Genetics screen of infertile men

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Male Infertility

In humans it accounts for 7% of all men

Men with azoospermia are at 25% risk of being carriers of genetic anomalies

Genetic screening

Helps in diagnosing cause of azoospermia and severe oligospermia

Helps in counseling the would be parents about risk of transmission to offspring

EAU guideline for karyotype

1. **Azoospermia**
2. **Oligospermia (sperm concentraion < 10 million/ml)**
3. **Recurrent spontaneous abortion**
4. **Family history of malformation or mental retardation**

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European Association of Urology

Platinum Priority – Brief Correspondence

Editorial by Michael L. Eisenberg on pp. 924–925 of this issue

When to Perform Karyotype Analysis in Infertile Men? Validation of the European Association of Urology Guidelines with the Proposal of a New Predictive Model

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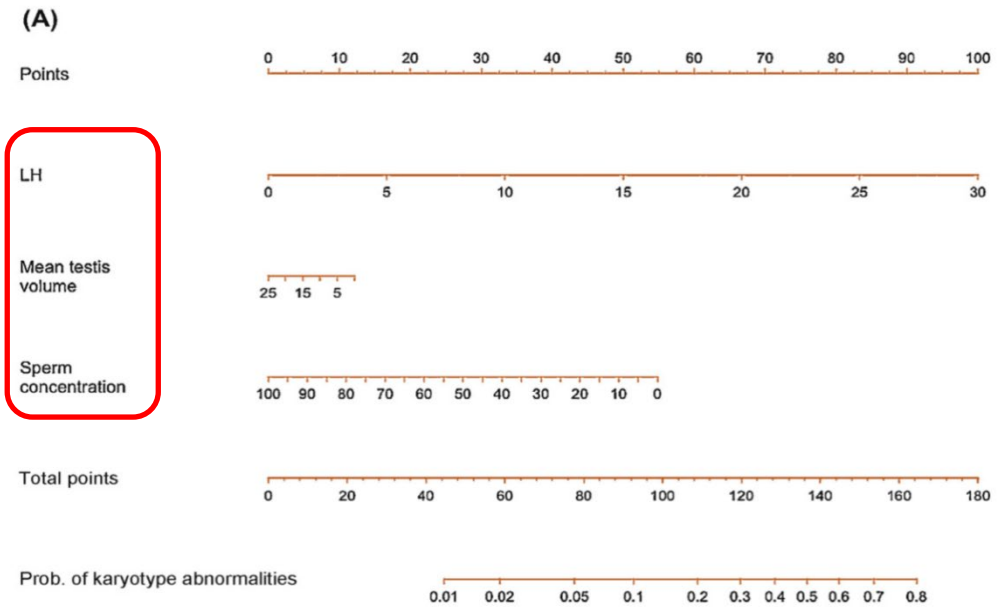


EAU guideline
Sensitivity 80%
Specificity 37%

Prob. threshold	Specificity	Sensitivity	PPV	NPV
1%	17%	97%	5%	99%
2%	33%	94%	6%	99%
5%	78%	61%	11%	98%
10%	96%	30%	26%	97%

Eur Urol 2016
70 920-923

New Chromosome screen thresholds

Table 1. Summary of current screening thresholds and new proposals

	Current recommended guidelines				
	ASRM [7]	**AUA [8]**	**EAU [9]**	**New data**	**New proposed thresholds**
Y chromosome microdeletions Thresholds	<5 million sperm/ml	No recommendation given	<5 million sperm/ml	Kohn *et al.* [14▪▪] meta-analysis – estimated frequency of YCM: >0–1 million sperm/ml = 5.0% >1–5 million sperm/mL = 0.8% >5–20 million sperm/ml = 0.5%	<1 million sperm/ml
Chromosomal Abnormalities Thresholds	<5 million sperm/ml	<5 million sperm/ml	<10 million sperm/ml	Dul *et al.* [18] review of literature – Frequency of chromosomal abnormalities: Azoospermic men = 15.4% >0–1 million sperm/ml = 3.0% >1–5 million sperm/ml = 2.1% >5–20 million sperm/ml = 2.7% >20 million sperm/ml = 2.9%	Only men nonobstructive azoospermia or specific patients with strong clinical history, such as recurrent pregnancy loss

ASRM, American Society for Reproductive Medicine; AUA, American Urological Association; EAU, European Association of Urology.

