

EUROPEAN ACADEMY OF ANDROLOGY

Dear EAA Members,

Happy New Year! First, a short info for our new members. These literature digests are a compiled to alert you about the latest noteworthy articles in all aspects of andrology. Original studies from established andrology centres, incl. EAA training Centres, and leading groups in reproductive biology are prioritised. Preprints and review articles are usually not included, unless ground-breaking, meta-analyses or especially valuable for clinical education. You are welcome to share the alerts with your students, and if you have a good publication to promote – send a note to the EAA Secretary.

In this edition – lots of excellent work for your attention! Keywords: diabetes complications, sperm DNA fragmentation, amyloidosis and osteoporosis, testicular torsion, hypospadias, testosterone and cancer risk, complete sequence of the Y chromosome, mouse KO phenocopies of OA and OAT, a new contraception candidate (SLO3), telomere length in ART children, Sertoli cell valve in rete testis, CX3CR1 and epididymitis, and lots of epigenetics!

Clinical andrology and epidemiology



A new special thematic issue “Andrological Aspects of Diabetes” has been published in Andrology! This issue, edited by EAA Academicians Giulia Rastrelli and Daniele Santi, comprises 18 articles and provides a comprehensive overview of the management of diabetes mellitus complications, incl. testosterone treatment, erectile dysfunction, obesity, sperm quality, and more.

Andrological Aspects of Diabetes: ***Andrology***, February 2023, Volume 11 (2), pp: 197-416
https://onlinelibrary.wiley.com/toc/20472927/2023/11/2

Biological Research BMC

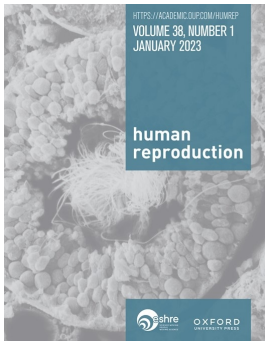
This study explored the effect of single- and double-stranded sperm DNA fragmentation (SDF) on impaired ICSI outcomes in double gamete donation cycles, and in sperm donation only.
Higher SDF had a detrimental impact on fertilization rates after ICSI, and delayed embryo development.

Ribas-Maynou J, Novo S, Torres M, Salas-Huetos A, Rovira S, Antich M, Yeste M. Sperm DNA integrity does play a crucial role for embryo development after ICSI, notably when good-quality oocytes from young donors are used. ***Biol Res***. 2022 Dec 26;55(1):41.
https://doi.org/10.1186/s40659-022-00409-y

Reproductive Biology and Endocrinology BMC

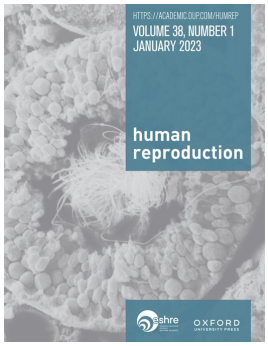
A meta-analytic study from the EAA centre in Budapest, evaluated 190 published studies of risk factors for increased sperm DNA fragmentation (SDF).
Varicocele, impaired glucose tolerance, testicular tumors, smoking, environmental pollution and age over 50 were associated with the highest SDF.

Szabó A, Váncsa S, Hegyi P, Váradi A, Forintos A, Filipov T, Ács J, Ács N, Szarvas T, Nyirády P, Kopa Z. Lifestyle-, environmental-, and additional health factors associated with an increased sperm DNA fragmentation: a systematic review and meta-analysis. ***Reprod Biol Endocrinol.*** 2023 Jan 18;21(1):5.
https://doi.org/10.1186/s12958-023-01054-0



In this population-based large cohort study, later maternal age at menarche was associated with impaired semen characteristics, lower testes volume and altered levels of reproductive hormones, while earlier maternal age at menarche was not strongly associated with reproductive outcomes in sons. The findings suggest some shared heritability of reproductive health or unknown shared environmental exposure.

