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From Genetics of Male Infertility to Male Contraception

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Next generation sequencing has revolutionized the field of genetics and has greatly contributed to the discovery of novel infertility genes. Currently the most widely used research **approach in androgenetics is based on whole exome sequencing (WES), which is able to provide** information on all protein coding genes of the human genome. It has been predicted that over 3000 genes are involved in spermatogenesis, and according to proteome data, 2274 genes show elevated expression, whereas 474 are detected exclusively in testis.

Collaborative studies, especially those carried out in the context of the International Male Infertility Genomics Consortium (IMIGC) have been highly successful in identifying candidate genes of non-obstructive azoospermia (NOA). An example is related to our WES study in a selected group of NOA patients who had no spermatozoa in their testis biopsy (TESE). In our cohort we identified 5 novel genes involved in meiosis and causing spermatocyte arrest; 4/5 of these novel candidate genes have been immediately validated in independent cohorts belonging to IMIGC. Since the phenotype of the mutation carriers is a TESE negative NOA and some of these genes show exclusive testicular expression, they may represent potentially interesting contraceptive targets.

Recently, we identified several novel X chromosome-linked genes, among them those belonging to the cancer testis antigen family (CTA). In physiological conditions genes are expressed only in the testis (mainly in spermatogonia), but they also can be aberrantly activated and expressed in various types of human cancer. Apart from protein coding NOA genes, there is a growing evidence to support the role of testis specific miRNAs in the etiology of NOA.

While the primary aim of genetic studies is related to improve the clinical management of NOA patients, these recent discoveries have also potential implications in male contraception. A stronger interaction between the field of androgenetics and male contraception is warranted in order to carry out joint studies in order to develop novel non-hormonal contraceptives.