Curr Opin Urol 2020, 30:317-323

Workflow for genetic tests

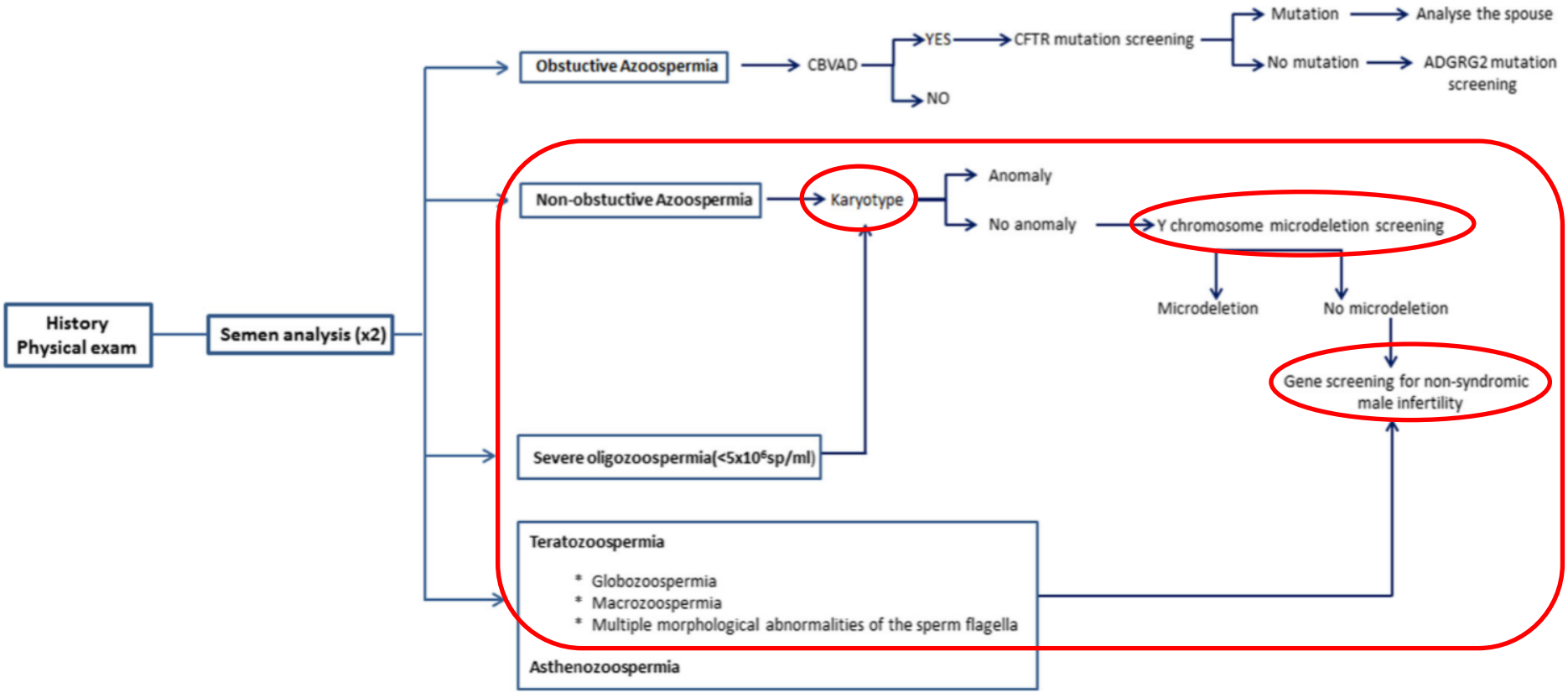


Fig. 1 The workflow for genetic tests in male infertility. According to semen analysis, karyotype, Y chromosome microdeletion testing or specific gene mutation screening can be suggested to patients

Genetic etiological categories

1. Spermatogenic quantitative defects
2. Ductal obstruction
3. Hypothalamic pituitary axis disturbances
4. Spermatogenic qualitative defects

Spermatogenic quantitative disturbance

Chromosome abnormality

Y chromosome deletions(AZFa, AZFb, AZFc)