Langergaard MJ, Ernst A, Brix N, Gaml-Sørensen A, Tøttenborg SS, Bonde JPE, Toft G, Hougaard KS, Ramlau-Hansen CH. Maternal age at menarche and reproductive health in young adult men: a cohort study. ***Hum Reprod.*** 2023 Jan 5;38(1):125-138.
https://doi.org/10.1093/humrep/deac231



Another population-based study found no differences in semen parameters in young men who had testicular torsion compared to controls. Men with prior torsion treated with unilateral orchiectomy had higher FSH and lower inhibin B levels than controls, while those treated with orchiopexy, had subtle alterations without clinical relevance.

Hansen AH, Priskorn L, Hansen LS, Carlsen E, Joensen UN, Jacobsen FM, Jensen CFS, Jørgensen N. Testicular torsion and subsequent testicular function in young men from the general population. ***Hum Reprod.*** 2023 Jan 4:deac271. Epub ahead of print.
https://doi.org/10.1093/humrep/deac271



A case-control study of Danish and Finnish mother-son pairs correlated the exposure to 6 classes of persistent organic pollutants (POP) in breast milk samples with the presence of hypospadias in the sons. Differences in quantitative exposures were detected by the composite score did not provide evidence for an association between hypospadias and exposure to POPs.

Tysman M, Toppari J, Main KM, Adamsson A, Wohlfahrt-Veje C, Antignac JP, Le Bizec B, Löyttyniemi E, Skakkebæk NE, Virtanen HE. Levels of persistent organic pollutants in breast milk samples representing Finnish and Danish boys with and without hypospadias. ***Chemosphere***. 2023 Feb;313:137343.
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Men with hypogonadism caused by a rare form of amyloidosis (Apo A-I Leu75Pro) under long-term testosterone therapy have a high burden of osteopenia-osteoporosis, especially the older patients with multi-organ disease.

Facondo P, Delbarba A, Pezzaioli LC, Ferlin A, Cappelli C. Osteoporosis in men with hypogonadism because of ApoA-I Leu75Pro amyloidosis under long-term testosterone therapy. ***Andrology***. 2023 Jan 9. Epub ahead of print.
10.1111/andr.13376



The authors examined associations between two forms of testosterone therapy (TT) and risks of 7 cancers among men, using SEER cancer registry and Medicare claims. TT was inversely associated with distant-stage prostate and colorectal cancers but was positively associated with distant-stage melanoma.

Butler EN, Zhou CK, Curry M, McMenamin Ú, Cardwell C, Bradley MC, Graubard BI, Cook MB. Testosterone therapy and cancer risks among men in the SEER-Medicare linked database. ***Br J Cancer.*** 2023 Jan;128(1):48-56.

Androgenetics

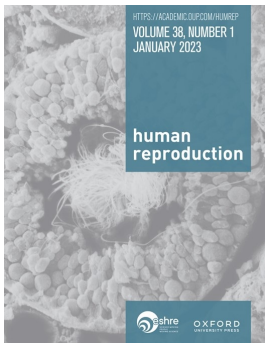
bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

A remarkable preprint, of immediate use for andro-geneticists. Because of its complex repeat structure, the human Y chromosome has been difficult to sequence.

The Telomere-to-Telomere (T2T) consortium presents the complete

sequence that adds >30 million bp and corrects errors in GRCh38-Y reference. The sequence revealed the complete ampliconic structures of *TSPY, DAZ, RBMY* and other protein-coding genes.

Rhie A, Nurk S, Cechova M, et al et Phillippy AM. The complete sequence of a human Y chromosome. ***bioRxiv*** (preprint), submitted December 2022.
https://doi.org/10.1101/2022.12.01.518724



This study identified by whole-exome sequencing a novel pathogenetic gene: IQUB possibly responsible for male infertility characterized by asthenospermia, involving sperm radial spoke defects.

Zhang Z, Zhou H, et al et Bao S. IQUB deficiency causes male infertility by affecting the activity of p-ERK1/2/RSPH3. ***Hum Reprod***. 2023 Jan 5;38(1):168-179. https://doi.org/10.1093/humrep/deac244

SCIENTIFIC REPORTS

This study from the EAA Centre in Estonia analysed the genome-wide CNV profile in 215 men with idiopathic spermatogenic failure (SBGF). A two-fold higher representation of >1 Mb CNVs was observed in men with SPGF compared to controls, 7 patients were carriers of microdeletions or microduplications linked to severe congenital conditions.

