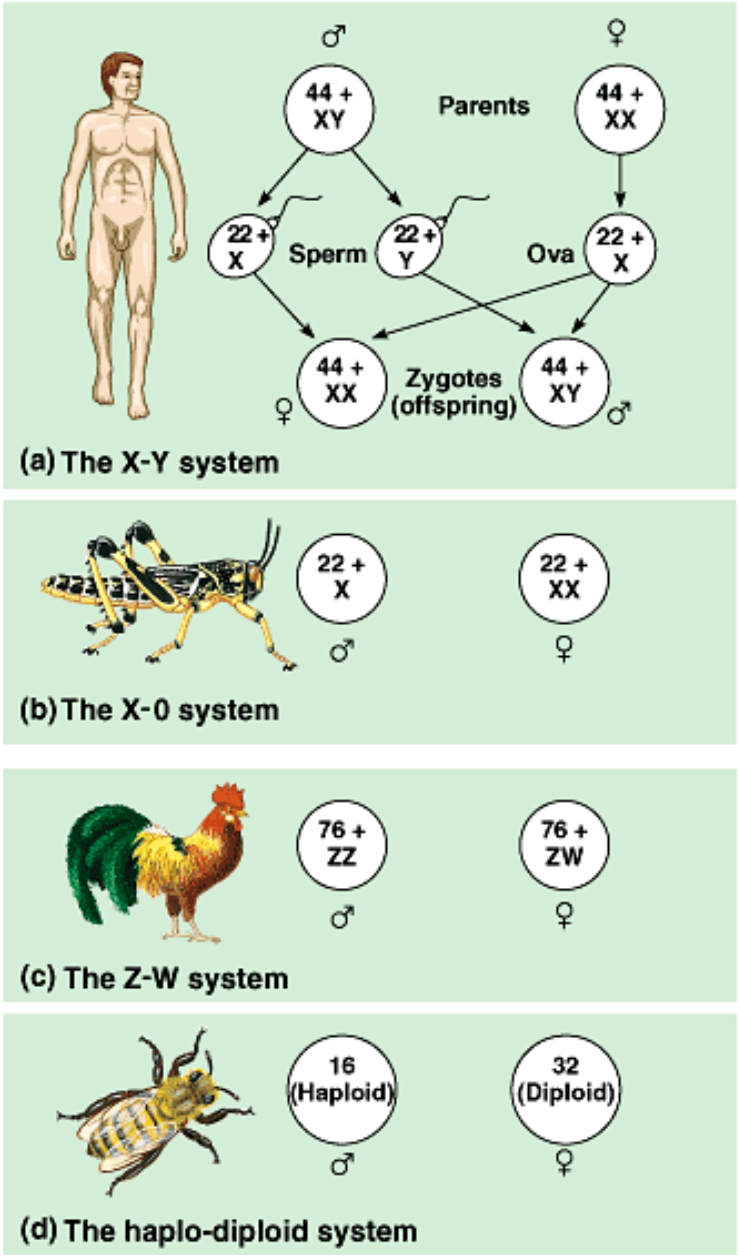
Molecular genetics of male infertility

new concepts on Y-chromosome

Sex Chromosomes

- Mammals use a chromosomal method of determining sex: XX is female and XY is male.
- Birds use a ZW system: ZZ is male and ZW is female.
  - the evolutionary origin of mammalian and bird sex chromosomes is different
- Some reptiles use developmental temperature to determine sex: depends on the species, but hot is male and cold is female in some.
- Drosophila also use an X-Y system (i.e. male is XY and female is XX), but the evolutionary origin and mode of action of Drosophila sex chromosomes is different form mammalian.



X and Y Homology

- The X is a large submetacentric chromosome with many genes on it, most of which are unrelated to sex.
- The Y is acrocentric and much smaller Only 83 active genes on the Y, most o which are related to sex determinatio and spermatogenesis.
- However, many homologues exist between the X and the Y, with the Y gene often a pseudogene. This sugges a common evolutionary origin.
- The tips of the X and Y pair in meiosis and undergo crossing over.
  - These regions are called the pseudoautosomal regions., PAR1 and PAR2.
  - a crossover in PAR1 is necessary in male meiosis to get proper segregation of the chromosomes.

X and Y chromosomes show several regions of homology in addition to the common pseudoautosomal regions

