Mutations in the CFAP-Coding Genes Lead to Male Infertility with Multiple Morphological Abnormalities of the Sperm Flagella

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Background: Sperm motility is vital to human reproduction. Malformations of sperm flagella can cause male infertility. Men with multiple morphological abnormalities of the flagella (MMAF) have abnormal spermatozoa with absent, short, coiled, bent, and/or irregular-caliber flagella, which impair sperm motility. Genetic factors are involved in the pathogenesis of MMAF.

Main Questions: The known MMAF-associated genes are only responsible for approximately half of human cases. Novel pathogenic mechanisms still remain to be elucidated in MMAF.

Experimental Design: We conducted genetic analyses using whole-exome sequencing and genome-wide comparative genomic hybridization microarrays in a multicenter cohort of 80 Chinese men affected by MMAF. Furthermore, the genome editing technology of CRISPR-Cas9 was employed to generate knockout mouse models for further functional investigations on our identified novel genes for MMAF.

Main Results: Biallelic mutations in the genes encoding cilia and flagella associated proteins (CFAPs) were identified in 15 (19% out of 80) cases with MMAF, including 7 in *CFAP43*, 2 in *CFAP44*, 4 in *CFAP65*, and 2 in *CFAP69*. These CFAP-coding genes are specifically or preferentially expressed in testis. Knockout mouse models of these four genes manifest short, coiled flagella and other phenotypes consistent with human MMAF.

Conclusions: Our experimental observations on human subjects and mouse models strongly suggest that biallelic mutations in *CFAP43*, *CFAP44*, *CFAP65*, and *CFAP69* can cause sperm flagellar abnormalities and impair sperm motility.

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