A177 · Short tandem repeat polymorphisms mediate transcriptional heterogeneity in Ewing sarcoma

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Ewing sarcoma (EwS) is a pediatric cancer driven by translocations between EWSR1, a ubiquitously expressed FET gene, and an ETS transcription factor, most commonly FLI1. EwS cancer fusions retain the DNA binding domain of the disrupted ETS transcription factor and bind GGAA-containing sequences, including ~10,000 GGAA-containing short-tandem repeats (STRs), where EWS-FLI binding imparts de novo enhancer activity, mediating the activation of critical secondary effectors. Naturally occurring polymorphisms alter the GGAA content of these STRs, potentially contributing to transcriptional heterogeneity between cases and broader EwS risk and development. To investigate this relationship, we performed long reads sequencing to genotype GGAA STRs in EwS model cell lines. We then correlated the GGAA content of different STR alleles with target gene expression, revealing hundreds of potential regulatory relationships where longer STR alleles are associated with enhanced gene expression. This revealed a polymorphic STR that mediates the activation of the oncofetal protein IGF2BP1, a selective EwS dependency. We find that IGF2BP1 is a critical post- transcriptional regulator in EwS that is responsible for the upregulation of more than one thousand target transcripts, including MYC, representing a substantial regulatory layer in the EWS-FLI gene expression program. Together with other key secondary effectors, this work can help decompose the broad transcriptional response to EWS-FLI expression into discrete regulatory programs, where STR polymorphisms control the level to which each of these subprograms contributes to the total EWS-FLI response. This in turn could explain transcriptional heterogeneity between EwS cases, informing more personalized approaches to tumor targeting and treatment.

Short tandem repeat polymorphisms mediate transcriptional heterogeneity in Ewing sarcoma

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