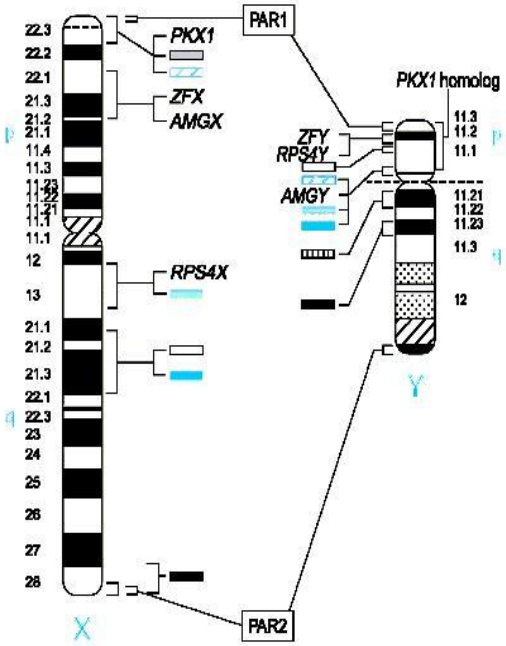


Fig. 14.9, Strachan and Read

Infertility

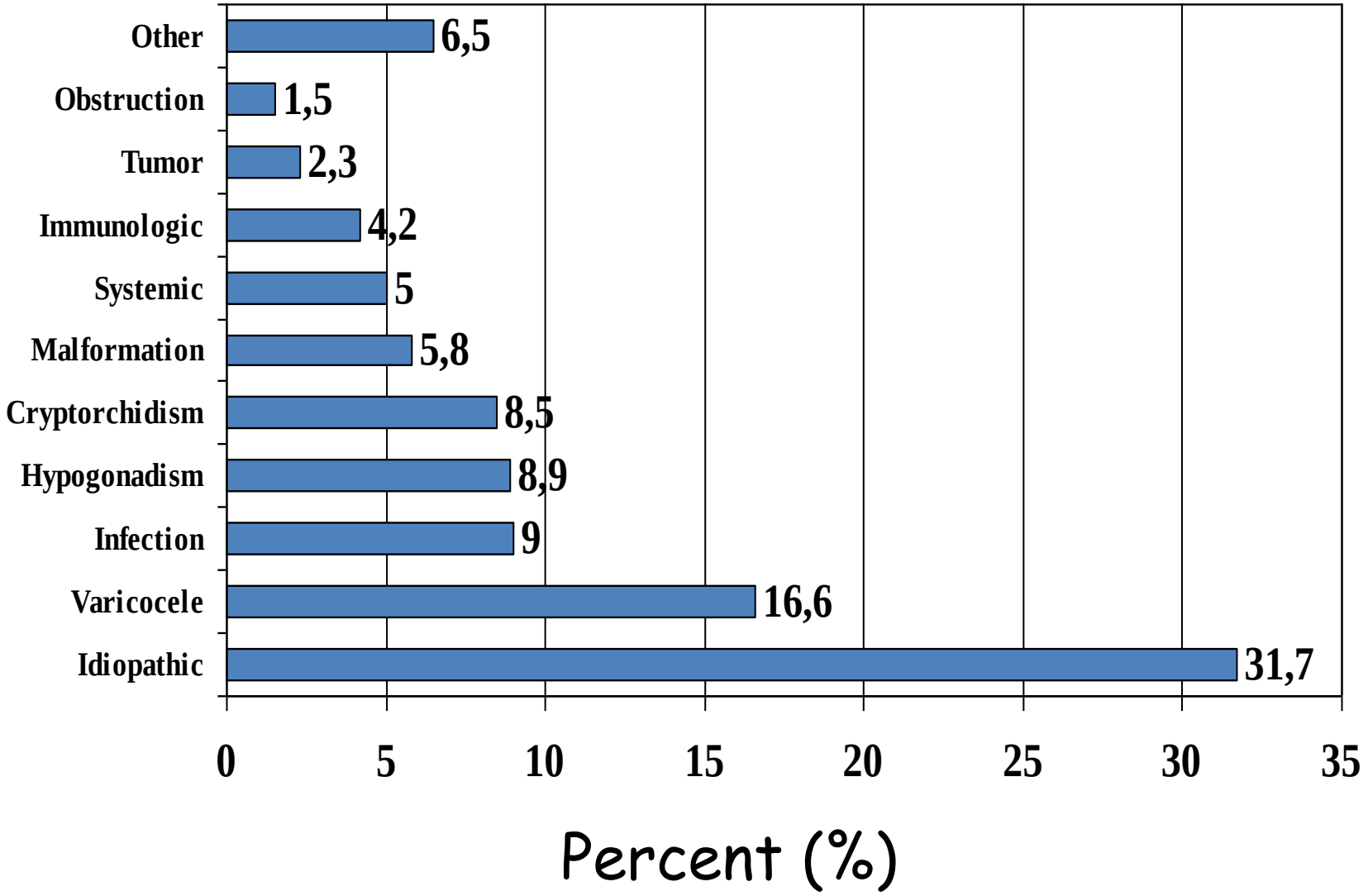
- Approx. 50% of infertility is female orginated
- 35% is male originated
- 15% is unexplained

