MAML1 mutations seem not sufficient to explain a 46,XY DSD phenotype. What else?

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Background The MAML1 gene (Xp28) is thought to cause disorder of sex development (DSD) in 46,XY patients, mostly presenting with hypospadias, and, recently, also gonadal dysgenesis. However, there is some controversy about the role of MAML1 in sex development.

Aims and Objectives We searched for MAML1 sequence variations in 108 46,XY DSD individuals presenting with a wide spectrum of DSD phenotypes. Identified variations were functionally tested in vitro, and findings were compared with reported cases and the literature of MAML1 focusing on sex development.

Methods and Results I

Nine MAML1 mutations (7 novel) in 9 46,XY DSD patients were detected by Sanger sequencing.

Methods and Results III

WT and mutant MAML1 expression was assessed in mouse Leydig MA-10 cells.

Conclusion

Most MAML1 variants acted similarly to the WT.

Effect of MAML1 on CYP17A1 activity in NCI-H295R cells

Effect of MAML1 on androgen production assessed by testing the CYP17A1 activity in the 3 cell lines. No effect of either WT or any MAML1 variant on CYP17A1 enzyme activity was found.

No difference for MAML1 protein expression was found, except for a shorter L210X.