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EAA Literature Alert
Edition May 2021

A selection of good articles of interest for andrologists and reproductive biologists. As usual, we especially highlight the work performed in EAA centres. Enjoy the reading! You are welcome to share this list with your colleagues and students. If you want your hot new original study included in the next alert, send a note to the EAA Secretary.

Clinical andrology and epidemiology



It is known that varicocele impairs semen quality and the tretament can reverse that to some extent. In this study, a detailed microscopic morphological sperm evaluation highlighted a reduction in sperm abnormalities after varicocele surgery.

Morini D, Spaggiari G, Daolio J, Melli B, Nicoli A, De Feo G, Valli B, Viola D, Garganigo S, Magnani E, Pilia A, Polese A, Colla R, Simoni M, Aguzzoli L, Villani MT, Santi D. Improvement of sperm morphology after surgical varicocele repair.
Andrology. 2021 - in pres,s doi: 10.1111/andr.13012. PMID: 33825345.

https://onlinelibrary.wiley.com/doi/10.1111/andr.13012



A new easy-to-apply method capable of estimating DNA fragmentation in membrane-intact spermatozoa has been validated. This new protocol has the potential of improving the diagnostic of male infertility and enabling a better understanding of sperm dysfunction.

Da Costa R, Redmann K, Schlatt S. Simultaneous detection of sperm membrane integrity and DNA fragmentation by flow cytometry: A novel and rapid tool for sperm analysis.
Andrology. 2021 Apr 8. doi: 10.1111/andr.13017. PMID: 33830681.

https://onlinelibrary.wiley.com/doi/10.1111/andr.13017

Vasectomy reversal is successfully completed in most of the men either with a vasovasostomy or a vasoepididymostomy, but in some the operation fails. This commentary outlines the reasons why a vasectomy reversal is not possible or successful and presents a useful pre-operative management algorithm.

Andino JJ, Gonzalez DC, Dupree JM, Marks S, Ramasamy R. Challenges in completing a successful vasectomy reversal.



Andrologia. 2021: in press, e14066. doi: 10.1111/and.14066. PMID: 33866579.

https://onlinelibrary.wiley.com/doi/10.1111/and.14066

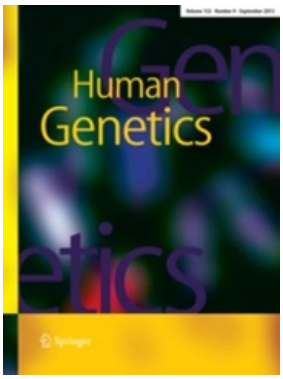


A question whether or not the anogenital distance (AGD) is a 'read-out' of testicular dysgenesis is still open. This study reports a possible association between testicular microlithiasis and a shorter AGD measured by magnetic resonance imaging (IMR).

Pedersen MRV, Osther PJ, Rafaelsen SR. Shorter anogenital distance is observed in patients with testicular microlithiasis using magnetic resonance imaging.
Insights Imaging. 2021;12(1):46. doi: PMID: 33846876.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8042061/

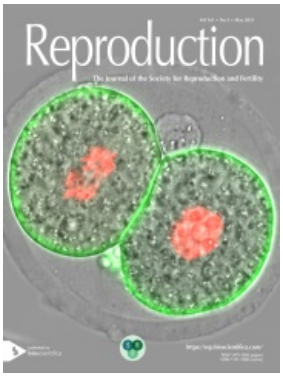
Androgenetics



A multicentre genomic study identified seven clinically relevant single-nucleotide variants (SNV) in X-linked germ-cell nuclear antigen (GCNA), a key factor for genome integrity in male meiosis. The authors propose that these variants disrupt structure and function of GCNA, ultimately arresting germ-cell division.

