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To identify and characterize novel male infertility associated genes using Drosophila melanogaster as a model organism

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Non-obstructive azoospermia (NOA), defined by the complete lack of spermatozoa in the ejaculate, is clinically the most severe form of male infertility. Despite of this knowledge, the precise cause and molecular diagnosis for the majority of NOA men remains elusive and are diagnosed as 'idiopathic'or unexplained infertility. With advent of next-generation sequencing methods, a continuously increasing number of monogenic causes of male infertility are being discovered at a pace which makes it challenging to validate the functional relevance of the genes for fertility. As such, within this study, I aim to functionally characterize novel human male infertility associated genes that were identified in exome sequencing data of infertile men to reveal the impact of these genes on spermatogenesis using Drosophila melanogaster. We identified loss-of-function and rare missense variants in GLUD2 and FAM47A in infertile men. Currently, no functional study or animal model exists to validate the relevance of GLUD2 and FAM47A in human male fertility. Testis-specific knockdown of GLUD2 orthologue in flies led to infertility due to disrupted individualization complex and empty seminal vesicles without mature sperm. Consistent with the testicular phenotype observed in infertile men –meiotic arrest and sertoli cells only. On the contrary, testis-specific knockdown of FAM47A orthologue in flies led to infertility due to loss of germ-cell in the testis which was evident by extremely small testicular size of the testis. Consistent with the sertoli cells only testicular phenotype observed in infertile men with variants in FAM47A. Taken together, this study highlights the significance of using Drosophila melanogaster as a model organism to investigate functional relevance of novel candidate genes in male fertility.

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