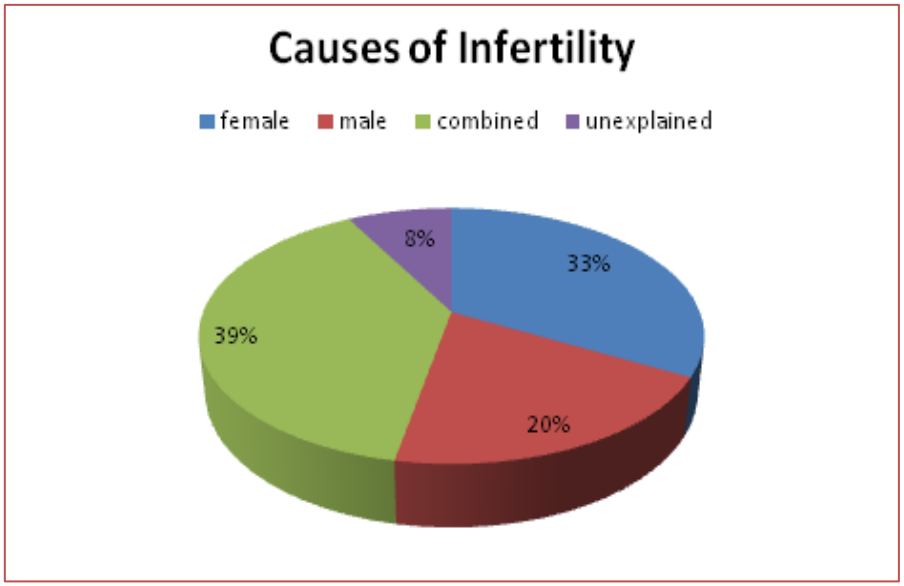
Male factor infertility

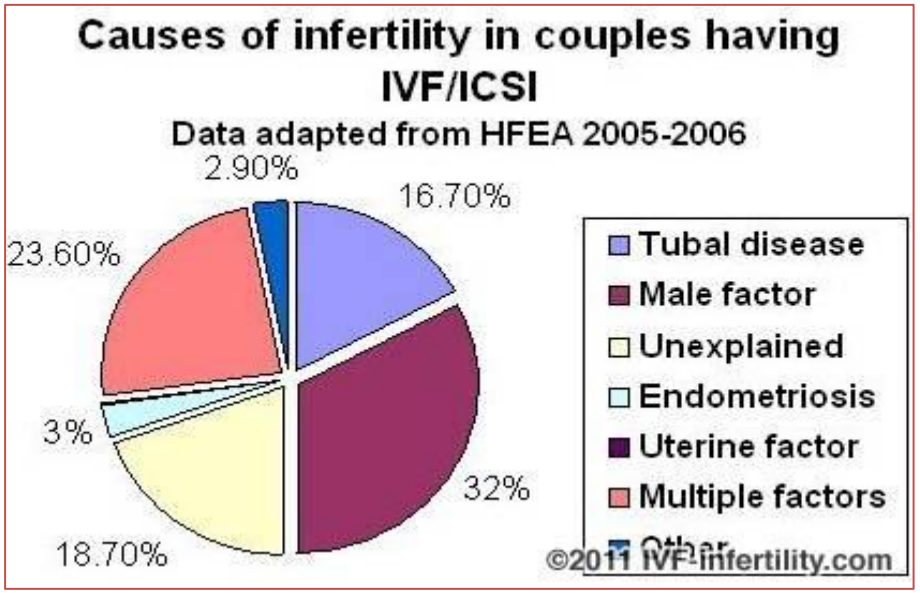
- Anatomic defects (hypospadias, retrograde ejac.)
- Genetic causes
- Trauma
- Infection
- Endocrine disorders
- Varicocele
- Idiopatic

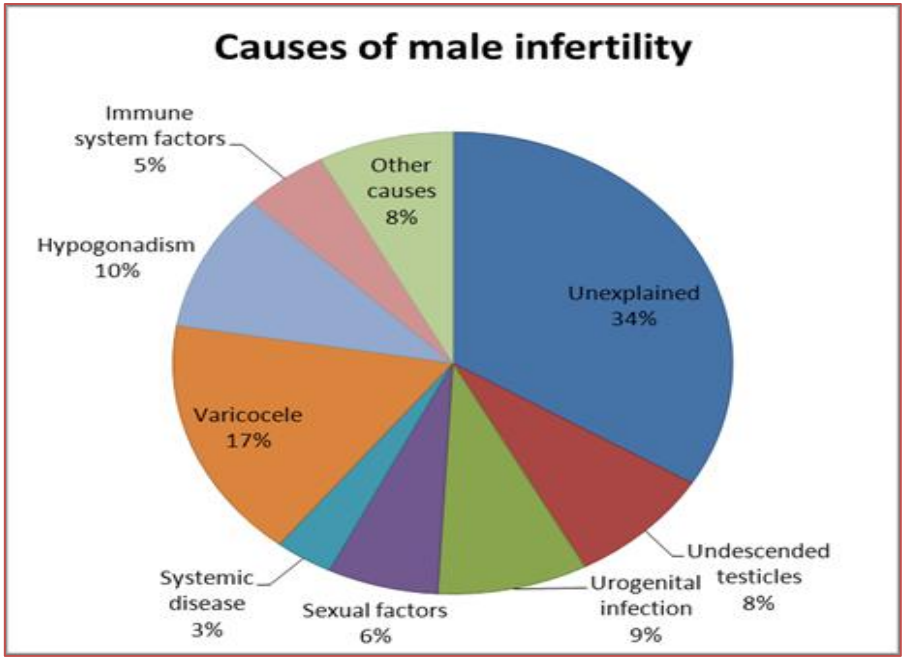
Male Infertility

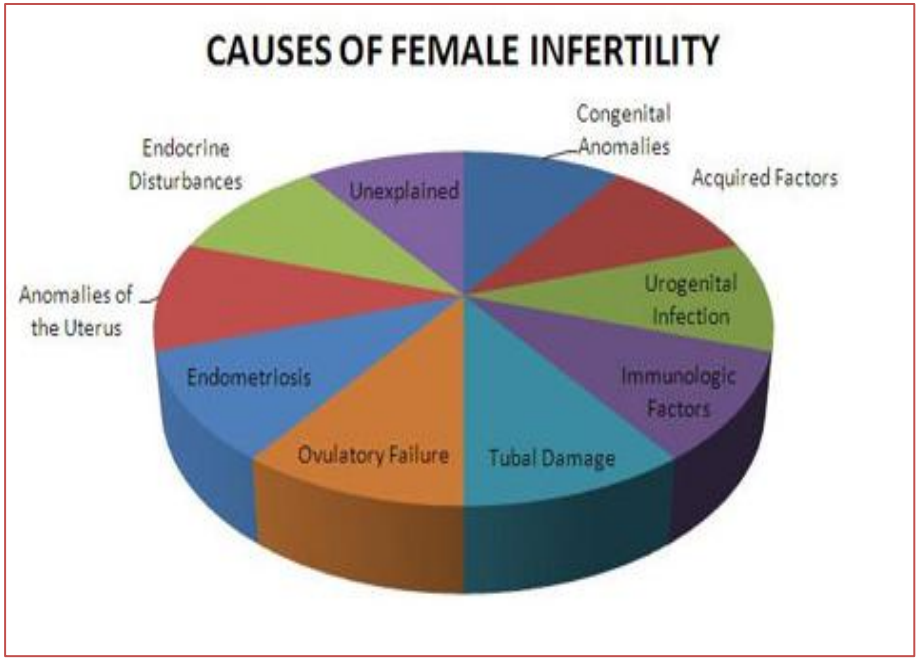
Hum Reprod Update 1999; 5(2): 120




Causes of Infertility
female
male
combined
unexplained
33%
20%
39%
8%


Causes of infertility in couples having IVF/ICSI
Data adapted from HFEA 2005-2006
2.90%
16.70%
23.60%
3%
32%
18.70%
Tubal disease
Male factor
Unexplained
Endometriosis
Uterine factor
Multiple factors
©2011 IVF-infertility.com


