Male reproductive disorders: gene-lifestyle-environment interaction?

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Conflict of interest declaration

- I declare no commercial relationships or other activities that might be perceived as a potential conflict of interest.

Learning objectives

To set focus on following aspects:

1. Indications of environmental and genetic factors influencing male reproductive function;
2. The concept of gene-environment interaction:
    a) In classical understanding;
    b) Specifically in relation to the reproductive function;
3. Examples of gene-environment interaction in relation to male reproductive disorders.

What will be my final conclusions

- Genetic factors can modify the impact of environment on male reproductive function;
- Environmental factors can modify DNA of the germ cells thereby, such changes possibly being transmitted to next generation(s).

Case

- Anna – 31 years and Adam – 33 years: 2 years with unprotected intercourses; no pregnancy;
- Gynecological investigation – no pathology;
- Adam:
  - 2 x oligo-astheno-teratozoospermia;
  - Sperm Chromatin Structure Assay shows a DFI of 35%
  - FSH↑; LH and Testosterone normal;
  - Testicular volume: 12/12 mL;
  - Scrotal palpation otherwise OK;
  - No cryptorchidism; No medication; No other diseases

WHY?

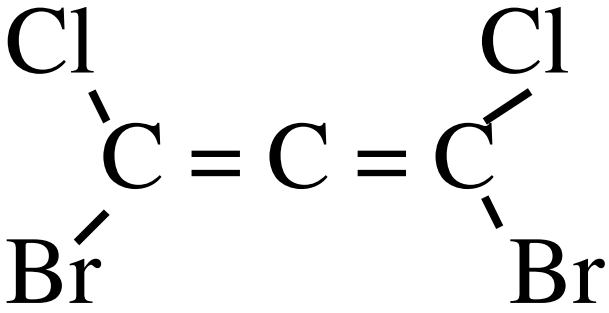
The majority of male reproductive disorders are still unexplained

- Cryptorchidism > 95%
- Testicular cancer > 95%
- Male-related infertility > 65%
- Prostate cancer > 95%

Genetic cause – Klinefelter syndrome

- 47, XXY
- The most common chromosomal abnormality (1:600)
- Serious testicular atrophy, commonly associated with:
  - Azoospermia
  - Hypogonadism

Environmental cause – DBCP exposure



DBCP- anti-fungicide

	DBCP exposed	Non-exposed
azoospermia	13%	3%
oligozoospermia	36%	6%
normozoospermia	51%	91%

Whorton *et al*, Lancet 1977

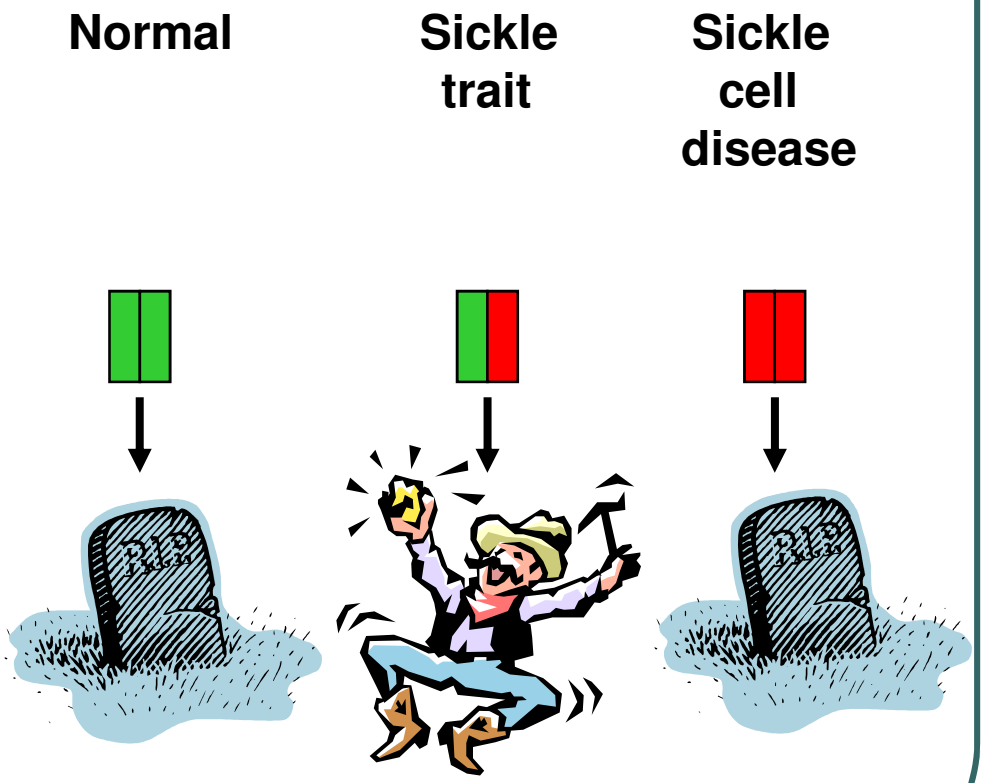
Gene-environment interaction - mechanism behind major diseases

- Cancer
- Asthma
- Diabetes
- Cardio-vascular diseases
- Neuro-degenerative diseases

What is gene-environment interaction – classical view

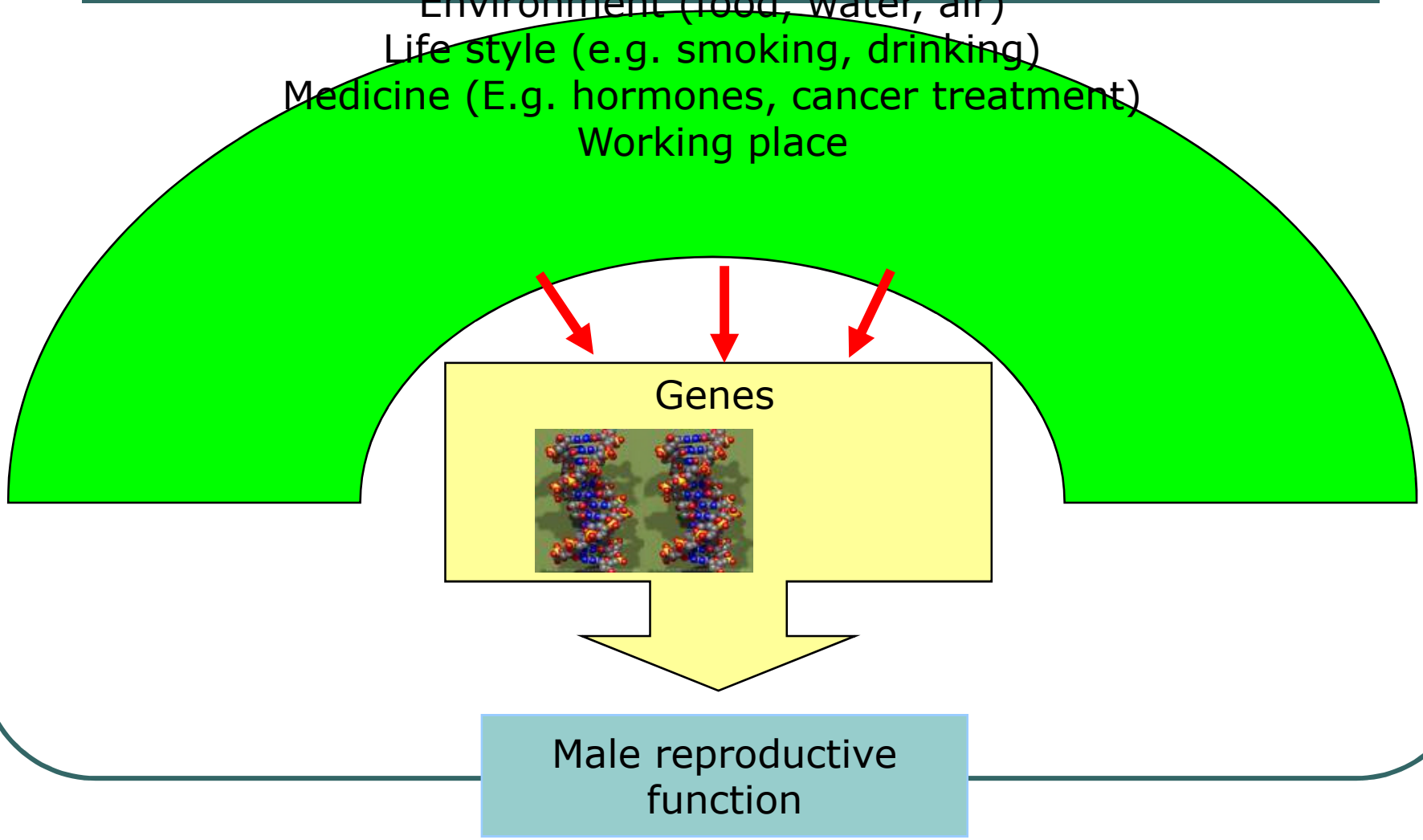
- The effects of ”environment” in determining the occurrence of the diseases are modified by the presence or absence of a gene or genes

