Medical & healthcare, Drug discovery, Livestock

Studies on the genomic structure and evolution of the mammalian sex-determining gene Sry

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Abstract

The mammalian sex-determining gene Sry induces male development. Since its discovery 30 years ago, Sry has been believed to be a single-exon gene. Here, we identified a cryptic second exon of mouse Sry and a corresponding two-exon type Sry (Sry-T) transcript. XY mice lacking Sry-T were sex-reversed, and ectopic expression of Sry-T in XX mice induced male development. Sry-T messenger RNA is expressed similarly to that of canonical single-exon type Sry (Sry-S), but SRY-T protein is expressed predominantly because of the absence of a degron in the C terminus of SRY-S. Our findings suggest that in nature, SRY-T, not SRY-S, is the bona fide testis-determining factor.

Background & Results

Sexual differentiation is essential for the survival and evolution of a species. Expression of the Y chromosomal gene Sry is required for male development in mammals. Since its discovery in 1990, Sry has been considered a single-exon gene encoding only one protein. Using a comprehensive transcriptomics approach, we identified a transcribed sequence within palindromic sequences flanking Sry. We identified this sequence as the 3′ portion of a novel Sry transcript that starts at the known Sry transcription start site and is spliced once, indicating that this sequence represents a second exon of Sry. Therefore, the Sry locus is found to produce two Sry transcripts, the known single-exon type (Sry-S) and a two-exon type (Sry-T). The predicted SRY-T protein shares amino acids 1 to 377 with SRY-S, including the high-mobility group DNA-binding domain and polyglutamine (poly-Q) sequences that are important for transcriptional activation. Beyond this, the C-terminal 15 amino acids of SRY-T are encoded by the second exon, whereas absence of splicing results in a different 18 amino acids at the C terminus of SRY-S. We found that the latter sequence encodes a protein-degradation motif, degron, but the former sequence does not. Protein expression of SRY-T predominates over that of SRY-S, because of the absence of a degron in the C terminus of SRY-S. XY mice lacking SRY-T were sex-reversed, and ectopic expression of SRY-T in XX mice induced male development. Our findings indicate that SRY-T, not SRY-S, is the bona fide testis-determining factor.

Significance of the research and Future perspective

Our findings overturn the conclusion that has prevailed for 30 years regarding the structure of Sry in the mouse, the most intensively studied mammalian model of sex determination. Further study of SRY-T will establish whether the second exon confers new functionalities on SRY in addition to protein stability and will provide a more complete understanding of how the sex-determining cascade is activated in mice compared with other mammalian species.

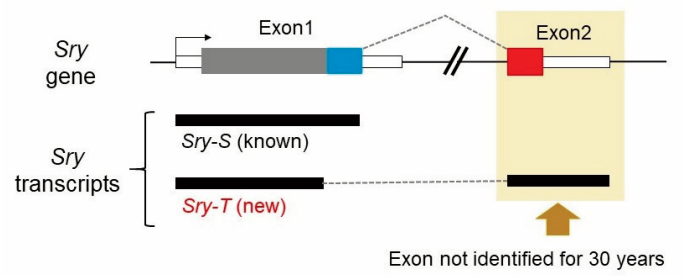

Figure 1. There is a "hidden" second exon in the *Sry* gene. The *Sry* gene produces two mRNA transcripts, the known single-exon type (*Sry-S*) and a two-exon type (*Sry-T*).

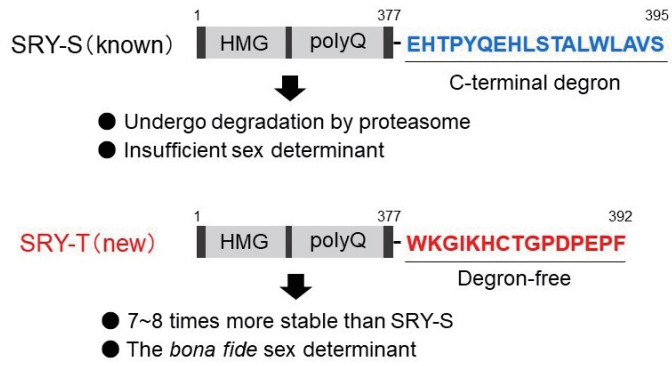

Figure 2. Differences in sequence and function between SRY-S and SRY-T.

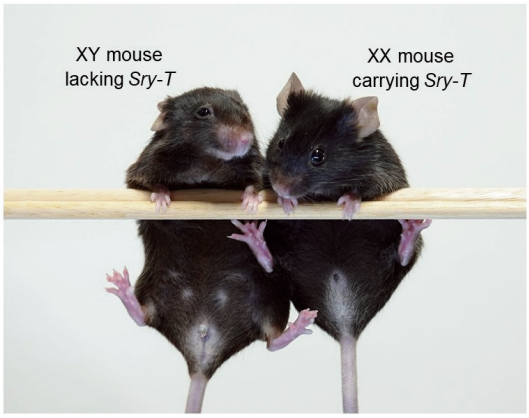

Figure 3. XY mouse lacking *Sry*-T differentiated into female, whereas XX mice carrying *Sry-T* differentiated into male.

Patent

Treatise Miyawaki, Shingo; Kuroki, Shunsuke; Maeda, Ryo et al. The mouse Sry locus harbors a cryptic exon that is essential for male sex determination. Science 2020; 370(6512): 121-124. DOI: 10.1126/science.abb6430

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Keyword sex-determining gene, evolution, mammal, protein degradation