Kikas T, Punab AM, Kasak L, Poolamets O, Vihljajev V, Pomm K, Reiman M, Tjagur S, Korrovits P, Punab M, Laan M. Microdeletions and microduplications linked to severe congenital disorders in infertile men. ***Sci Rep***. 2023 Jan 11;13(1):574.
https://www.nature.com/articles/s41598-023-27750-w

International Journal of *Molecular Sciences*

The authors attempted to associate gene polymorphisms with phenotypes in 100 men with different states of fertility.

GWAS identified 12 non-synonymous SNPs, localized to 9 genes, previously linked to male fertility: *ANAPC1, CES1, FAM131C, HLA-DRB1, KMT2C, NOMO1, SAA1, SRGAP2*, and *SUSD2*, some linked to each other functionally.

Greither T, Behre HM, Herlyn H. Genome-Wide Association Screening Determines Peripheral Players in Male Fertility Maintenance. ***Int J Mol Sci***. 2022 Dec 28;24(1):524.
https://doi.org/10.3390/ijms24010524

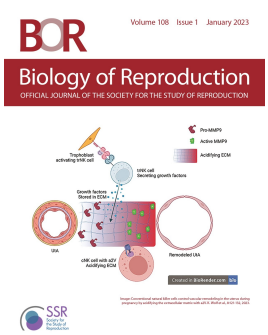


This excellent study examined the role of the adhesion receptor ADGRA3 (GPR125), a known spermatogonial marker, in a KO mouse model (Adgra3$^{-/-}$). Most of the males were infertile despite normal spermatogenesis, but had transient dilation of the epididymis, with a blockage between the ejaculatory duct and the urethra mimicking the obstructive azoospermia found in humans.

Nybo ML, Kvam JM, Nielsen JE, Frederiksen H, Spiess K, Jensen KHR, Gadgaard S, Walser ALS, Thomsen JS, Cowin P, Juul A, Jensen MB, Rosenkilde MM. Loss of Adgra3 causes obstructive azoospermia with high penetrance in male mice. FASEB J. 2023 Feb;37(2):e22781.
https://doi.org/10.1096/fj.202200762rr

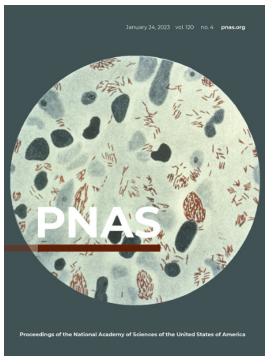
This study found that actin-like 7b (ACTL7B), an orphan testis-specific actin-related protein, is expressed in human and mouse spermatids. Male Actl7b KO mice were infertile, with severe oligoteratozoospermia (OAT) and abnormalities of the flagellum (MMAF) and sperm head. These defects phenocopy human OAT and MMAF, leading causes of idiopathic male infertility.

Clement TM, Geyer CB, Willis WD, Goulding EH, Upadhyay S, Eddy EM. Actin-related protein ACTL7B ablation leads to OAT with multiple morphological abnormalities of the flagellum and male infertility in mice.



Biol Reprod. 2023 Jan 6:ioad001. Epub ahead of print.
https://doi.org/10.1093/biolre/ioad001

Translational and basic studies



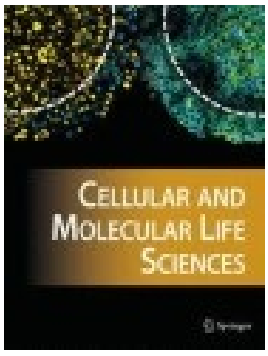
In this work, the first selective SLO3 inhibitor was identified. It caused a complete block of endogenous K^+ currents in human sperm, preventing sperm from hyperpolarizing and acrosome reaction. SLO3 is a good candidate for contraceptive development, and mutation of this gene could be a possible cause of idiopathic male infertility.