Causes of male infertility
Immune system factors 5%
Other causes 8%
Hypogonadism 10%
Unexplained 34%
Varicocele 17%
Undescended testicles 8%
Systemic disease 3%
Sexual factors 6%
Urogenital infection 9%


CAUSES OF FEMALE INFERTILITY
Congenital Anomalies
Endocrine Disturbances
Acquired Factors
Unexplained
Anomalies of the Uterus
Urogenital Infection
Endometriosis
Immunologic Factors
Ovulatory Failure
Tubal Damage

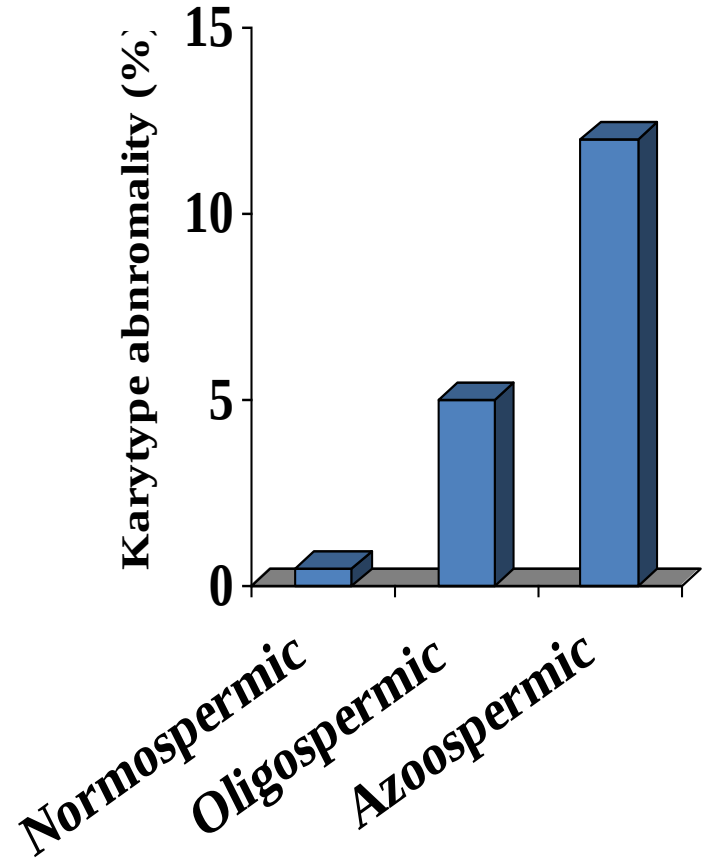
Male Infertility

- Infertile males with oligospermia or azoospermia (n = 9766)
  - Oligospermia: less than 20million/ml
  - Azoospermia: alive or not no sperm at all
  - 5.8% incidence of chromosomal abnormalities
    - 4.2% sex chromosome
    - 1.5% autosome
  - Baseline fertile males: 0.5%

Johnson, Fertil Steril 1998

Karyotypic Abnormalities

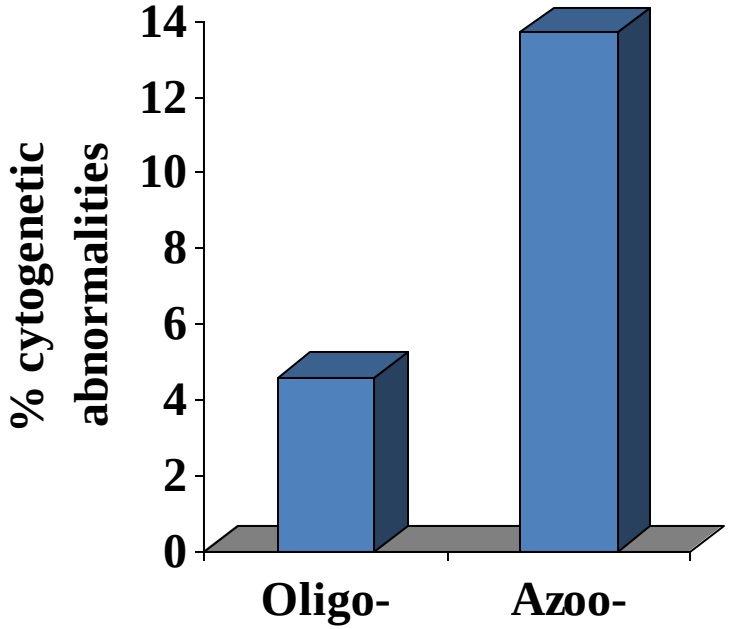
- Frequency is inversely proportional to sperm concentration
- Most common anomaly is Klinefelter syndrome
  - atrophic hyalinized testes depleted of germ cells



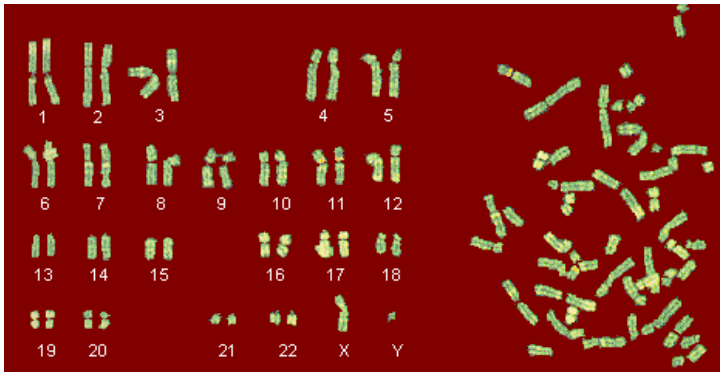
Sharlip et al. Fertil Steril 2002

Male Infertility

- Cytogenetic surveys of oligospermic and azoospermic males
  - oligo-: 4.6 % with cytogenetic abnormalities
    - 1.6 % sex chromosomal
    - 3.0 % autosomal
  - azoo-: 13.7 % with cytogenetic abnormalities
    - 12.6 % sex chromosomal
    - 1.1 % autosomal



DNA damage in sper



- N=66
- Ages 20-57
- Gradual increased in DNA damage
  - Most pronounced after age 35
- ?Apoptosis decreases with age?

