Identifying the genetic causes of human infertility

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Estimates from the World Health Organisation suggests that infertility affects up to 17% of couples worldwide[1], with around 50% of cases attributable to male factor disease[2]. Male fertility relies primarily upon the production of mature spermatozoa via spermatogenesis in the testis. Ten percent of men with infertility have complete absence of sperm in the ejaculate and primary loss of gonadal function due to defective spermatogenesis, which is termed non-obstructive azoospermia (NOA). Chromosomal disorders such as Klinefelter syndrome and Y chromosome microdeletions, cryptorchidism and environmental causes for testicular damage account for 25-40% of NOA cases. Thus, the majority of NOA cases are classified as idiopathic and remain untreatable. Over the last decade, potentially pathogenic variants of testis-expressed genes have been described in men with NOA using whole exome or genome sequencing (WES/WGS)[3]. However, despite the identification of predicted pathogenic mutations in dozens of genes, including in several meiotic genes[2], few of these have undergone functional validation to prove a causative role in NOA. Furthermore, the mechanistic role in spermatogenesis for most candidate NOA genes remains unexplored. Therefore, there is an urgent need to develop functional high-throughput screening methods to capitalise on ongoing sequencing efforts of NOA patients. To address this, we have established methods to use the nematode *C. elegans* as an experimental organism to model mutations identified in infertile patients. *C. elegans* shares with humans the basic mechanisms underpinning fertility, is amenable to genome editing using CRISPR/Cas9, and has a rapid generation time, making it an ideal experimental system for functional studies of reproductive biology. *C. elegans* is particularly well suited for the investigation of meiosis, the specialized cell division programme that produces haploid gametes from diploid germ cells and that is an essential aspect of spermatogenesis and oogenesis.

The main goal of this project is to is identify genetic causes of human infertility (male and female) exploiting ongoing sequencing efforts of infertile patients and using *C. elegans* as a model organism. The project is a collaboration between the Martinez-Perez group at the LMS (meiosis and *C. elegans* genetics[4]), the Jayasena group at Imperial College (consultant in reproductive endocrinology[5]), and the Veltman group in Edinburgh (human reproductive genomics[6]). The project is part of the LMS Team Science initiative “Reproductive health and fertility: aging, sex, and the environment”, which includes two additional PhD studentships and three postdoctoral researchers. An important goal of this transdisciplinary team will be the identification of genetic networks controlling fertility during male and female gametogenesis and how these networks change during aging and in disease. These efforts will feed into the current PhD project by providing genes without previous connections to reproduction that will be functionally tested exploiting the *C. elegans* model system. For genes or mutations deemed of highest relevance there will be opportunities to model them in mouse models or using in vitro models of gametogenesis developed by others in team.

Students with an interest in reproductive biology, human genetics, meiosis, and functional studies with model organisms are encouraged to apply.

References (max 6) - *optional*:

1 Agarwal, A. *et al.* Male infertility. *Lancet* **397**, 319-333 (2021). https://doi.org:10.1016/S0140-6736(20)32667-2

2 Krausz, C. *et al.* Genetic dissection of spermatogenic arrest through exome analysis: clinical implications for the management of azoospermic men. *Genet Med* **22**, 1956-1966 (2020). https://doi.org:10.1038/s41436-020-0907-1

3 Oud, M. S. *et al.* A systematic review and standardized clinical validity assessment of male infertility genes. *Hum Reprod* **34**, 932-941 (2019). https://doi.org:10.1093/humrep/dez022

4 Castellano-Pozo, M. *et al.* Surveillance of cohesin-supported chromosome structure controls meiotic progression. *Nat Commun* **11**, 4345 (2020). https://doi.org:10.1038/s41467-020-18219-9

5 Sharma, A. *et al.* Improvements in Sperm Motility Following Low- or High-Intensity Dietary Interventions in Men With Obesity. *J Clin Endocrinol Metab* **109**, 449-460 (2024). https://doi.org:10.1210/clinem/dgad523

6 Oud, M. S. *et al.* A de novo paradigm for male infertility. *Nat Commun* **13**, 154 (2022). https://doi.org:10.1038/s41467-021-27132-8