

Defects in efferent duct multiciliogenesis underlie male infertility in GEMC1, MCIDAS or CCNO deficient mice

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Abstract

GEMC1 and MCIDAS are Geminin family proteins that transcriptionally activate E2F4/5-target genes during multiciliogenesis, including *FoxJ1* and *Ccno*. Male mice lacking *Gemc1*, *Mcidas* or *Ccno* were found to be infertile, but the origin of this defect has remained unclear. Here we show that all three genes are necessary for the generation of functional multiciliated cells in the efferent ducts that are required for spermatozoa to enter the epididymis. In mice mutant for *Gemc1*, *Mcidas* or *Ccno*, we observed a similar spectrum of phenotypes, including thinning of the seminiferous tubule epithelia, dilation of the rete testes, sperm agglutinations in the efferent ducts and lack of spermatozoa in the epididymis (azoospermia). These data suggest that defective efferent duct development is the dominant cause of male infertility in these mouse models and this likely extends to patients with the ciliopathy Reduced Generation of Multiple Motile Cilia with mutations in *MCIDAS* and *CCNO*.

Figure

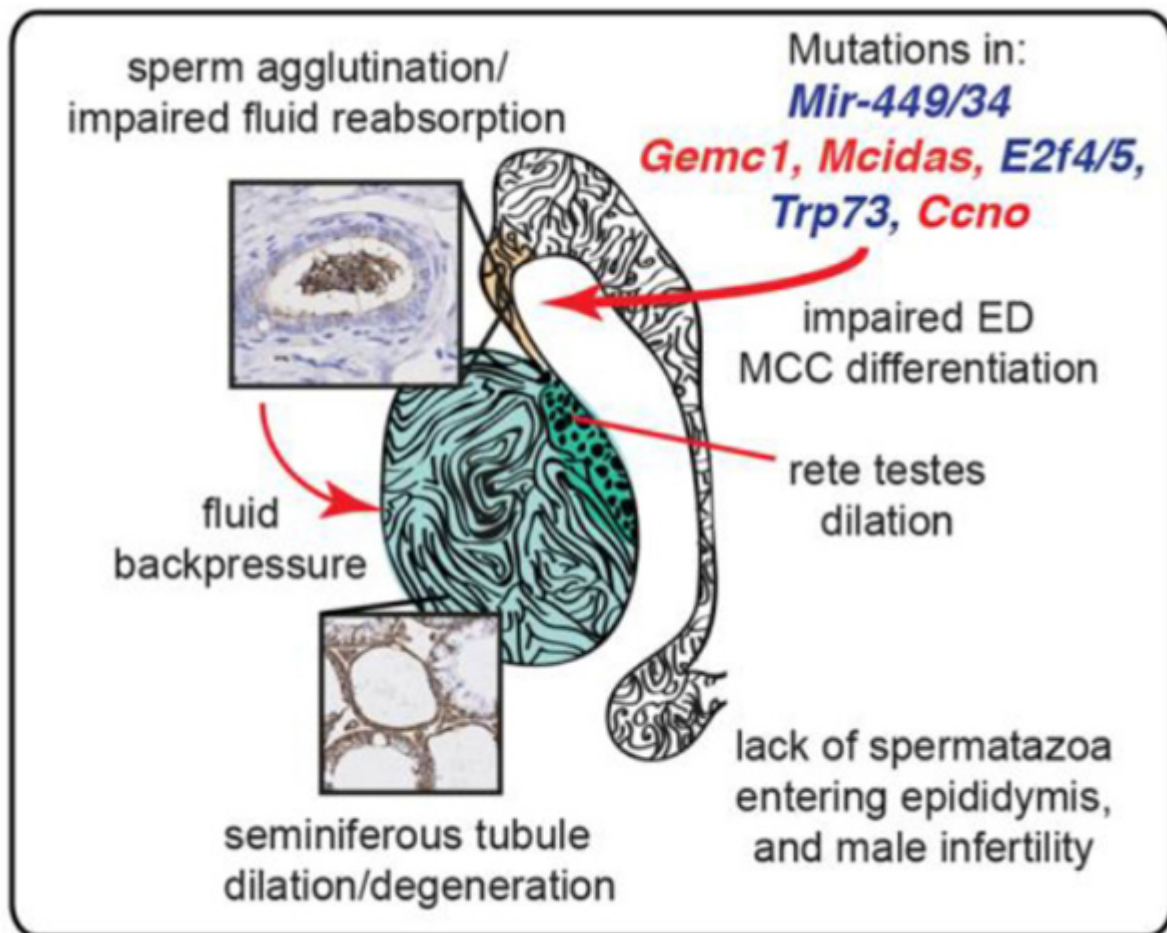


Figure Legend: Mice with mutations in *Mir449/34*, *Gemc1*, *Mcidas*, *E2f4/5*, *Trp73* and *Ccno* exhibit defects in multiciliated cell (MCC) development, and a similar phenotypic spectrum that includes dilation of the seminiferous tubules and rete testes, Sertoli cell degeneration, and lack of spermatozoa in the epididymis (azoospermia). We propose that the failure of the efferent ducts (ED) and resulting agglutination of spermatozoa contributes directly to fluid backpressure, preventing spermatozoa from entering the epididymis. This potentially occurs in human RGMC patients with *MCIDAS* or *CCNO* mutations.