Abstract

Retinitis pigmentosa (RP) is an eye disorder impacting around two million people worldwide. In this work, we analyzed the effect of an amino acid substitution within the RNA helicase DHX38 (Prp16), which gives rise to RP. In yeast, Prp16 has been identified as a helicase necessary for the second step of splicing. Our research showed DHX38's interaction with crucial splicing components relevant to both steps of splicing, although we did not observe that the RP mutation changes these interactions. We then downregulated DHX38 and monitored splicing changes. While we noted only minor changes in overall splicing, we detected 71 altered alternative splicing events. We then investigated the role of DHX38 in the splicing of genes specific to the retina. Our results spotlighted the dependence of FSCN2 splicing on DHX38. Intriguingly, the DHX38 RP variant exhibited an inhibition on RHO splicing. Lastly, we showed that the overexpression of DHX38 promoted the usage of both canonical and cryptic 5' splice sites within the HBB splicing reporter. In summary, our data show that DHX38 is a splicing factor that promotes the splicing of cryptic splice sites and it is involved in alternative splicing. Furthermore, we provide evidence suggesting that the RP-associated substitution G332D influences the splicing activity of DHX38.