

The *Bloom* DNA helicase is a member of the RecQ family of ATP-dependent helicases. The *Drosophila* ortholog, *blm*, is encoded by the *mus309* locus. Absence in humans gives rise to Bloom's Syndrome (BS), a rare, autosomal recessive disorder characterized by sterility and predisposition to many different cancers. BS cells express extreme genetic instability characterized by chromosomal breaks and sister chromatid exchanges. People with Bloom Syndrome also express proportional dwarfism that as-yet has no clear explanation.

We created a complete deletion of all 4 exons of the *Drosophila blm* gene (the *blm*^{ES} allele). We obtained mutant flies with different genotypes (*blm*^{ES}/*blm*^{ES}, *blm*^{ES}/+, +/+) using the *blm*^{ES} allele and compared their phenotypes at both cellular and tissue/organ levels. We discovered that while *blm*^{ES}/*blm*^{ES} flies escape the embryonic lethality caused by the absence of the *blm* gene, adult mutants lack the capacity to produce new offspring. When comparing the overall body weight, wing width and depth between homozygous (*blm*^{ES}/*blm*^{ES}) and heterozygous (*blm*^{ES}/+) mutants, we discovered that homozygous flies had smaller bodies and wings than heterozygous siblings. Although it is known that *blm* deficiency causes genomic instability, the reason for this growth retardation has not been determined. Currently, there are two main competing ideas: (i) that *blm* deficiency leads to a lengthened the cell cycle time, which in turn causes a decrease in the number of cells, and (ii) that increased DNA damage increases the rate of apoptosis in mutant cells. The *blm*^{ES} allele closely recapitulates the human small size phenotype, allowing us to address these ideas, as well as other persistent gaps in the study of *Bloom* function.

Our work has led us to a third hypothesis, (iii) that the relationship between *blm* and *rDNA* (ribosomal DNA) contributes to the small size phenotype. Analysis of BS clinical entities and patient-derived cell lines show a defect preferentially in hard-to-replicate DNAs including *rDNA*. *blm* enhanced the bobbed *rDNA* deficiency phenotype, mostly through a persistent *blm*-mediated loss of *rDNA* copy number. This reduction was attended by cytological defects in nucleolar structure. *blm* mutants also produced rare magnified *rDNA* arrays, indicating *blm* mutation generally destabilizes chromosome at the *rDNA*. We determined *rDNA* copy numbers by qPCR in 3 different human cell lines as well as in blood samples collected from Bloom syndrome patients. Mutations in the *blm* gene cause hypervariability in the *rDNA* copy number, as they did in *Drosophila*. Our data suggest that *blm* stabilizes *rDNA*, and defects lead to hypervariability – usually appearing as loss, but occasionally appearing as gains – in *rDNA* copy number. We will continue to investigate if and how this instability contributes to the small size phenotype in both humans and *Drosophila*.