Malaria and sickle cell anemia- examples of gene-environment interaction

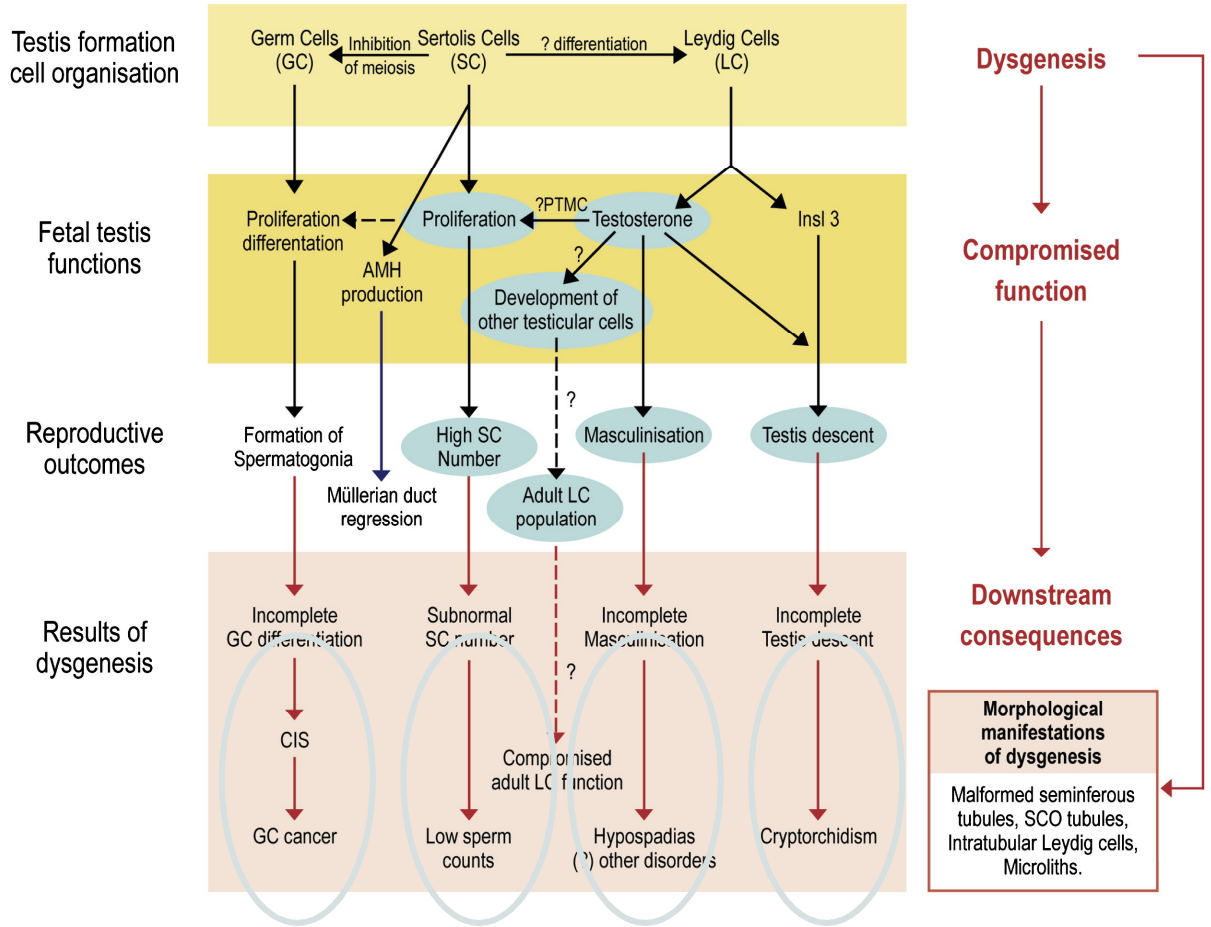


Gene-environment interaction

Environment (food, water, air)
Life style (e.g. smoking, drinking)
Medicine (E.g. hormones, cancer treatment)
Working place