Hardy JJ, Wyrwoll MJ, Mcfadden W, Malcher A, Rotte N, Pollock NC, Munyoki S, Veroli MV, Houston BJ, Xavier MJ, Kasak L, Punab M, Laan M, Kliesch S, Schlegel P, Jaffe T, Hwang K, Vukina J, Brieño-Enríquez MA, Orwig K, Yanowitz J, Buszczak M, Veltman JA, Oud M, Nagirnaja L, Olszewska M, O'Bryan MK, Conrad DF, Kurpisz M, Tüttelmann F, Yatsenko AN; GEMINI Consortium. Variants in GCNA, X-linked germ-cell genome integrity gene, identified in men with primary spermatogenic failure.
Human Genetics 2021 May 7. doi: 10.1007/s00439-021-02287-y. PMID: 33963445.

https://link.springer.com/article/10.1007%2Fs00439-021-02287-y



Screening for mutations performed in Chinese men with non-obstructive azoospermia (NOA) and meiotic arrest identified a homozygous frameshift mutation (c.231_232del) in ZSWIM7, which causes decreased meiotic recombination, spermatogenesis arrest, and infertility. Mice with a corresponding Zswim7 mutation displayed a similar phenotype.

Li Y, Wu Y, Zhou J, Zhang H, Zhang Y, Ma H, Jiang X, Shi Q. A recurrent ZSWIM7 mutation causes male infertility resulting from decreased meiotic recombination.
Human Reproduction, 2021; 36: (5), 1436–1445. doi: 10.1093/humrep/deab046. PMID: 33713115.

https://doi.org/10.1093/humrep/deab046

medRxiv THE PREPRINT SERVER FOR HEALTH SCIENCES BMJ Yale

The International Male Infertility Genomics Consortium (IMIGC) has performed a systematic review (PRISMA) and an updated clinical validity assessment for a total of 657 male infertility or abnormal genitourinary development gene-

disease relationships. They identified 120 genes that were moderately, strongly or definitively linked to 104 infertility phenotypes. These results may help to design relevant ‘gene panels’ and improve genetic testing in male infertility research and diagnostics.

ouston BJ, Riera-Escamilla A, Wyrwoll MJ, Salas-Huetos A, Xavier MJ, Nagirnaja L, Friedrich C, Conrad DF, Aston KI, Krausz C, Tüttelmann F, O’Bryan MK, Veltman JA, Oud MS. A systematic review of the validated monogenic causes of human male infertility: 2020 update and a discussion of emerging gene-disease relationships Running title: Validated genetic causes of human male infertility
medRxiv PREPRINT 2021

https://doi.org/10.1101/2021.05.01.21256465

De novo mutations (DNMs) in sperm are more frequent in ageing men. Some DNMs associated with congenital disorders are considered ‘selfish mutations’ because they can cause expansion of the male germline. Using ultra-deep duplex sequencing, the authors examined the *FGFR3* in sperm DNA, and found highly mutable sites at a higher frequency in older donors.

R Salazar, B Arbeithuber, M Ivankovic, M Heinzl, Moura S, Hartl I, Mair T, Heissl A, Ebner T, Shebl O, Pröll J, Tiemann-Boege. Discovery of an unusual high number of de novo mutations in sperm of older men using duplex sequencing.
bioRxiv PREPRINT, 2021

https://doi.org/10.1101/2021.04.26.441422

Translational and basic andrology

A novel pathway regulating male reproductive function discovered! The authors of this ground-breaking translational study demonstrated that the NF-kB ligand (RANKL)/RANK/OPG signalling system, a known regulator of bone resorption, is also active in mouse and human testis, epidymis and reproductive tract. Mice with genetic suppression of Rankl have increased male fertility and sperm counts. Infertile men have higher soluble-RANKL levels in seminal fluid than normal men. In the infertile men, Denosumab (RANKL-inhibitor used for treatment of osteoporosis) increased serum Inhibin-B and AMH levels, opening a possibility of a novel therapy for some forms of male infertility.