Spermatogenic quantitative disturbance

Chromosome abnormality

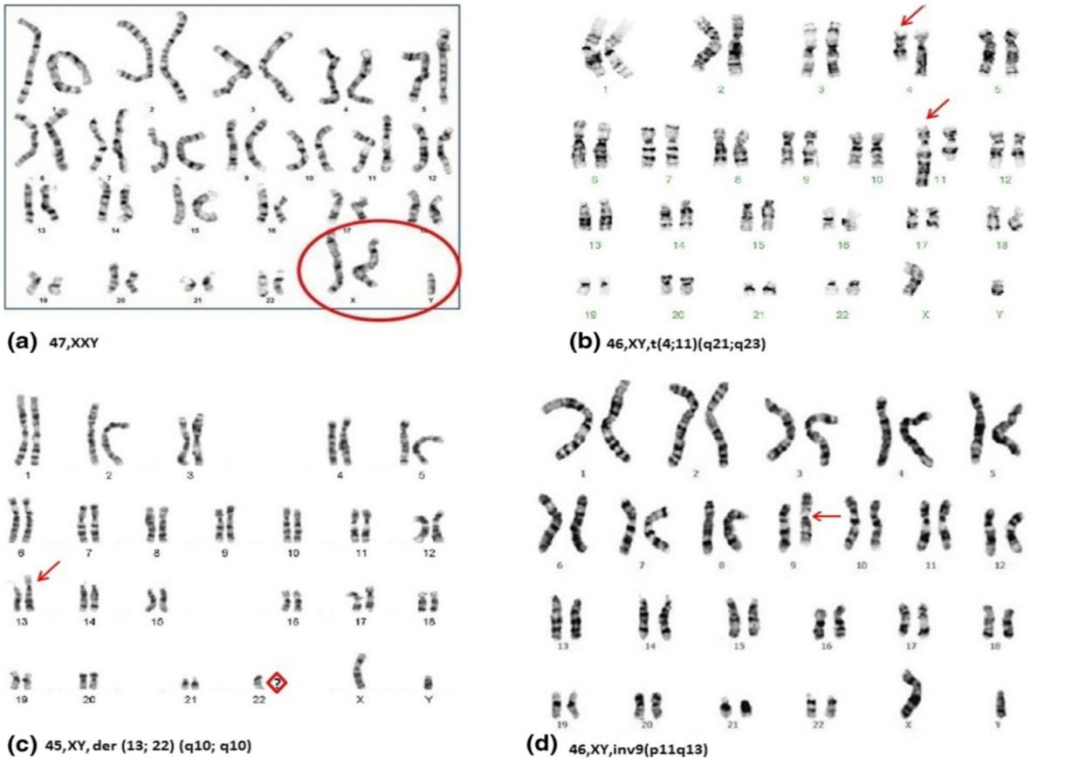
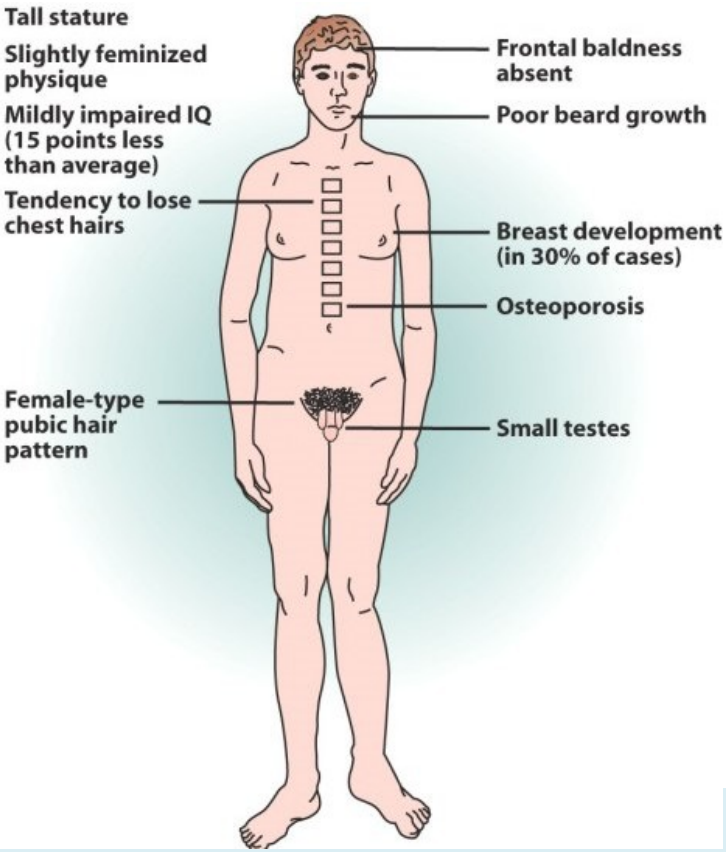