Singh et al. Fertil Steril 2003

Four genetic factor for male infertility

1. Y-chromosome microdeletions (7-10%)
2. Cystic fibrosis gen mutation that couses congenital vas deferens agenesis (1-2%)
3. Chromosomal aberations (1 in 500)
4. Genetic factors that effects the sperm functions

Chomosomal aberations

Chromosome Nomenclature: 47, XXY, 48, XXXY, 48,XXYY, 49, XXXXY, 50, XXXXXY

Chromosome formula: 2n+1; 2n+2; 2n+2; 2n+3; 2n+4

Clinical Syndrome: Klinefelter

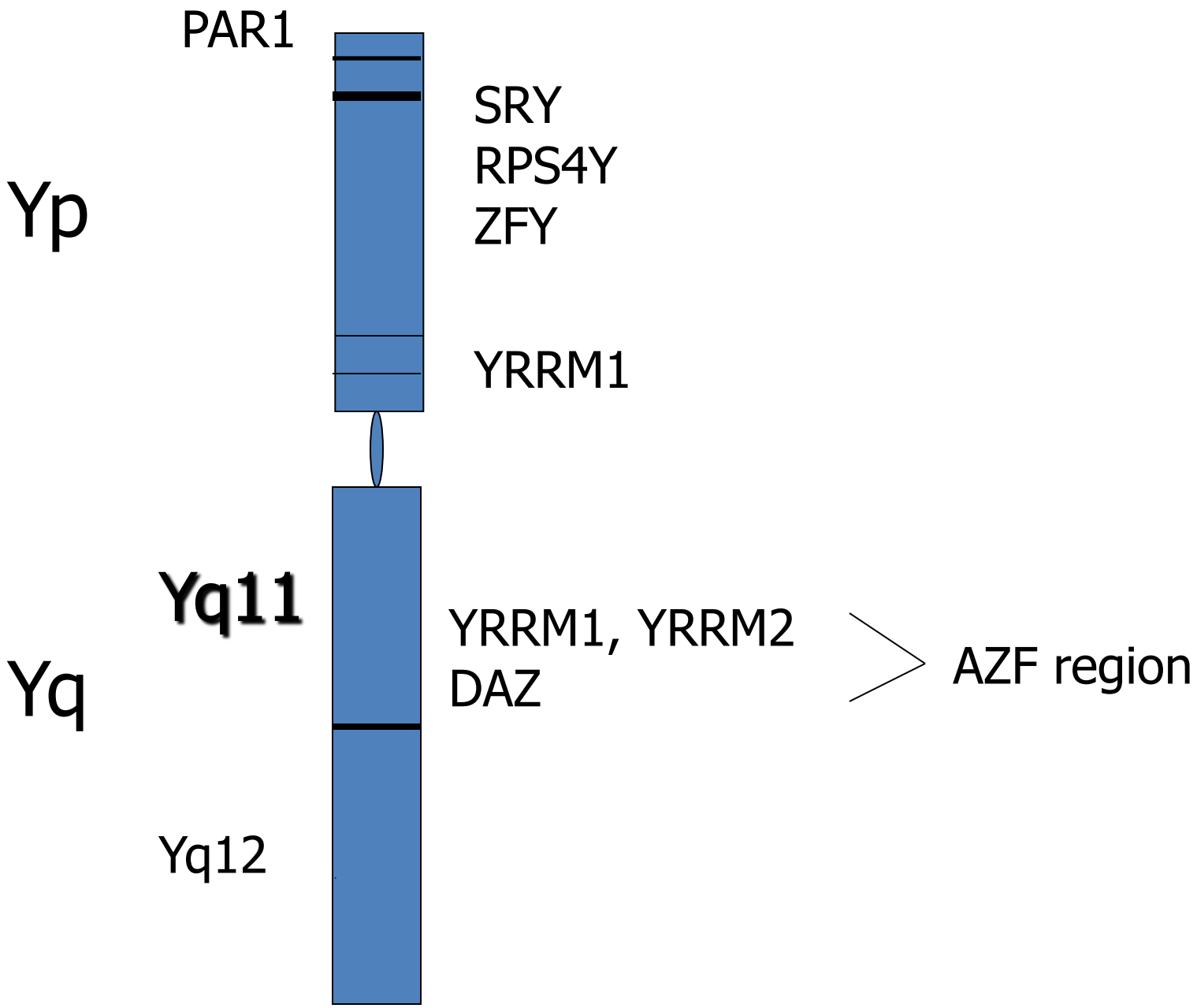
Estimated Frequency Birth: 1/500 male borth

Main Phenotypic Characteristics:

Pitched voice, Male, subfertile with small testes, developed breasts, feminine, long limbs.