Blomberg Jensen M, Andreassen CH, Jørgensen A, Nielsen JE, Juel Mortensen L, Boisen IM, Schwarz P, Toppari J, Baron R, Lanske B, Juul A. RANKL regulates male reproductive function.
Nature Communications 2021; 12(1):2450. doi: 10.1038/s41467-021-22734-8. PMID: 33893301.

https://doi.org/10.1038/s41467-021-22734-8



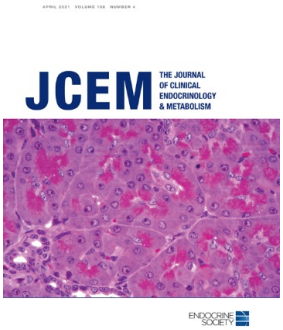
Cancer/Testis (CT) genes are induced in germ cells, repressed in somatic cells and de-repressed in somatic tumors. Using a GeneChip-based RNA profiling analysis, database mining and cancer tissue microarrays for validation at the protein level, the authors identified novel CT genes that may be of clinical interest as therapeutical targets or biomarkers.

Jamin SP, Hikmet F, Mathieu R, Jégou B, Lindskog C, Chalmel F, Primig M. Combined RNA/tissue profiling identifies novel Cancer/Testis genes.
Molecular Oncology. 2021, in press. doi: 10.1002/1878-0261.12900. PMID: 33426787.

https://febs.onlinelibrary.wiley.com/doi/10.1002/1878-0261.12900

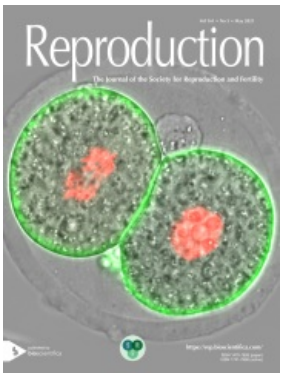
This study investigated the role of the calcium-sensing receptor (CaSR) in human spermatozoa and reported that CaSR is important for the sensing of Ca2+, Mg2+, and HCO3- in spermatozoa, and loss-of-function may impair male sperm function.

Boisen IM, Rehfeld A, Mos I, Poulsen NN, Nielsen JE,



Schwarz P, Rejnmark L, Dissing S, Bach-Mortensen P, Juul A, Bräuner-Osborne H, Lanske B, Blomberg Jensen M. The Calcium-Sensing Receptor Is Essential for Calcium and Bicarbonate Sensitivity in Human Spermatozoa.
J Clin Endocrinol Metab. 2021; 106(4):e1775-e1792. PMID: 33340048.

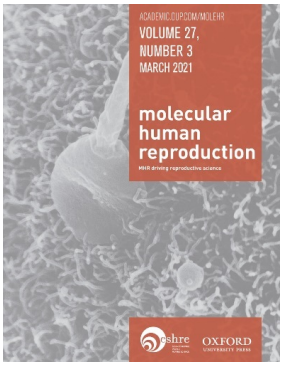
https://academic.oup.com/jcem/article-abstract/106/4/e1775/6041880?redirectedFrom=fulltext



Finasteride (commonly used to treat hair loss) has a structure similar to progesterone. This study showed that finasteride did not interfere with progesterone-induced Ca2+ signalling but may affect Ca2+ signalling in human sperm through an interaction with the PGE1-binding site.

Birch MR, Dissing S, Skakkebæk NE, Rehfeld A. Finasteride interferes with prostaglandin-induced CatSper signalling in human sperm.
Reproduction. 2021; 161(5):561-572. doi: 10.1530/REP-20-0287. PMID: 33729179.

Finasteride interferes with prostaglandin-induced CatSper signalling in human sperm in: Reproduction Volume 161 Issue 5 (2021) (bioscientifica.com)



This study evaluated the levels of seminal tRNA-derived fragments (tRFs), a novel class of regulatory small RNAs, and found that levels of 5'tRF-Glu-CTC, 5'tRF-Lys-CTT, and 5'tRF-Gly-GCC were significantly elevated in semen samples from cases with repeatedly failed ICSI cycles. This group of men had also lower seminal testosterone, and higher levels of sperm DNA fragmentation.

