PATERNAL AGE AND REPRODUCTIVE RISK

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INTRODUCTION AND OBJECTIVES

A delay in fatherhood has been observed in recent years.

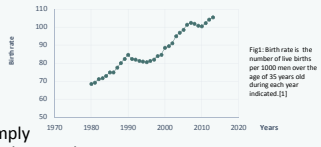

Fig1: Birth rate is the number of live births per 1000 men over the age of 35 years old during each year indicated.[1]

Lot of research has been done about the effects of maternal age while the risks that an advanced paternal age imply are not so well-studied and known by the population.
However, advanced paternal age has been associated with an increase of miscarriages and birth defects in the offspring (genetic mutations, psychiatric disorders and other diseases).

The paternal age effect is an epidemiological concept which describes the fact that the offspring of older men more frequently suffer from some spontaneous disorders.

OBJECTIVE → A review of the paternal age effect, in particular all the molecular mechanisms that could explain a link between advanced paternal age and a risk for the offspring.

Methodology: Bibliographic research using Pubmed and key words like "paternal age", "reproductive risk", "father age", "advanced"... Papers were selected according to data of publication, journal and relevancy. References cited in some of those papers were also included in the selection.

MUTAGENESIS AND FATHER AGE

Germline mutation rate in human males, especially older men, is generally much higher than in females. Why?

↑ Age →
- ↑ Cell divisions and chromosome replications spermatozoa have suffered
- Reduced fidelity of DNA replication and inefficiency of DNA repair machinery
- Accumulation of external mutagens
- ↓ Antioxidants
- ↓ Environmental quality ↓Number of Sertoli and Leyding cells

→ ↑*de novo* mutations in the sperm

Lots of diseases associated with father age are autosomal dominant, produced by *de novo* mutations in the father germline (mainly base substitutions).

Base substitutions: occur primarily in males and are age-dependent.
Small chromosome changes (like intragenic deletions or aneuploidies): not a clear relationship with age.

SELFISH SPERMATOGONIAL SELECTION

Some disorders , called PAE disorders share 3 unusual features:

- Extreme bias in paternal origin of mutations
- Strong paternal age effect
- A high germline mutation rate

→ CAN NOT BE EXPLAINED ONLY BY MUTATION ACCUMULATION IN THE SPERM WITH AGE

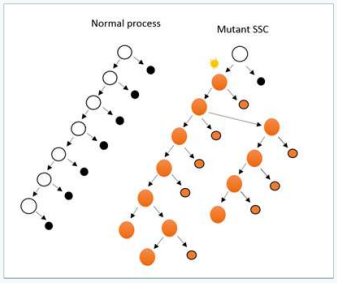

Fig2: Example of selfish spermatogonial selection with symmetrical divisions

Possible explanations:
☒ Hot spot mutations: REJECTED because the mutations are distributed in clusters in the testis.
☑ **Selfish spermatogonial selection:** Some mutations, which occur randomly during mitotic divisions of spermatogonial stem cells confer a selective/growth advantage (for example symmetrical divisions) to the mutant SSC.
Therefore: ↑mutant SSC ↑mutant spermatozoa

PAE genes are related with RAS pathway, dysregulation of which alters growth and proliferative properties of SSC.
However, any mutation that arise in the SSC in any gene controlling homeostatic and cellular properties is a potential target for selfish selection.

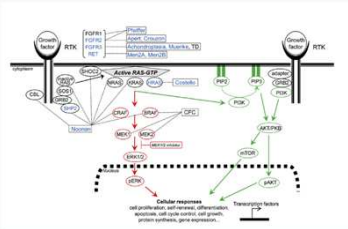

Fig3: Ras-signaling pathway related to PAE disorders [2].

Depending on the advantage conferred by the mutation the selection will be stronger or weaker and depending on the effect in the offspring these mutations will accumulate over generations or not.

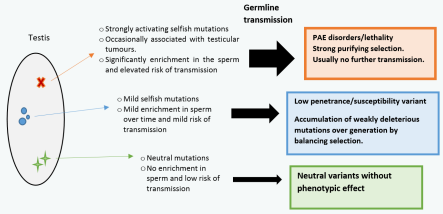

Fig4: Long-term consequences of Selfish Selection in the Testis.

EPIGENETICS

Epigenetics: heritable modifications in gene expression without modification of DNA sequence (DNA methylation, histone modification...).

Neuropsychiatric disorders, some forms of cancers... ↑incidence in offspring of older fathers. Epigenetics likely play a role. Some studies have seen

↑Age ↑ changes in sperm DNA methylation in genes implicated in autism, bipolar disorders and schizophrenia

Why are some regions more susceptible to epigenetic alterations?
- Nucleosome retention associated with hypomethylation
- DNA sequence
- Selfish spermatogonial selection

Modifications have to escape epigenetic reprogramming in order to affect the offspring.

Epigenetic modifications ⟷ Mutations

CONCLUSIONS

Clear relationship between paternal age and
- Miscarriages
- Rare autosomal diseases
- Neuropsychiatric disorders...

"Selfish spermatogonial selection"

Why? Not fully understood

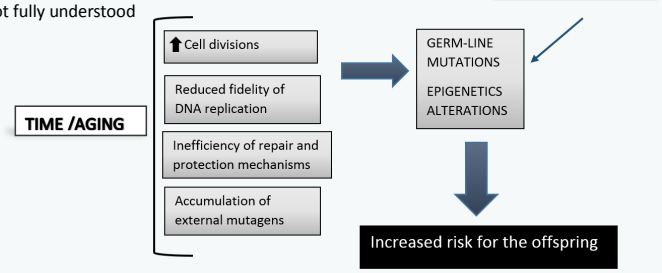

Fig5: Impact of father aging on the offspring

Considerations and implications:

- **Important health issue: immediate effect on the offspring and possible accumulation of mutations over generations.**
- **Necessary do further investigation and advise couples.**
- **Possible prenatal screening targeting PAE diseases.**
- **Absence of an universal definition. What is advanced paternal age?**

References

[1] J. Martin, B. E. Hamilton, S. J. Ventura, M. J. . Osterman, and T. J. Mathews, "Births: Final Data for 2013. National Vital Statistics Reports.," vol. 64, no. 1, 2015.
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