Fig. 2 Examples of karyotype anomalies. **a** Klinefelter syndrome—47,XXY (adopted from www.qfg.com.au). **b** Reciprocal translocation involving chromosome 4 and 11 (adopted from http://what-when-how.com/genetics). **c** Karyotype in patient with Robertsonian translocation involving chromosome 13 and 14 (adopted from Răchişan et al. 2017 [17]). **d** Karyotype of a patient with inversion 9 (adopted from Jeong et al. 2010 [18])

Chromosome abnormality

- Klinefelter syndrome
- (47 XXY, mosaics 46 XY, 47XXY)



Frequency of 1 in 600 in the general population
In patients with NOA, the frequency is 1 in 7

Affected individuals typically have small, firm testes with spermatogenic failure

Chromosome abnormality

- Klinefelter syndrome

Klinefelter syndrome is associated with a general health problems **metabolic syndrome, autoimmune diseases, venous thromboembolism, and cognitive or psychiatric disturbances**

Age is the most important predictive factor for **testicular sperm retrieval** in patients with Klinefelter syndrome who are azoospermia

Success rates are improved in men **below the age of 31 years**

Chromosome abnormality

46 XX male

46,XX male syndrome (de la Chapelle syndrome) has a frequency of 1 in 20,000

Smaller stature and a higher incidence of maldescended testes and azoospermia

Translocation of sex-determining region Y protein (*SRY*) on the X chromosome is responsible

Chromosome abnormality

- 46 XX male

m-TESE is not advised for these patients

(unlike for men with Klinefelter syndrome) owing to the lack of Y chromosome- linked azoospermia factor (AZF) regions, meaning

focal sperm production in the testis is impossible

Chromosome abnormality

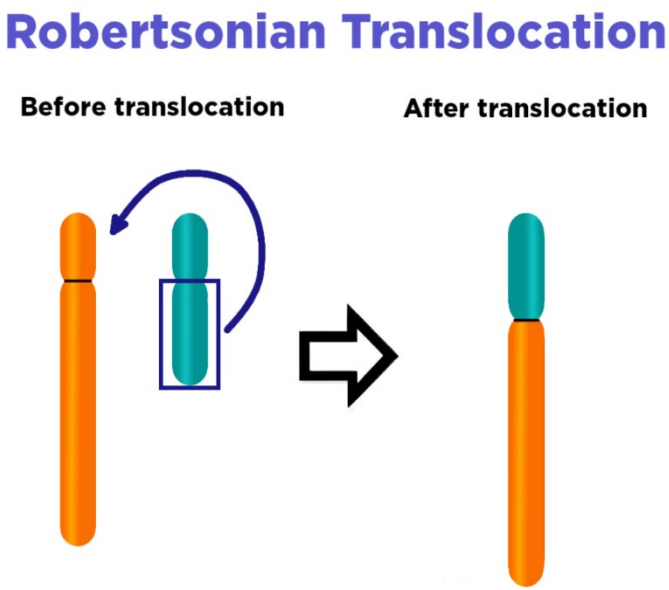
- **Translocation**

These types of aberrations are **10-fold more frequent in men**
with oligozoospermia (4–8%) than in men with normozoospermia

Undergoing **IVF, PGD** should be performed because the presence of structural chromosomal anomalies in the sperm **increases the risk of aneuploidy**

Chromosome abnormality

- Robertsonian translocations



Occur when two acrocentric chromosomes (**chromosomes 13, 14, 15, 21, and 22**) Fuse their long arms, leading to the loss of the genetic material on the short arms

