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MICRO AND MACROSATELLITE REPEATS IN HUMAN DISEASE: SIMILAR FEATURES AND DISTINCT MECHANISMS

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We have shown that expansion of the CTG repeats at the DM1 locus induces regional heterochromatin and suppresses expression of the adjacent SIX5 gene. In an effort to determine the mechanism of heterochromatin formation, we identified bidirectional RNA transcription through the repeats that is associated with the formation of small siRNA-like fragments. This occurs at the non-expanded wild-type repeat as well and is associated with a very localized region of heterochromatin: the nucleosome occupying the CTG repeat has H3K9 methylation and HP1 recruitment. Flanking CTCF sites appear to restrict the spread of the heterochromatin. The bidirectional transcription and flanking CTCF sites is also present at multiple other CTG/CAG repeats in the genome.

We have extended our studies to the CGG repeats at the FMR1 locus. Similar to the CTG/CAG repeats, we find bidirectional transcription and flanking CTCF sites. However, at the FMR1 locus, the antisense transcript is spliced, polyadenylated, and associated with ribosomes. The antisense transcript also contains a potential open reading frame that can produce a protein rich in proline residues. Similar to FMR1, the antisense transcript (ASFMR1) is elevated in premutation alleles and suppressed in full mutation alleles. Of note, there is an alternative splice product associated with premutation alleles that is predicted to enhance protein translation. Therefore, in the case of the FMR1 locus, the antisense transcript might contribute to the FXTAS syndrome.

Recently we have examined the D4Z4 macrosatellite repeat at the FSHD locus. Similar to the DXZ4 macrosatellite repeat on the X-chromosome, the D4Z4 repeat is also bidirectionally transcribed and generates small siRNA-like fragments.

In summary, there is a consistent pattern of transcription at both microsatellite and macrosatelllite repeats that might suggest common regulatory mechanisms.