causing intron exonisation. Results We present a boy with severe growth delay, a bird-like face, hyperpigmentation, T cell lymphopenia and hypogammaglobulinemia. Increased sister chromatid exchanges (SCEs) were observed, a pathognomonic sign for BS. Total RNA was extracted from a short-term phytohemagglutinin stimulated lymphocyte culture and converted to cDNA. Thorough analysis at both the gDNA and cDNA level revealed a novel nonsense variant c.3379C>T, p. (Gln1127Ter) in exon 18 and an interesting deep intronic variant c.3020-258A>G in intron 15 of the BLM gene. cDNA analysis showed that the deep intronic variant creates a high- quality de novo donor splice site, which leads to retention of two intron segments. Both pseudo-exons introduce a premature stop codon and abolish BLM protein expression. This was confirmed by western blot analysis on phytohemagglutinin stimulated T cells. Conclusions Here we describe a not yet reported pathogenic mechanism in Bloom Syndrome. These findings illustrate the role of non-coding variation in Mendelian disorders and herewith highlight a currently unmet need in routine genetic testing, being the added value of RNA-based approaches to solve missing heritability and provide a complete molecular diagnosis.