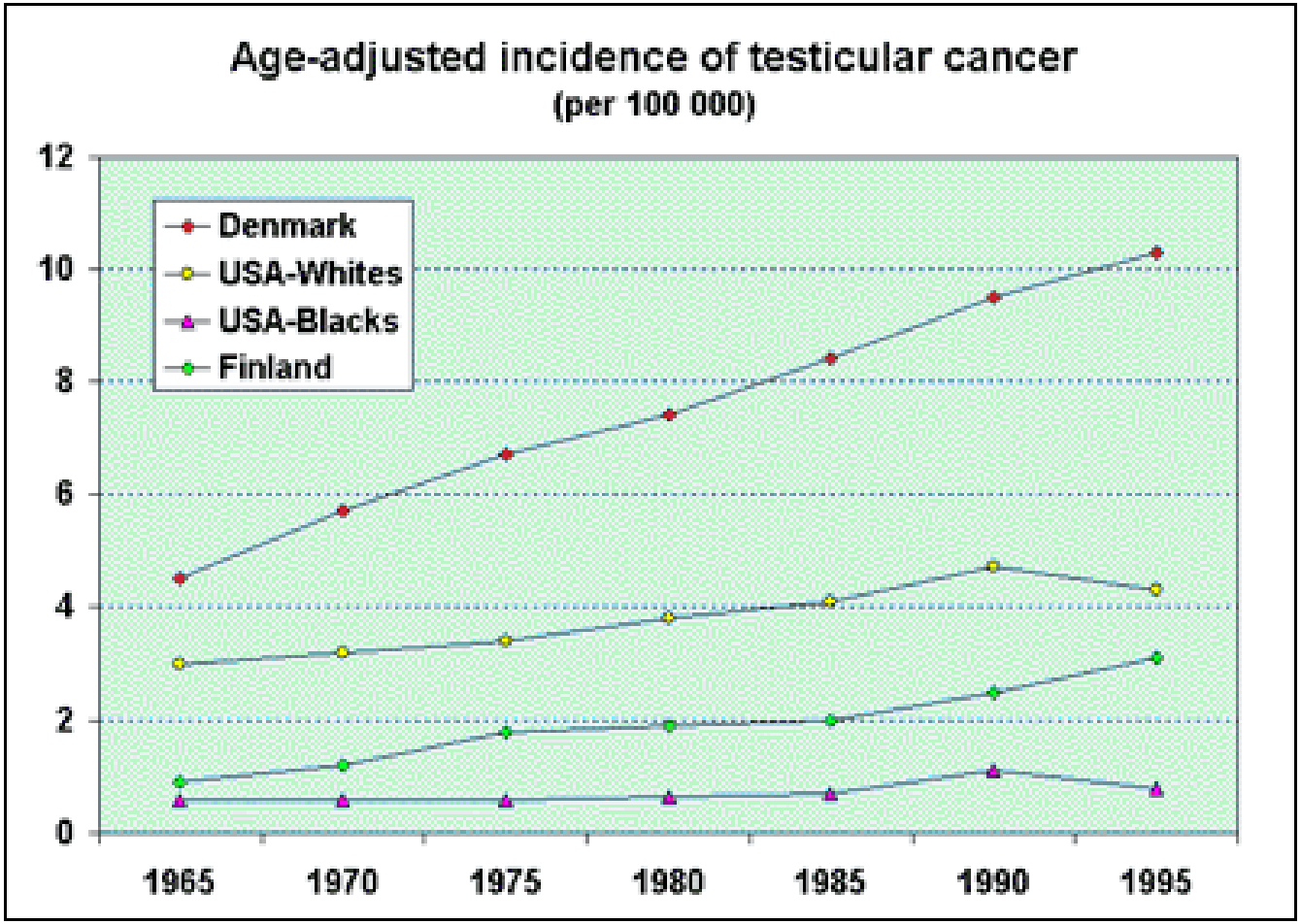


Testicular dysgenesis syndrome (TDS)?

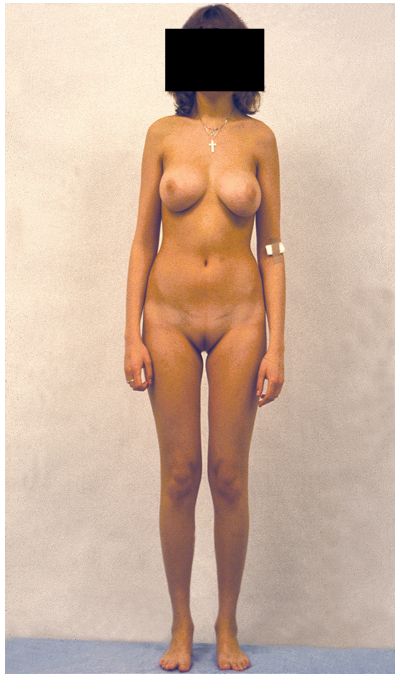


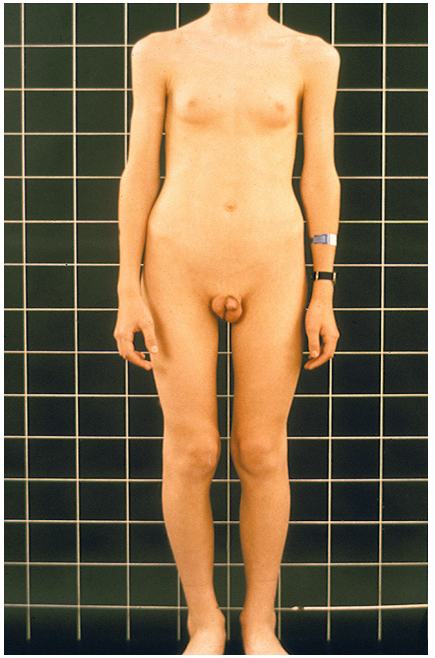
Skakkebaek *et al*, Human Reprod 2001; Sharpe & Skakkebaek, Fertil Steril 2008

Do we have any indication of gene-environment interaction in relation to male reproductive disorders?



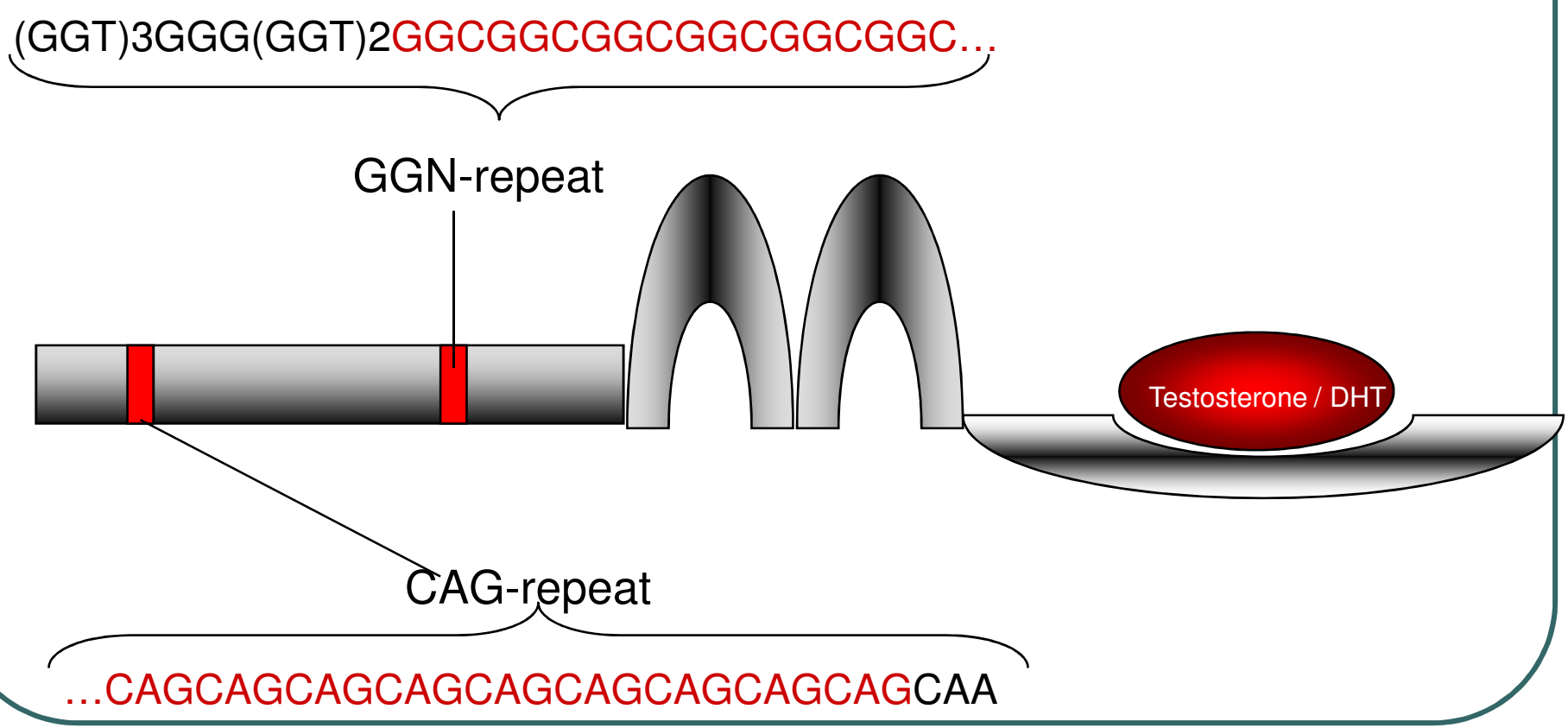
Androgens and androgen receptor – key players in the developemnt and function of male reproductive function