Lyon M, Li P, Ferreira JJ, Lazarenko RM, Kharade SV, Kramer M, McClenahan SJ, Days E, Bauer JA, Spitznagel BD, Weaver CD, Borrego Alvarez A, Puga Molina LC, Lybaert P, Khambekar S, Liu A, Lindsley CW, Denton J, Santi CM. A selective inhibitor of the sperm-specific potassium channel SLO3 impairs human sperm function. ***Proc Natl Acad Sci USA***. 2023 Jan 24;120(4):e2212338120.
https://doi.org/10.1073/pnas.2212338120

nature COMMUNICATIONS

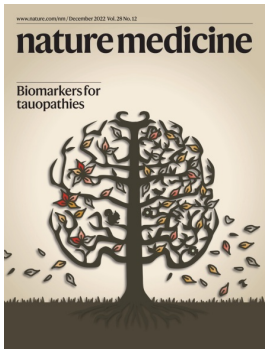
This excellent study from Japan identified the expression of Sox17 in rete testis (RT) epithelium and created conditional KO (Sox17-cKO) male mice.
They found disruption of the Sertoli cell valve, inducing a backflow of RT fluid into the seminiferous tubules, which caused detachment of immature spermatids, despite proper function of Sertoli cells.

Uchida A, Imaimatsu K, Suzuki H, et al et Kanai Y. SOX17-positive rete testis epithelium is required for Sertoli valve formation and normal spermiogenesis in the male mouse. ***Nature Commun***. 2022 Dec 21;13(1):7860.



This study examined the effect of a functional lack of CX3CR1 in KO mice on immune responses during epididymitis. The authors provided evidence that mononuclear phagocytes are gatekeepers of the immunological blood-epididymis barrier and revealed the role of the CX3CR1 receptor in regulating the monocyte population in epididymal mucosa.

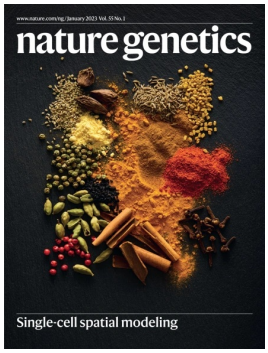
Barrachina F, Ottino K, Tu LJ, Soberman RJ, Brown D, Breton S, Battistone MA. CX3CR1 deficiency leads to impairment of immune surveillance in the epididymis. ***Cell Mol Life Sci***. 2022 Dec 23;80(1):15. doi: 10.1007/s00018-022-04664-w. PMID: 36550225.
https://doi.org/10.1007/s00018-022-04664-w



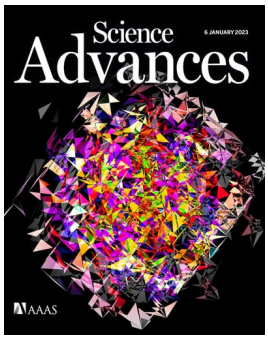
The leukocyte telomere length (LTL), an indicator of age-related phenotypes, was estimated in 1,137 individuals. Children conceived by ART had shorter LTLs than those conceived spontaneously. Blastocyst-stage embryo transfer resulted in shorter telomere lengths in a mice model. The findings demonstrate the need to evaluate the long-term consequences of ART, particularly for aging-related phenotypes.

Wang C, Gu Y, et al et Shen H, Hu Z. Leukocyte telomere length in children born following blastocyst-stage embryo transfer. ***Nature Medicine*** 2022 Dec;28(12):2646-2653.
https://doi.org/10.1038/s41591-022-02108-3

Two important studies exploring DNA methylation reprogramming during early embryonic and germ cell development. The first study characterised DNA 5-



hydroxymethylcytosine (5hmC) in mouse early embryos. DNA hydroxymethylation strongly correlated with DNA demethylation but 5hmC was targeted to particular *de novo* methylated sites in post-implantation epiblasts. Mouse zygotes with maternal deficiency of Nlrp14 had impaired 5hmC deposition, revealing the divergence between genome-wide 5mC maintenance and Tet-mediated oxidation.



The second study characterised the epigenome of hypomethylated human primordial germ cells (hPGCs) and revealed mechanisms preventing the widespread derepression of genes and transposable elements (TEs). The study found that hPGCs exhibit a neutral or paused epigenetic state without transcriptional activation. Transcriptional repression in hPGCs presents a balanced system relying on local maintenance of heterochromatic features and a lack of inductive cues.