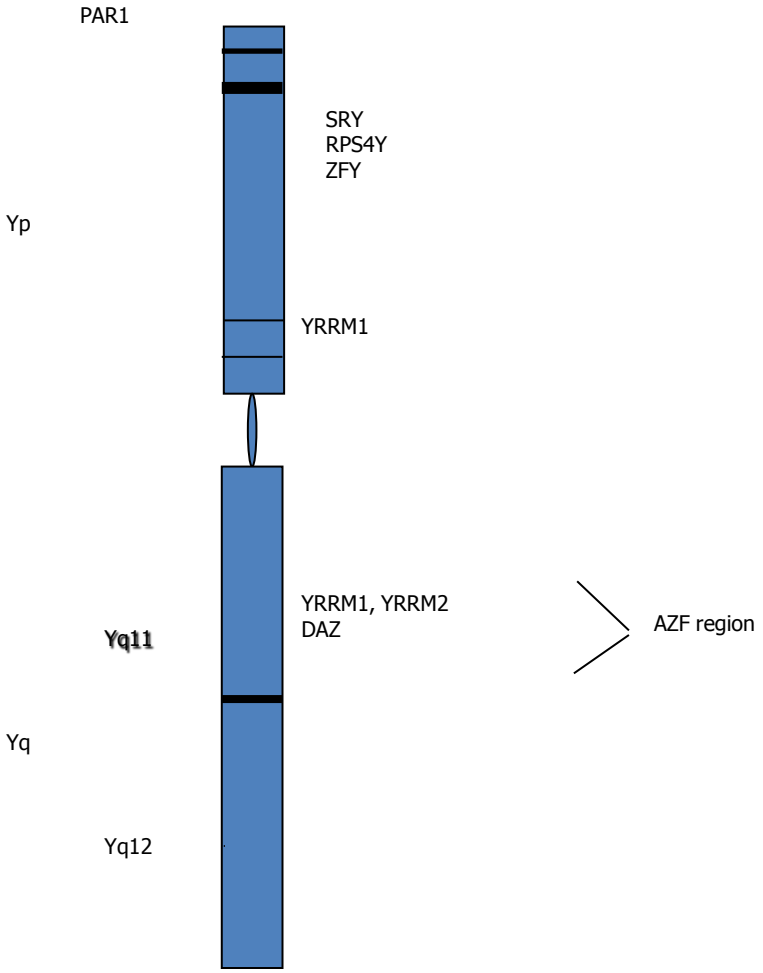
SRY gene= Testis Determining gene

- The SRY gene on the Y chromosome is the master gene for male sex determination
  - Triggers formation of testes, which produce the male sex hormone (testosterone)
  - Without testosterone, ovaries develop and produce female sex hormones (estrogens)


PAR1
SRY
RPS4Y
ZFY
Yp
YRRM1
Yq11
YRRM1, YRRM2
DAZ
Yq
AZF region
Yq12

Microdeletions

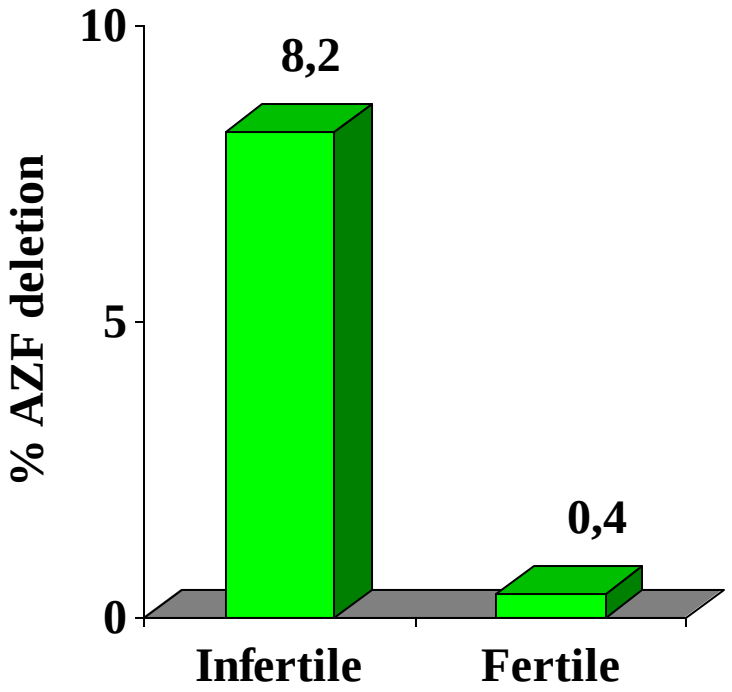
- Yq11 microdeletions
  - 10-15% azo- / severely oligozoospermic men
  - AZF =azoospermia factor
  - AZFa to AZFc in the Yq11.21-23 region
  - To small to be detected by karyotyping
  - Can be detected by PCR