Robertsonian translocations are the most common structural abnormalities, found in 1/1000 newborns and in 0.9 % of the infertile men

Chromosome abnormality

- Robertsonian translocations

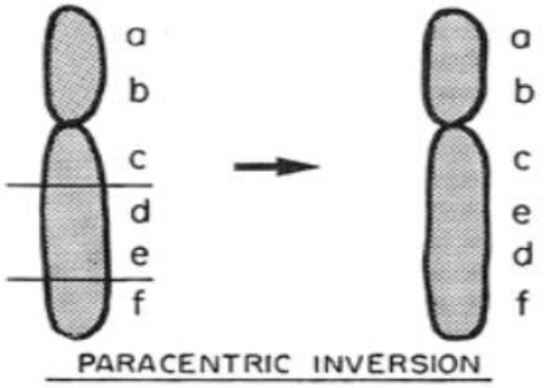
A Robertsonian translocation in **balanced form** results in no excess or deficit of genetic material and causes no health difficulties

In **unbalanced forms, Robertsonian translocations cause chromosomal deletions or addition** and result in syndromes of multiple malformations, including **trisomy 13 (Patau syndrome) and trisomy 21 (Down syndrome)**

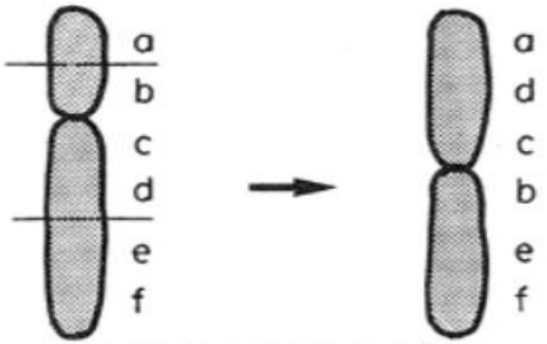
Chromosome abnormality

- Inversion

Male carriers of **chromosome 9 inversions** may show **azoospermia, oligospermia, asthenozoospermia, or normozoospermia**



