ABSTRACTS COLLECTION

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Presenting author names **are bold** in the contributor lists.

e-Posters

EP01 Reproductive Genetics

EP01.001 Correlations between cytogenetic findings and spermatogenic failure in Bulgarian infertile men

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Background/Objectives: Chromosomal aberrations have a great impact on spermatogenesis, semen quality, and successful conception. The objective of our study was to determine the type and frequency of chromosomal aberrations and polymorphisms in men with different degrees of spermatogenic failure in comparison to men with normozoospermia, in order to find some correlations between cytogenetic findings and the abnormal results of semen analysis.

Methods: In our study, we have performed cytogenetic analysis in 901 infertile men, divided into 5 groups according to semen analysis—normozoospermia, asthenozoospermia, oligoasthenozoospermia, severe male factor and azoospermia.

Results: The frequency of polymorphisms was similar in all groups (11–16%, without significant differences). The frequency of numerical and structural aberrations increases with the degree of the spermatogenic failure (3.5% in normozoospermia, 5.6% in asthenozoospermia, 9.8% in oligoasthenozoospermia, 9% in severe male factor and 13.5% in azoospermia). We have found significantly higher incidence of numerical chromosome aberrations in severe male factor (7%) and azoospermia (9.3%). Oligoasthenozoospermia was associated with chromosomal translocations, as it occurs in 45% of cases with translocation, compared to 20% in the group with normal karyotype.

Conclusion: We revealed that chromosomal translocations are significantly associated with oligoasthenozoospermia, whereas numerical chromosomal aberrations—with severe male factor and azoospermia. These are important aspects of genetic counseling for those cytogenetic findings. Chromosome polymorphisms don't seem to disturb significantly spermatogenesis and their impact should be studied in regard to unsuccessful pregnancy achievement, even in patients with normozoospermia.

References:

Grants:

Conflict of Interest: None declared.

EP01.002 Comparison of carrier status among patients with or without family history of disease using targeted and expanded panels

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EP18.012 MIXER: a Machine-learning method to detect genomic Imbalances exploiting X chromosome exome reads

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Background/Objectives: Whole Exome Sequencing (WES) is rapidly becoming a first-tier test, thanks to declining costs and automatic clinical pipelines. However, while identification of small variants follows standardized workflows, there is no agreement on methods for detection of Copy Number Variants (CNVs). A plethora of WES-based CNV callers have been developed, each showing good performance towards only a limited range of CNV classes/sizes. As clinical CNVs extend from large rearrangements to single genes, more versatile approaches are needed to be of enhanced diagnostic use.

Methods: MIXER is a machine learning method exploiting the naturally occurring presence of one or two copies of the non-pseudoautosomal X-chromosome WES regions in male and female samples, respectively, to simulate deletion/duplication states.

Results: Compared to popular tools (GATK4 gCNV, ExomeDepth, DECoN, CNVkit, EXCAVATOR2), MIXER showed higher stability, identifying in NA12878 WES sample both synthetic deletions and duplications (0.87 and 0.82 F1-score, respectively) encompassing from 2 to >50 target regions. Evaluated on a collection of WES data ($n = 251$) sequenced by the Epi25 collaborative, MIXER correctly discovered all clinical exonic CNVs previously identified by SNP-arrays.

Conclusion: CNVs are an important source of clinical variation. Providing the WES diagnostic setting with robust and flexible methods is essential, but current tools have biases that prevent their ready use in clinical practice. MIXER, introducing an original machine-learning solution, establishes itself as a way to reduce this gap towards higher accuracy and wider applicability.

References:

Grants: This study partly uses WES and SNP-array data generated by Epi25 Collaborative, https://epi-25.org.

Conflict of Interest: None declared.

EP18.013 Evaluation of TCRγ generation probability using Bayesian statistics

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Background/Objectives: T cell receptors (TCRs) have an essential role in adaptive immunity against tumor cells and viral infections. They are formed during V(D)J recombination, which includes a selection of the genomically encoded segments (V, D, and J for α/γ chains; or V and J for β/δ), their trimming and insertions of random nucleotides on the junctions. Previously, Murugan's group described this process with Bayesian methods and suggested the models to estimate the probability of recombination event distribution for TCRβ and TCRα [1]. In this study, we present the first computational model for TCRγ with proven robustness and reliability.

Methods: As a DNA source, we used PMBC samples obtained from healthy donors and enriched with TCRγ sequences using multiplex PCR. Raw NGS data was processed with MiXCR toolkit to extract TCR repertoires. To obtain rearrangement models we used IGoR.

Results: We assumed on frequencies of observed and expected V-J combinations for DNA- and RNA-based repertoires, that V and J usage are cross-dependent. Basing on Kullback–Leibler divergence between two rearrangement models we evaluated the minimal number of clonotypes necessary to calculate model parameters. The generated TCRγ dataset had similar probability distribution to the real one obtained from healthy individuals.

Conclusion: Our model is able to estimate TCRγ generation probability with a high accuracy.

References: [1] Murugan, A., Mora, T., Walczak, A. M., & Callan, C.G. (2012). Statistical inference of the generation probability of T-cell receptors from sequence repertoires. Proceedings of the National Academy of Sciences, 109(40), 16161-16166.

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Conflict of Interest: None declared.

EP18.014 GeneTree: an innovative solution to build simultaneously a pedigree, downloadable in BOADICEA and CanRisk files, and the clinical history of a family

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Background/Objectives: To date, no free solution allows the generation of a family pedigree that can be quickly modified and exported with the corresponding text.

Methods: I build a web application host by GitHub servers.

Results: This application is an integrated tool to help doctors and genetic counsellors in their genetic counselling. The application is available without priori installation in French and English: https://jimouse.github.io/GeneTree/.

It has a specific mode for oncogenetic consultation and a mode using HPO phenotypes. The family can be loaded (JSON or BOADICEA files) or created from a standard or custom structure, then completed via a table or a graphical interface, both interconnected.

The pedigree can be exported in several file formats and modified by a vector editor (PDF, SVG) or can be printed directly.

Finally, this application allows the automatic generation of text based on the content of the table.

Moreover, a second interface, specifically designed for patients, allow them to fill their familial information prior to the consultation.

Conclusion: This tool is extremely time-saver and has been particularly optimised for oncogenetic consultations to avoid triple entry (text-tree-boadicea risk score). This is the first application allowing text-generation based on a pedigree.

References: CanRisk Tool—A Web Interface for the Prediction of Breast and Ovarian Cancer Risk and the Likelihood of Carrying