Brandell et al. Hum Repro 1998

Microdeletions

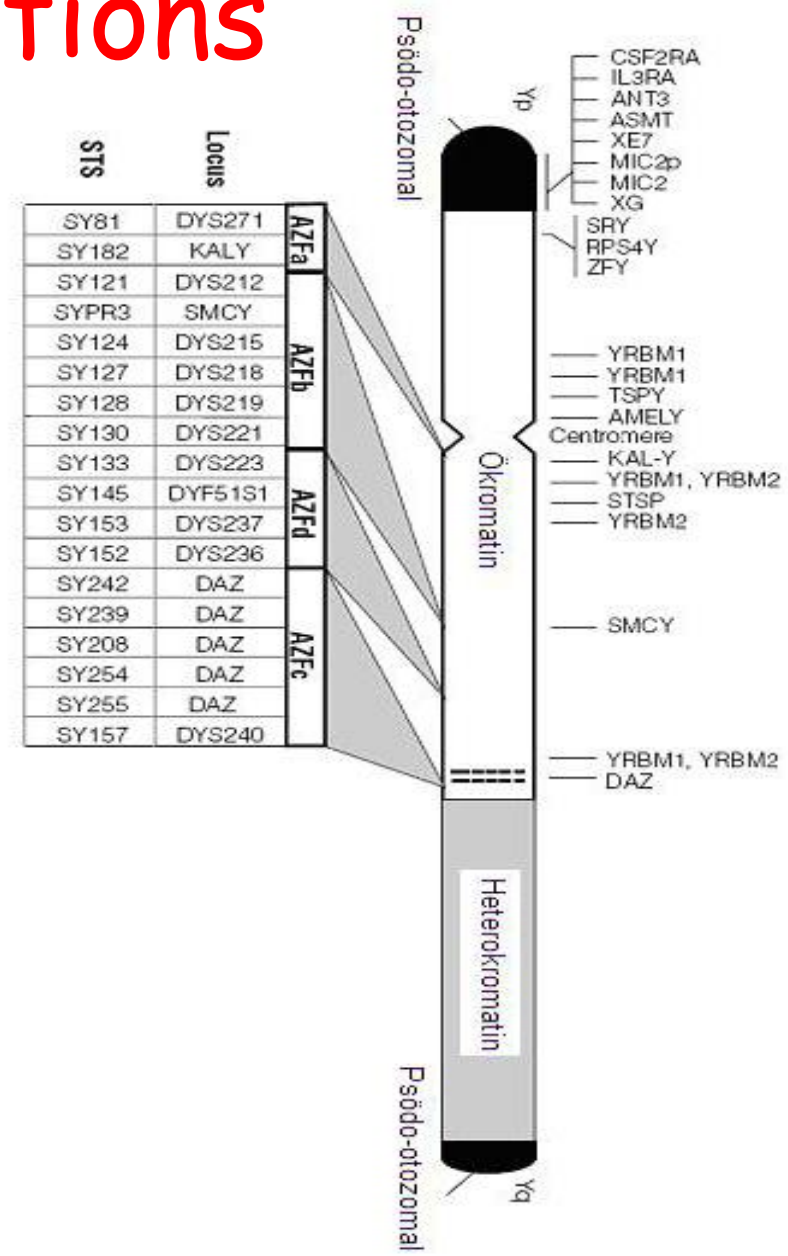
- N=5000 infertile males screened for Y-chromosome mutations in the AZF region
  - 8.2% infertile males
  - 0.4% fertile males



Foresta et al. Endo Rev 2001

Microdeletions

- In 1996 Vogt et al., defined 3 region.
- These are AZFa, AZFb ve AZFc. Later on AZFd has been included into this group
- 14 protein coding gene is localized at AZFa, AZFb ve AZFc



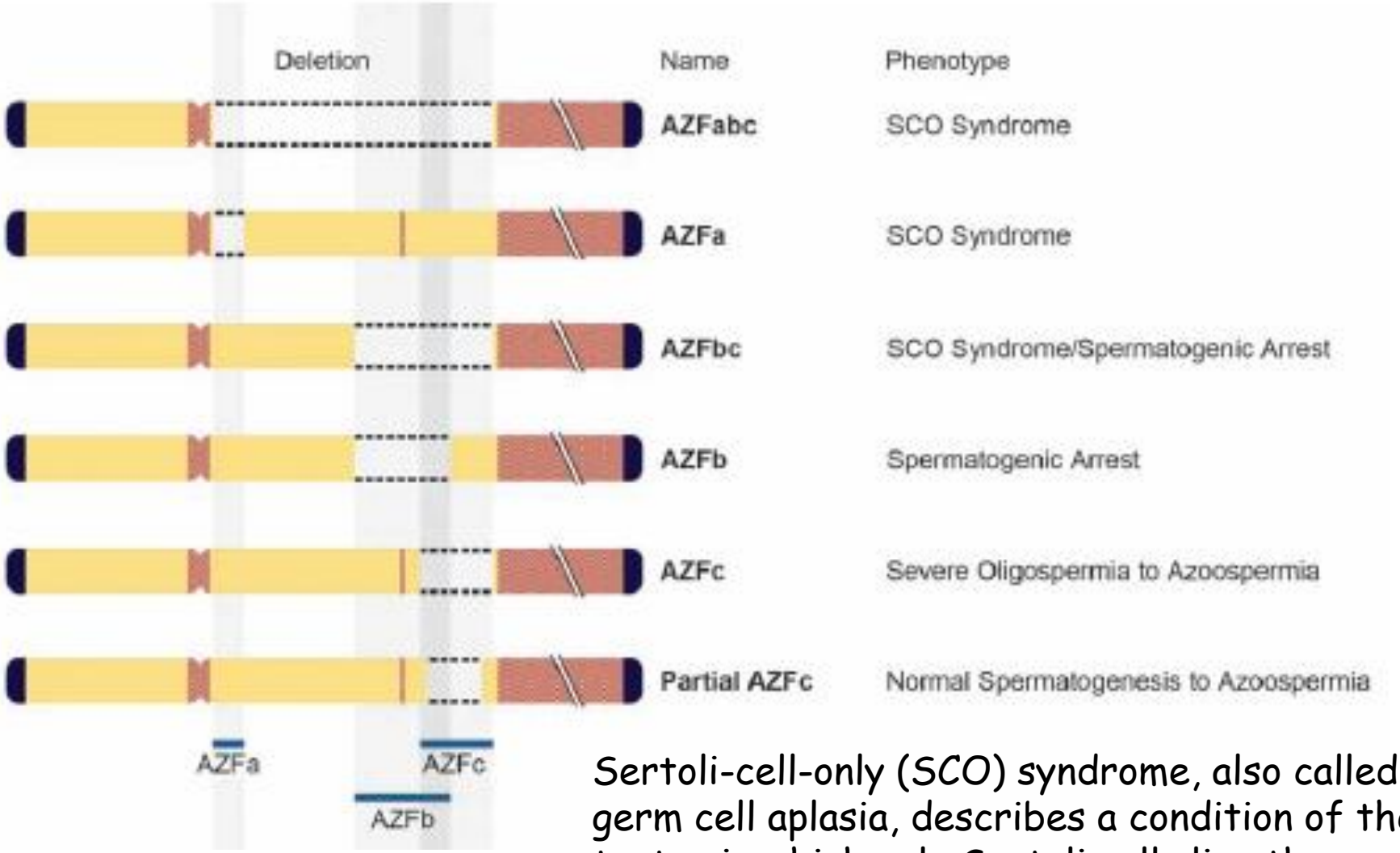
Microdeletions

Table 1. Protein-Encoding Gene Families on the Azoospermia Factor Regions[21,26,32]