Grosso JB, Zoff L, Calvo KL, Maraval MB, Perez M, Carbonaro M, Brignardello C, Morente C, Spinelli SV. Levels of seminal tRNA-derived fragments from normozoospermic men correlate with the success rate of ART.
Mol Hum Reprod. 2021;27(4):gaab017. doi: 10.1093/molehr/gaab017. PMID: 33693947.

https://doi.org/10.1093/molehr/gaab017

COVID-19

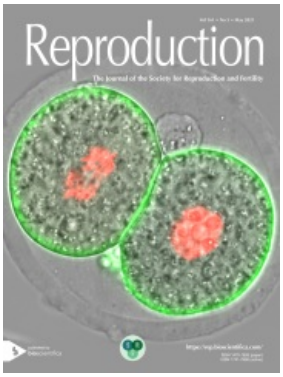


If you donated your DNA sample to '23 & Me' and filled a questionnaire, you might be among participants in this genome-wide association study, based on >15,000 reports of positive SARS-CoV-2 test, including 1,131 hospitalizations. A strong association between blood type and COVID-19 diagnosis was confirmed *(you are lucky if you are 0)* as well as between the outcome severity and a gene-rich locus on chr 3p21.31, more pronounced in male sex. Candidate genes include: SLC6A20 (forming a complex with ACE2), LZFTL1 (implicated in ciliogenesis), CXCR6 and CCR9 (involved in immune response).

Shelton, J.F., Shastri, A.J., Ye, C. et al. Trans-ancestry analysis reveals genetic and nongenetic associations with COVID-19 susceptibility and severity.
Nature Genetics (Apr 2021).

https://doi.org/10.1038/s41588-021-00854-7

In this prospective longitudinal study, increased seminal ACE2 activity, rise in markers of inflammation and oxidative stress, and significant



impairment in semen quality parameters, were found in male patients with COVID-19. These changes persisted over time, hence, the reproductive function of the patients recovering from COVID-19 should be followed.

Hajizadeh Maleki B, Tartibian B. COVID-19 and male reproductive function: a prospective, longitudinal cohort study.
Reproduction. 2021;161(3):319-331. doi: 10.1530/REP-20-0382. PMID: 33522983.

https://doi.org/10.1530/REP-20-0382

Reproduction and general health



Testosterone is a critical determinant of health in both genders. This study based on the data from UK Biobank examined the associations of serum testosterone (total and free) with mortality in >150.000 men and >90.000 postmenopausal women. They found that high levels of circulating testosterone may be beneficial for all-cause and cancer mortality in men but detrimental in postmenopausal women.

Wang J, Fan X, Yang M, Song M, Wang K, Giovannucci E, Ma H, Jin G, Hu Z, Shen H, Hang D. Sex-specific associations of circulating testosterone levels with all-cause and cause-specific mortality.
Eur J Endocrinol. 2021; 184(5):723-732. doi: 10.1530/EJE-20-1253. PMID: 33690154.

https://eje.bioscientifica.com/view/journals/eje/184/5/EJE-20-1253.xml

human reproduction

This Danish prospective cohort study found a positive association between fecundity, measured as self-reported time to first pregnancy (TTP), and increased mortality among women and higher hospitalization rates for both women and men.

L J Ahrenfeldt, S Möller, M J Wensink, M L Eisenberg, K Christensen, T K Jensen, R Lindahl-Jacobsen. Impaired fecundity as a marker of health and survival: a Danish twin cohort study.
Human Reproduction, deab077

https://doi.org/10.1093/humrep/deab077

frontiers in Endocrinology

Eat more vegetables and less fries! This study found a link between consumption of healthy or unhealthy ("fast") foods and methylation at imprint regulatory regions in DNA of sperm. If carried into the next generation paternal unhealthy dietary patterns may result in adverse metabolic conditions in offspring.

Soubry A, Murphy SK, Vansant G, He Y, Price TM, Hoyo C. Opposing Epigenetic Signatures in Human Sperm by Intake of Fast Food Versus Healthy Food.
Frontiers in Endocrinology (Lausanne). 2021; 12:625204. doi: 10.3389/fendo.2021.625204. PMID: 33967953.

https://doi.org/10.3389/fendo.2021.625204

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