Lundberg Giwercman *et al,* Hum Genet. 1998

Androgen receptor

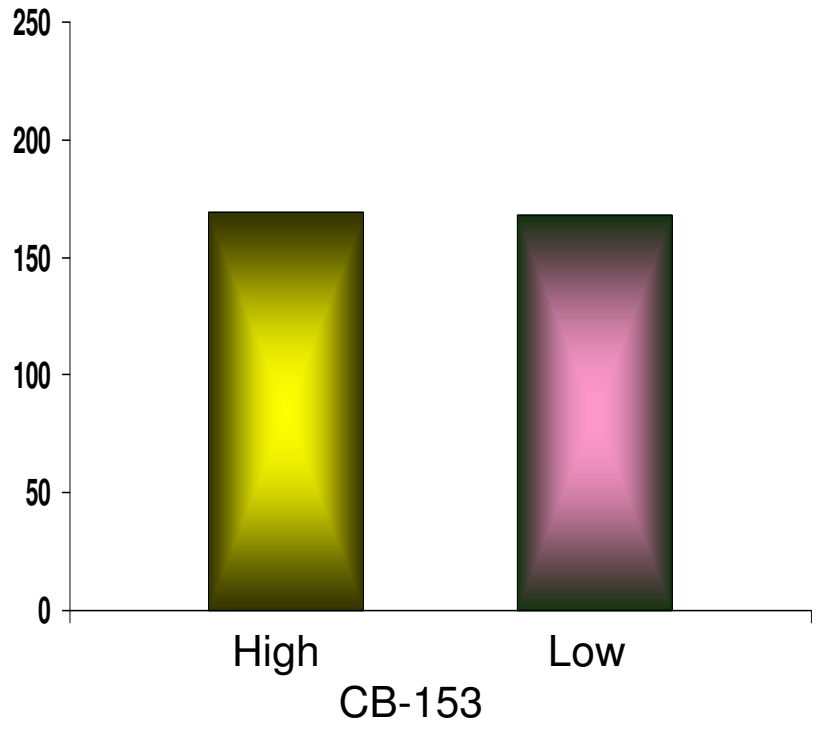


European Commission R&D Projekt:

Human Fertility at risk from Biopersistent Organochlorines in the Environment?

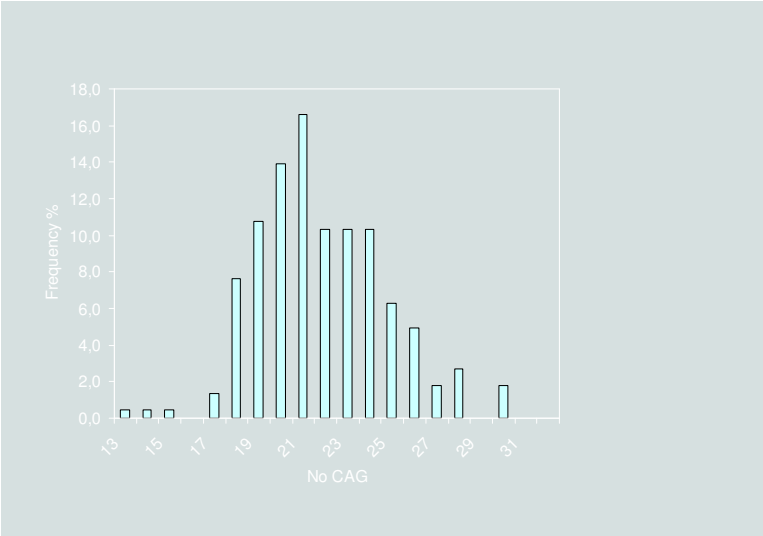
No effect of PCB on sperm number?

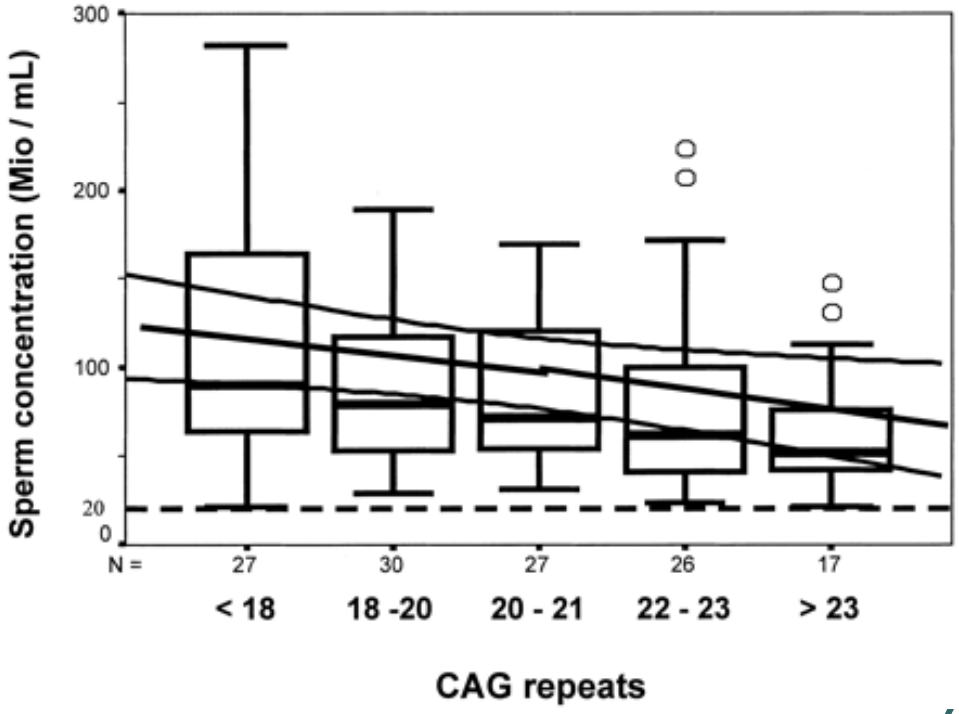
Total sperm number (x 10^6)



Toft *et al,* Epidemiology 2006

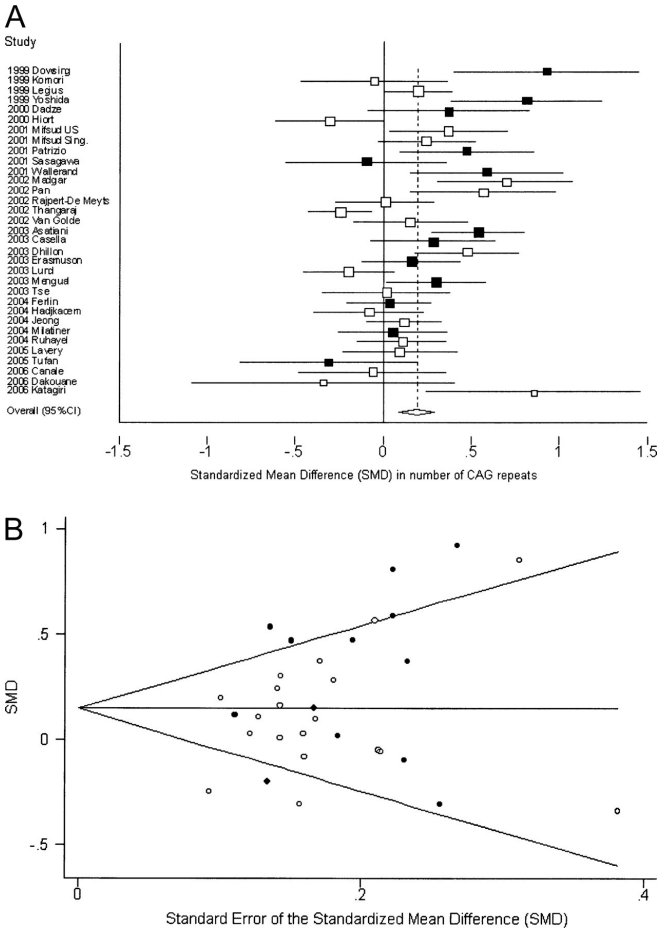
Correlation between CAG number and sperm concentration