Gene Symbol	Gene Name	Number of Copies	Expression	Location	AZF Location	Number of Deleted Copies			
						Complete AZFa	Complete AZFb (P5/Proximal P1)	AZFbc (P5/dIstal P1)	AZFc*
USP9Y	Ubiquitin Specific Protease 9 Y	1	Ubiquitous	X-Degenerate	AZFa	1	0	0	0
DBY	Dead Body Y	1	Ubiquitous	X-Degenerate	AZFa	1	0	0	0
RBMY	RNA-Binding Motif Y-Linked	6	Only Testis	Amplicons	AZFb	0	6	6	0
HSFY	Heat-shock Transcription Factor Y	2	Testis, Kidney	Amplicons	AZFb	0	2	2	0
PRY	PTP-BL Reloated Y	2	Only Testis	Amplicons	AZFb	0	2	2	0
XKRY	X-Kell Blood Group Precursor Related Y	2	Only Testis	Amplicons	AZFb	0	1	1	0
RPS4Y2	Ribosomal Protein S4 Y Linked 2	1	Testis, Prostate	X-Degenerate	AZFb	0	1	1	0
SMCY	Selected Mouse C DNA Y	1	Ubiquitous	X-Degenerate	AZFb	0	1	1	0
EIF1AY	Essential Initiation Translation Factor 1A Y	1	Ubiquitous	X-Degenerate	AZFb	0	1	1	0
CDY	Chromodomain Y	4	Only Testis	Amplicons	AZFb and AZFc†	0	2	2	0 to 2
DAZ	Deleted in Azoospermia	4	Only Testis	Amplicons	AZFc	0	2	4	0 to 4
BPY2	Basic Protein Y 2	3	Only testis	Amplicons	AZFc	0	1	3	0 to 3
CSPG4LY	Chondroitin sulfate proteoglycan 4 Like Y	2	Only Testis	Amplicons	AZFc	0	0	2	0 to 2
GOLGA2LY	Golgi Autoantigen, Golgin Subfamily a2 Like Y	2	Only Testis	Amplicons	AZFc	0	0	2	0 to 2

*Complete and partial AZFc deletions usually show variations in the deletions of the genes.
†CDY1 is located in the AZFc and CDY2, in the AZFb. One copy of the CDY1 is in the overlapped region of the AZFc with AZFb.

Microdeletion vs phenotype



Sertoli-cell-only (SCO) syndrome, also called germ cell aplasia, describes a condition of the testes in which only Sertoli cells line the seminiferous tubules.

Relative frequency of specific AZF deletions in men

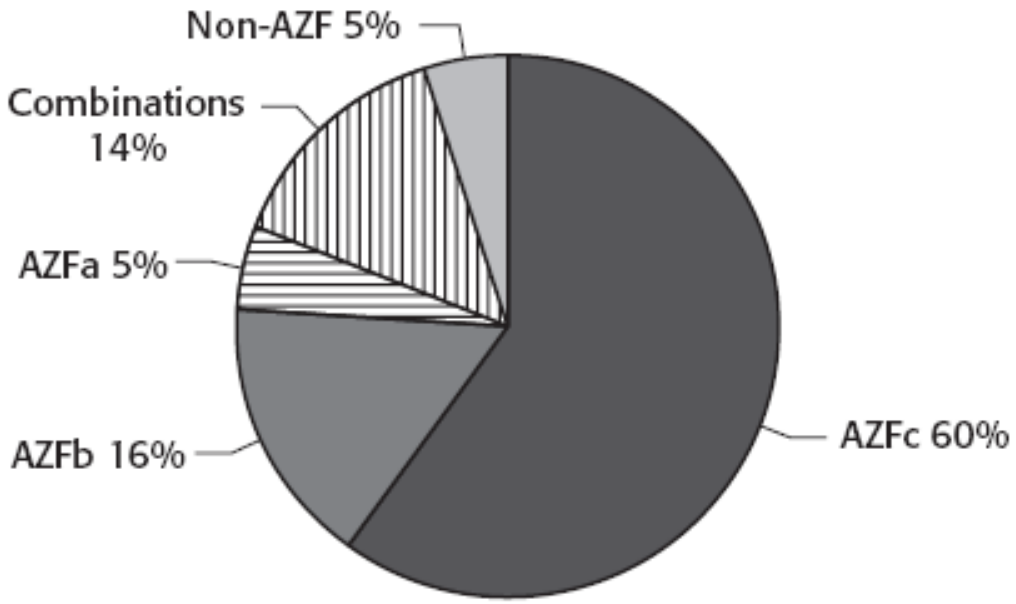


Figure 10.1 Relative frequency of specific AZF deletions in men (n = 5000) with Yq microdeletions (Foresta *et al.*, 2001a)

DAZ (Deleted in azoospermia) gen

- Shown in azospermic men
- 4 copy gene (DAZ1/DAZ2 ve DAZ3/DAZ4)