Yan R, Cheng X, Gu C, Xu Y, Long X, Zhai J, Sun F, Qian J, Du Y, Wang H, Guo F. Dynamics of DNA hydroxymethylation and methylation during mouse embryonic and germline development. Nature Genet. 2023 Jan;55(1):130-143.
https://doi.org/10.1038/s41588-022-01258-x
Gruhn WH, Tang WWC, Dietmann S, Alves-Lopes JP, Penfold CA, Wong FCK, Ramakrishna NB, Surani MA. Epigenetic resetting in the human germ line entails histone modification remodeling. Science Adv. 2023 Jan 18;9(3):eade1257. doi: 10.1126/sciadv.ade1257. Epub 2023 Jan 18. PMID: 36652508.
https://doi.org/10.1126/sciadv.ade1257



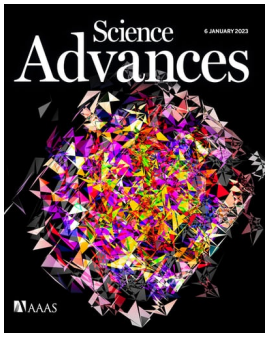
SCIENTIFIC REPORTS

Three epigenetic studies relevant for testicular dysgenesis syndrome (TDS). In the first study, infertile men with shortened anogenital distance had increased presence of estrogen response elements in the hypomethylated regulatory sequences in fractions of sperm DNA. The second study showed distinct sperm DNA methylation signatures present pre- and post-treatment in men with Hodgkin disease and testicular cancer. Abnormalities in the sperm epigenome may contribute to birth defects in the offspring. The third study investigated hypospadias. Large numbers of differential DNA methylation regions (DMRs), observed in the foreskin in mild hypospadias, were reduced in moderate and very low in severe hypospadias. The DMR were found in novel hypospadias associated genes and pathways.

Stenz L, Beyens M, Gill ME, Paoloni-Giacobino A, De Geyter C. Altered DNA methylation in estrogen-responsive repetitive sequences of spermatozoa of infertile men with shortened anogenital distance. ***Clin Epigenetics***. 2022 Dec 26;14(1):185.
https://doi.org/10.1186/s13148-022-01409-1
Chan D, Oros Klein K, Riera-Escamilla A, Krausz C, O'Flaherty C, Chan P, Robaire B, Trasler JM. Sperm DNA methylome abnormalities occur both pre- and post-treatment in men with Hodgkin disease and testicular cancer. ***Clin Epigenetics.*** 2023 Jan 7;15(1):5.
https://doi.org/10.1186/s13148-022-01417-1
Kaefer M, Rink R, Misseri R, Winchester P, Proctor C, Ben Maamar M, Beck D, Nilsson E, Skinner MK. Role of epigenetics in the etiology of hypospadias through penile foreskin DNA methylation alterations. ***Sci Rep***. 2023 Jan 11;13(1):555.
https://doi.org/10.1038/s41598-023-27763-5

Methodology

The absence of an appropriate, accessible in vitro system is a major obstacle in understanding mechanisms of sex-determination and its disorders (DSD). This article describes protocols for differentiation of mouse and human pluripotent cells toward gonadal progenitors. Sertoli-like cells derived from 46,XY human induced pluripotent stem cells (hiPSCs) exhibited sustained expression of testis-specific genes, secreted anti-



Müllerian hormone, migrated, and formed tubular structures.

Gonen N, Eozenou C, Mitter R, Elzaiat M, Stévant I, Aviram R, Bernardo AS, Chervova A, Wankanit S, Frachon E, Commère PH, Brailly-Tabard S, Valon L, Barrio Cano L, Levayer R, Mazen I, Gobaa S, Smith JC, McElreavey K, Lovell-Badge R, Bashamboo A. In vitro cellular reprogramming to model gonad development and its disorders. ***Science Adv.*** 2023 Jan 4;9(1):eabn9793.
https://doi.org/10.1126/sciadv.abn9793

European Academy of Andrology
Office: Szent István Krt. 7., 1055, Budapest, Hungary

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