# A novel missense mutation in the high mobility group domain of SRY drastically reduces its DNA-binding capacity and causes paternally transmitted 46,XY complete gonadal dysgenesis



**ID** 1193492
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**Year** 2011
**Title** A novel missense mutation in the high mobility group domain of SRY drastically reduces its DNA-binding capacity and causes paternally transmitted 46,XY complete gonadal dysgenesis
**Journal** Fertility and sterility
**Volume** 96
**Number** 4
**Pages** / **Article-Number** 851-855
**Keywords** Swyer syndrome, 46,XY complete gonadal dysgenesis, SRY, gonadal mosaicism, HMG domain, c.347T > C
To investigate the familial segregation, role, and function of a novel SRY missense mutation c.347Tin two half-sisters affected by 46,XY complete gonadal dysgenesis (CDG) compatible with a successful pregnancy outcome.; Phenotypic, mutational, and functional study.; Academic research unit.; Two half-sisters, their common father, and 100 healthy control individuals.; Chromosome, molecular cytogenetic analysis, and Sanger sequencing of the SRY gene in blood lymphocytes of the proband, her affected half-sister, and in inflammatory tissue of the father postmortem. Cloning and expression of high mobility group box carboxy-terminal domains of Sry and electrophoretic mobility shift assay were performed.; Not applicable.; A novel SRY missense mutation c.347T(p.Leu116Ser) was identified in two half-sisters and segregates with the CGD phenotype. It is present in the common healthy father in a mosaic state. Functional analyses demonstrate the pathogenic effect of the mutation by a strong reduction of DNA affinity for the mutant p.Leu116Ser SRY protein.; The missense mutation c.347Tin the high mobility group domain of SRY causes 46,XY CGD. Paternal gonadal mosaicism is likely to explain the familial occurrence of 46,XY CGD suggesting a de novo mutational event during the early stages of embryonic development. This novel mutation is compatible with a successful pregnancy outcome.
**Publisher** Elsevier
**ISSN/ISBN** 0015-0282
**edoc-URL** http://edoc.unibas.ch/dok/A6003735
**Full Text on edoc** No;
**Digital Object Identifier DOI** 10.1016/j.fertnstert.2011.07.1137
**PubMed ID** http://www.ncbi.nlm.nih.gov/pubmed/21868002
**Document type (ISI)** Article