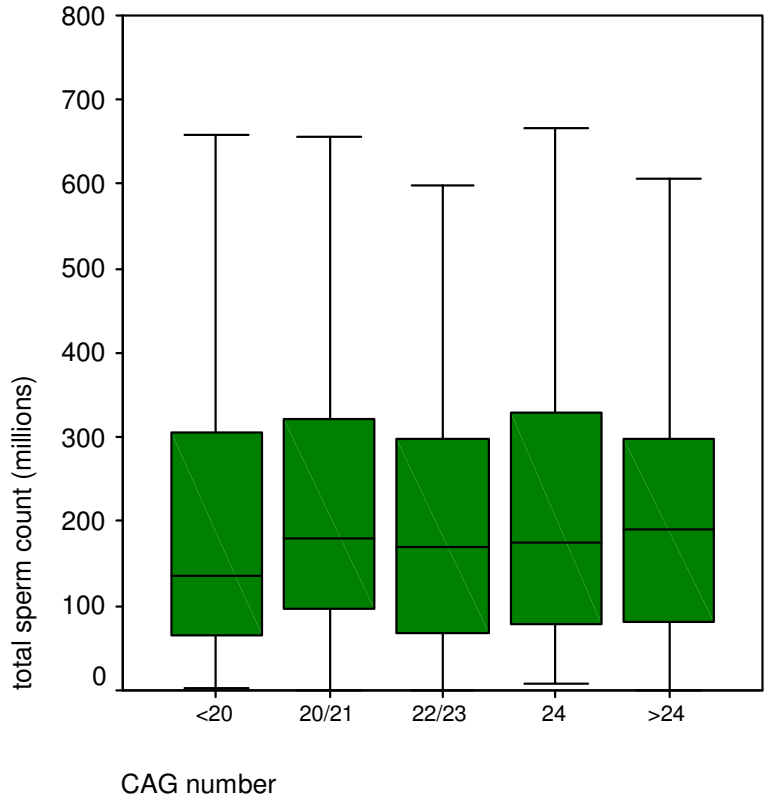
von Eckardstein *et al*, JCEM 2001

Only slight impact of CAG repeat length on the risk of infertility



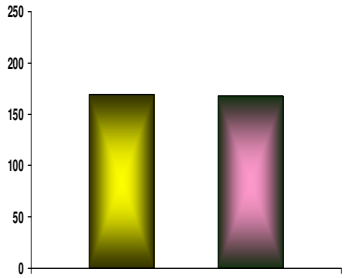
Davis-Dao *et al*. J Clin Endocrinol Metab 2007

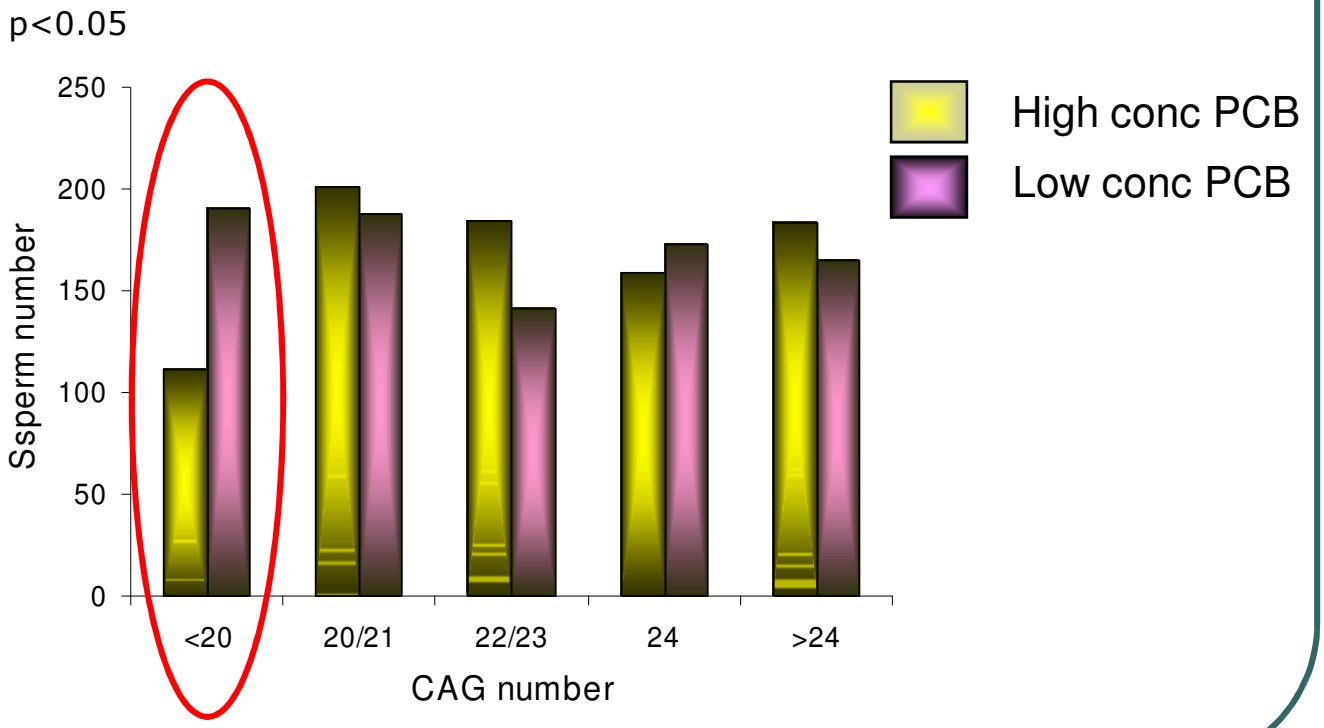
Inuendo - no association between CAG number and sperm counts



Giwercman *et al,* Pharmacogenet Genomics, 2007

CAG as modifier of PCB effect on sperm number?



