Structure-based assessment of missense mutations in the HMGB domain of SRY identified in 46,XY females with sex reversal

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1 Summary

The SRY (sex-determining region of the Y chromosome) plays a key role in mammalian sex determination, as expression of the SRY gene initiates the process of testicular differentiation [1]. Mutations in the SRY gene are responsible for ~15% of 46,XY male-to-female sex reversal in humans. A total of 28 mutant proteins harboring sex-reversal missense mutations located in the conserved high-mobility group box (HMGB) domain of SRY were examined here. Comparative model building techniques were used to generate atomic structures of mutant proteins based on the NMR solution structure of HMGB domain of human SRY-DNA complex [2]. The impact of the missense mutations on the three-dimensional structure, stability, and surface electrostatic charge distribution of the HMGB domain of SRY are examined here. Seventeen missense mutations are located on the inner concave face of the HMGB domain; this region is involved in making contacts with the DNA recognition site as well as in nuclear localization. Nine specific missense mutations interfere with the pairwise interactions needed to stabilize the hydrophobic core of the HMGB domain. The mutant models have been compared to the wild-type protein in order to better understand the structural factors underlying these sex-reversal mutations.

References

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