Do Bainbridge-Ropers Syndrome Causing ASXL3 Mutations Influence Transcript Stability and Exon Exclusion/Inclusion by Disrupting Exonic Splicing Enhancer Sequences?

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Bainbridge-Ropers Syndrome is a rare autosomal dominant neurodevelopmental disease characterized by predicted truncating mutations in the ASXL3 gene. Around 200 children have been diagnosed worldwide and currently there is no cure. Recent studies in the field of molecular genetics predict that many human genetic diseases associated with mutations within exons may be caused by the inactivation of exonic splicing enhancer (ESE) sequences, which promote regulated and constitutive splicing. This study aimed to determine if BRS-causing mutations occur within ESE sequences and further evaluate if they have an impact on pre-mRNA splicing. A total of 55 BRS-causing mutations were collected from an extensive literature review and of those, 48 were cataloged onto the sequence analysis application MacVector. Predicted ESE sequences were collected with ESEfinder, a web-based resource that searched for four different ESE consensus sequences each primarily bound to one of four human SR proteins provided: SF2/ASF, SRp55, SC35, and SRp40. A total of 391 ESE sequences were inputted into MacVector and analyzed for alignment with BRS-causing mutations. This novel study demonstrates that the BRS-causing mutations 1189C>T, 1314_1316delinsA, 1369G>T, 1783C>T, 1978_1981del, 1975_1978delACAG, and 3127_3128dup inactivated the predicted ESE sequences they had alignment with. It is likely that other pre-mRNA splicing mechanisms may also be disrupted by these mutations, and future studies that explore cryptic splice site activations or other forms of potential pre-mRNA splicing disruptions will be imperative to better understanding how these mutations drive the BRS phenotype.

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