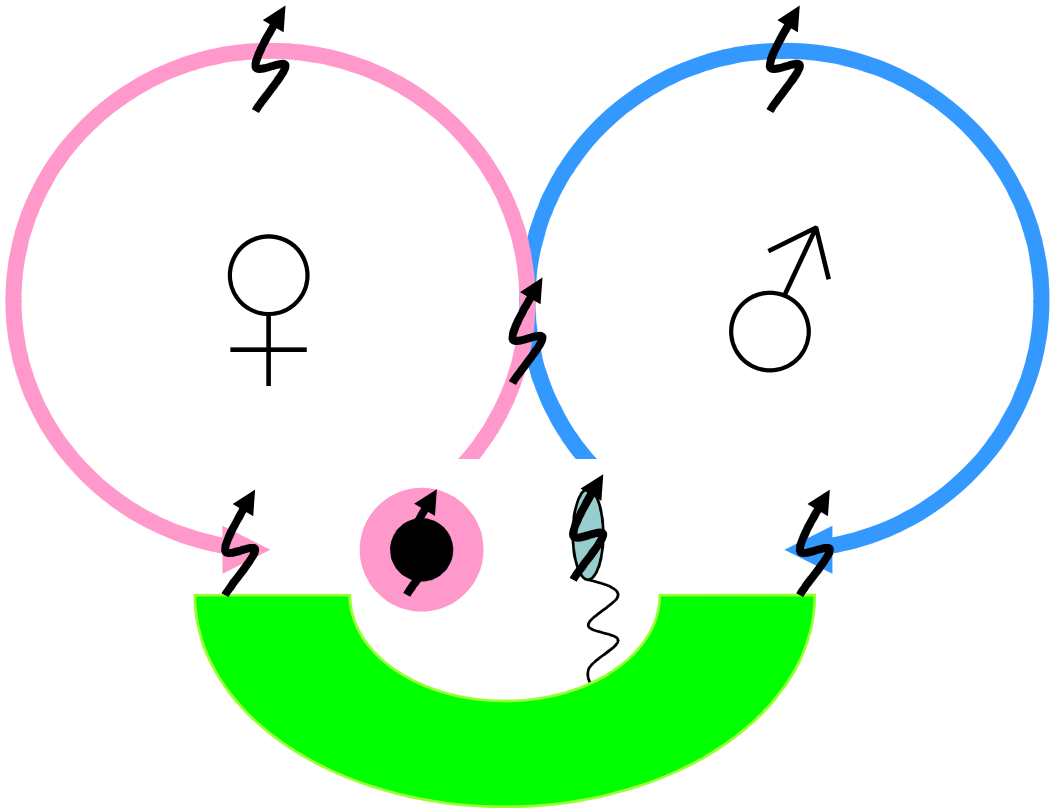


Giwercman *et al,* Pharmacogenet Genomics, 2007

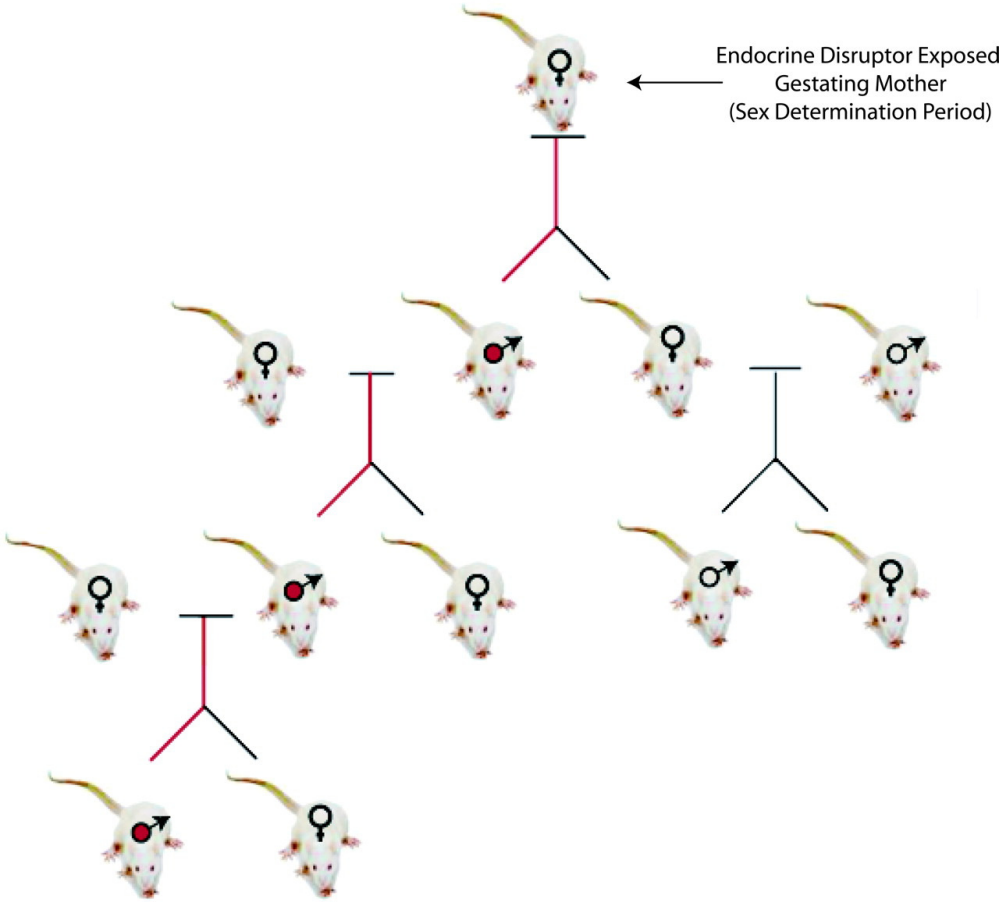
Do AR polymorphisms modify the effect of POPs on male reproductive function?

- Effect
  - Directly through the AR?
  - Through the aryl hydrocarbon receptor?
- Binding of the ligand to the receptor?
- Binding of co-activators/co-repressors?

Another aspect of gene-environment interaction in relation to the reproductive system

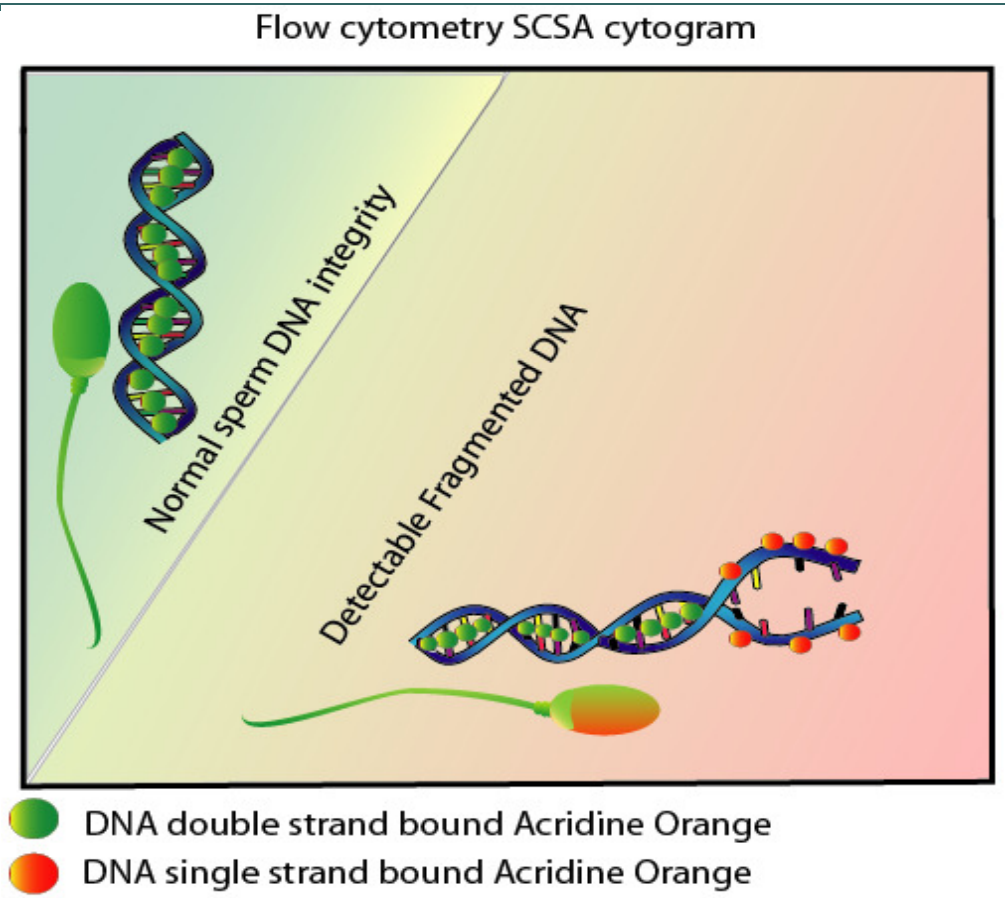


Actions of endocrine disruptors through the male germ line

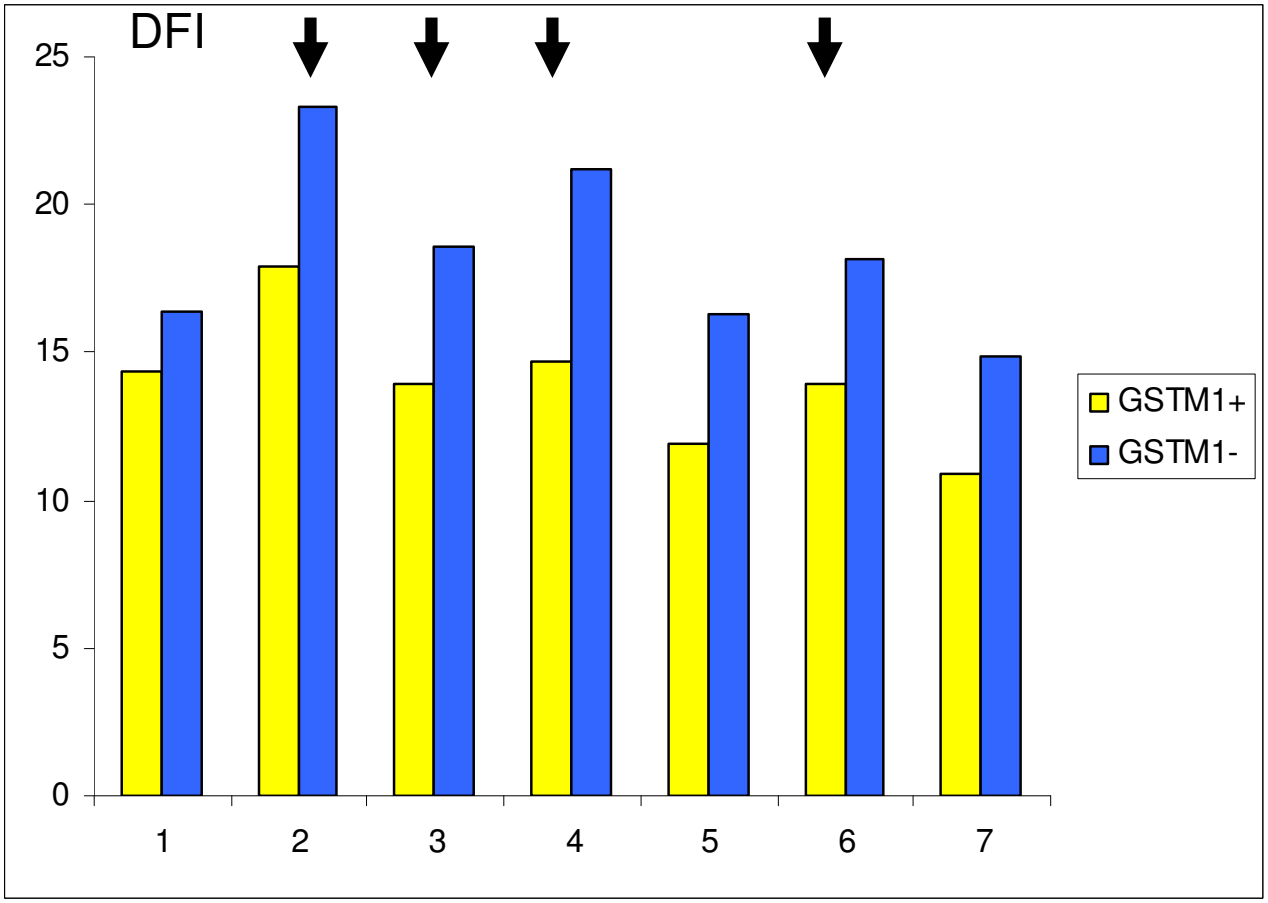


Anway and Skinner, Endocrinology 2006

Sperm Chromatin Structure Assay (SCSA)

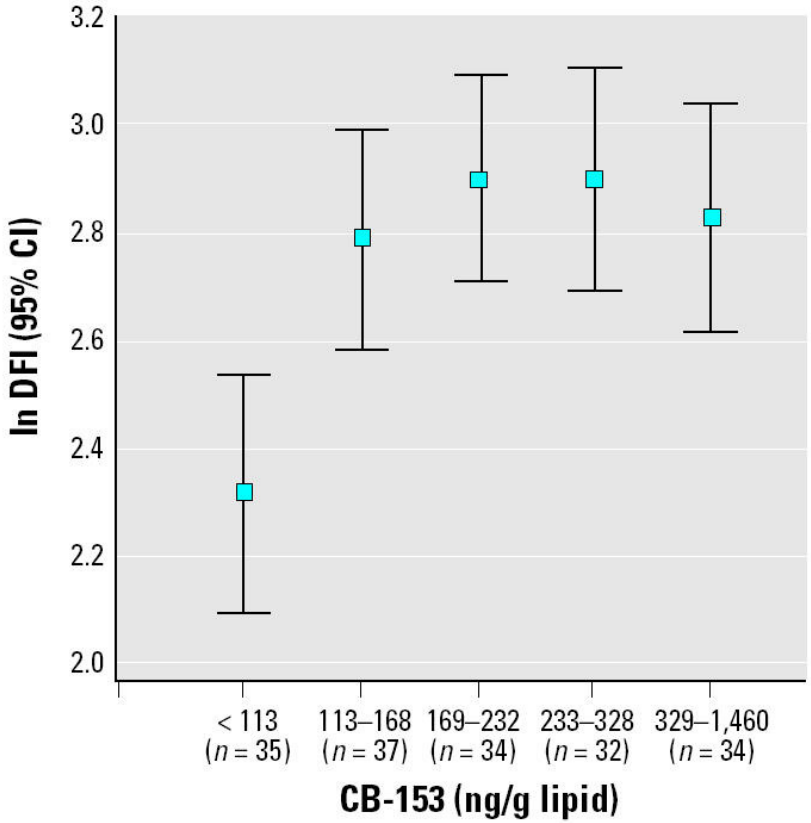


GSTM genotype as modifier of the impact of air pollution on sperm DNA integrity



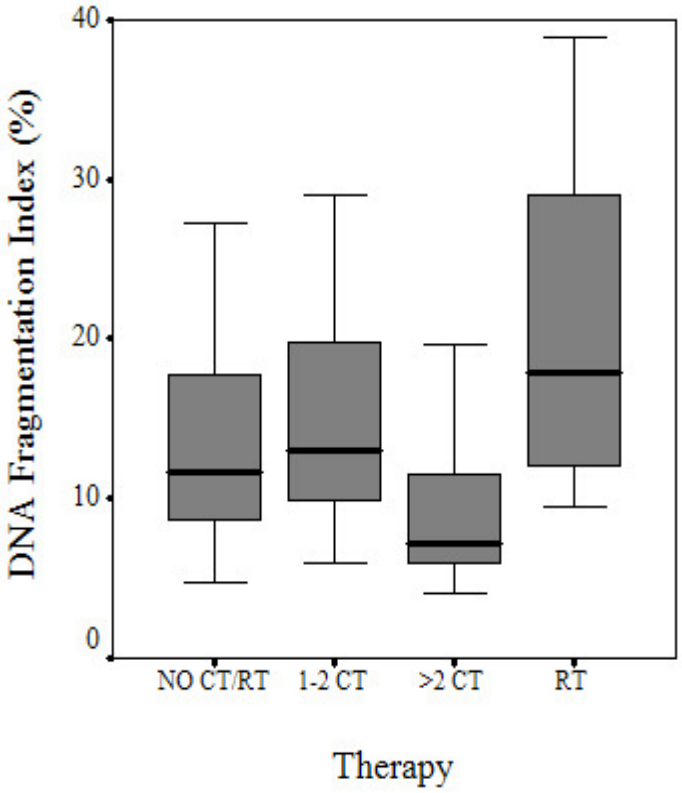
Rubes *et al,* Mut Research 2007

PCB exposure and sperm-DNA integrity



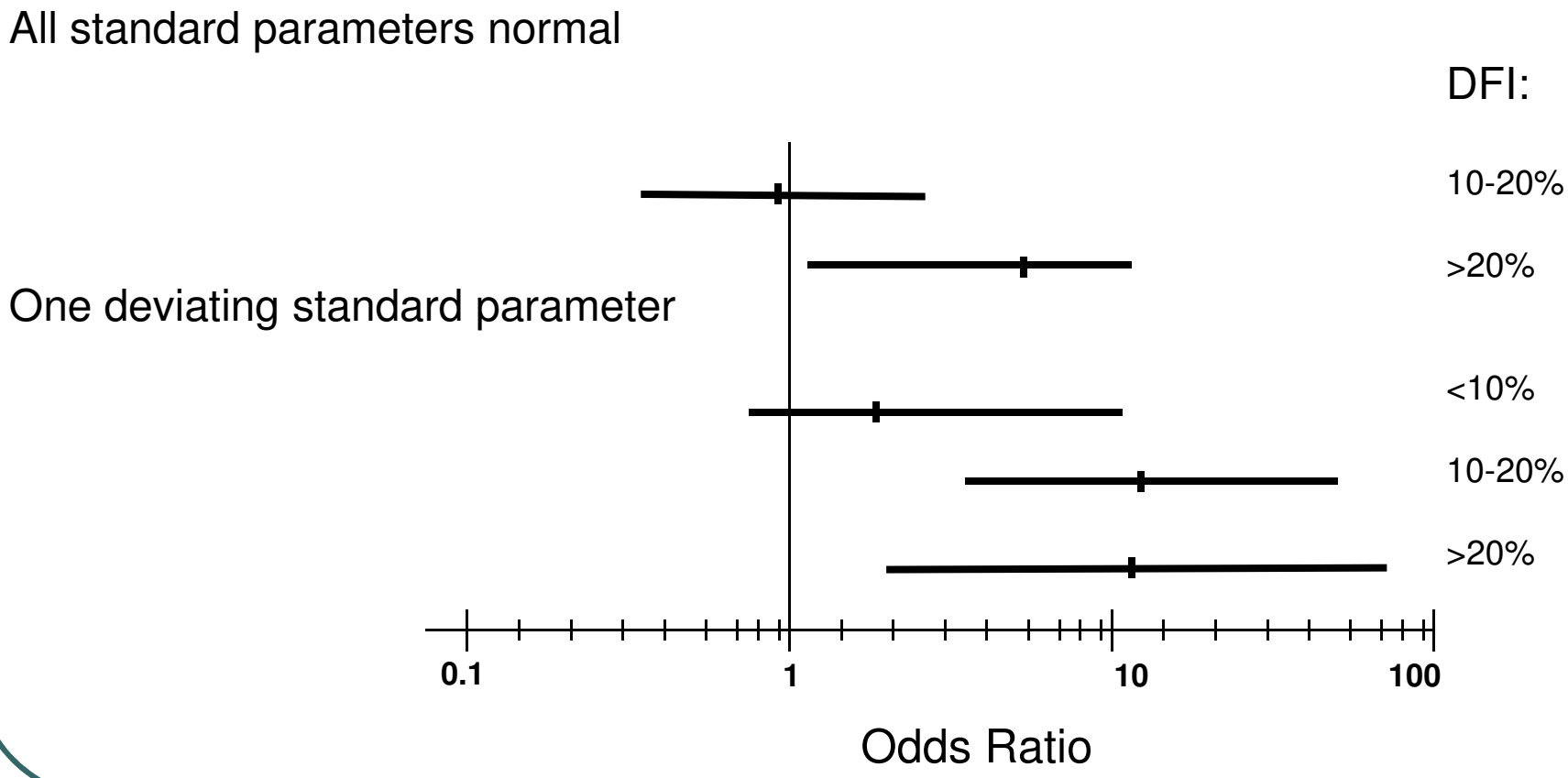
Rignell-Hydbom *et al,*Environ Health Perspect,2005

Sperm DNA integrity and testicular cancer treatment



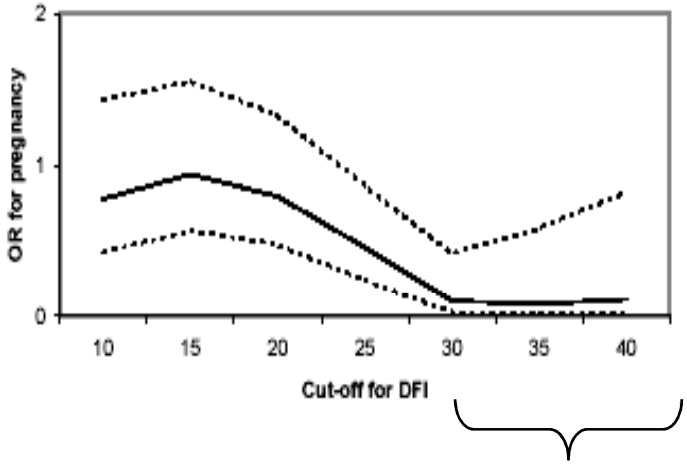
Ståhl *et al*, Cancer 2004

Odds ratio of *in vivo* infertility in relation to DFI and standard sperm parameters



Giwercman *et al*, Int J Androl, in press

Sperm DNA integrity and intrauterine insemination (IUI)



387 IUI

Bungum *et al,* Human Reprod 2007

Some concluding remarks

- There are some indictions of modifying effects of genetic factors on the sensitivity to the effects of envoronment/life style on male reproductive function;
- Studying gene-environment interaction is a new challenge in epidemiological studies;
- May also become of clinical relevance:
  - In diagnosis;
  - In targeting protective measures

Acknowledgements

Molecular biology

- Yvonne L. Giwercman
- Kristina B. Lundin
- Hamideh Rasthkani
- Christel Björk
- Hannah Nenonen
- Pål-Andre Skjaerpe
- Elin Aschim

Clinicial work

- Jonas Richthoff
- Yasir Ruhayel
- Olof Ståhl
- Jakob Eberhard

Inuendo

- Jens Peter Bonde
- Gunnar Toft
- Anna Rignell.Hydbom
- Bo Jönsson
- Marcello Spano
- Henning Petersen
- Jan Ludwicki
- Valentina Zvezaday

Statistics

- Lars Rylander

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