PARACENTRIC INVERSION

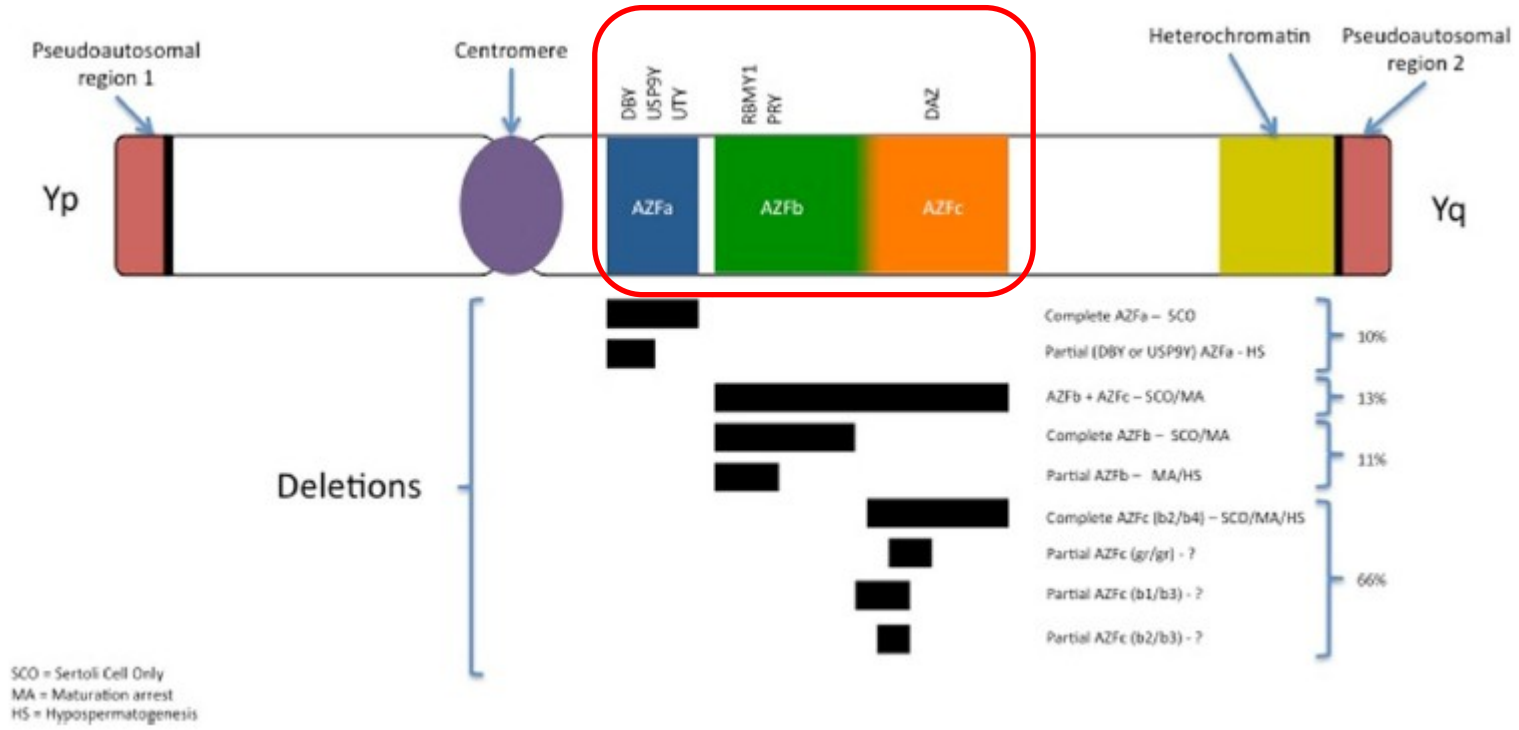


PERICENTRIC INVERSION

They have a **higher incidence of sperm aneuploidy**

Chromosome abnormality

- Y chromosome Microdeletion



Chromosome abnormality

- Y chromosome Microdeletion

These genes are divided in three groups based on their location: **AZFa, AZFb, and AZFc**

Microdeletions located in these zones may impair fertility and are present in **10% of men with NOA** and in **5% of those with severe oligospermia**

Chromosome abnormality

- Y chromosome Microdeletion

Complete deletion of **AZFa is rare (3%)** and carries the **poorest prognosis** of all YCMD

AZFa group contains three main genes: **DBY, USP9Y, and UTY** men have azoospermia and SCO, and **no sperm is found using micro TESE**

These patients should not be submitted to micro-TESE
-> Referred for **donor sperm**

Chromosome abnormality

- Y chromosome Microdeletion

The **AZFb group** is affected in 15 % of YCMD cases, it contains two genes important to spermatogenesis, the **RBMY1 and PRY genes**

RBMY1 : testis-specific splicing factor expressed in the nucleus of spermatogonia, spermatocytes, and round spermatids

PRY : Regulation of GCs apoptosis

Testicular biopsy usually shows SCO

AZFb group patients must use **donor sperm ->Micro-TESE not rec.**

Chromosome abnormality

- Y chromosome Microdeletion

AZFc deletions usually present with azoospermia or, more often, severe oligozoospermia

Histological patterns **vary from SCO, maturation arrest and hypospermatogenesis**

Hypothalamic-pituitary axis disturbances

- Kallman syndrome
- Isolated gonadotropic deficiency

Hypothalamic-pituitary axis disturbances

- Kallman syndrome

Kallmann syndrome has an incidence of 0.2 %

Kallmann syndrome is mainly characterized

by **hypogonadotropic hypogonadism, delayed puberty, infertility, and defective sense of smell**

(anosmia or hyposmia)

Hypothalamic-pituitary axis disturbances

- Kallman syndrome

The syndrome has genetic and phenotypic heterogeneity, and several genes have been associated with this condition **Kallmann syndrome 1 (KAL1)** and the **fibroblast growth factor receptor 1(FGFR1)** are the two most studied KLS genes

Hypothalamic-pituitary axis disturbances

- Kallman syndrome

Mutations affecting the KAL1 gene cause **migration arrest of GnRH-1 neurons**

FGFR1 gene is located on the chromosome 8, and its encoded receptor is part of a signaling pathway implicated in the **olfactory system and GnRH neuron**

Qualitative spermatigenic disturbance

Macrozoospermia

Globozoospermia

Multiple morphological abnormalities of the sperm flagella (MMAF)

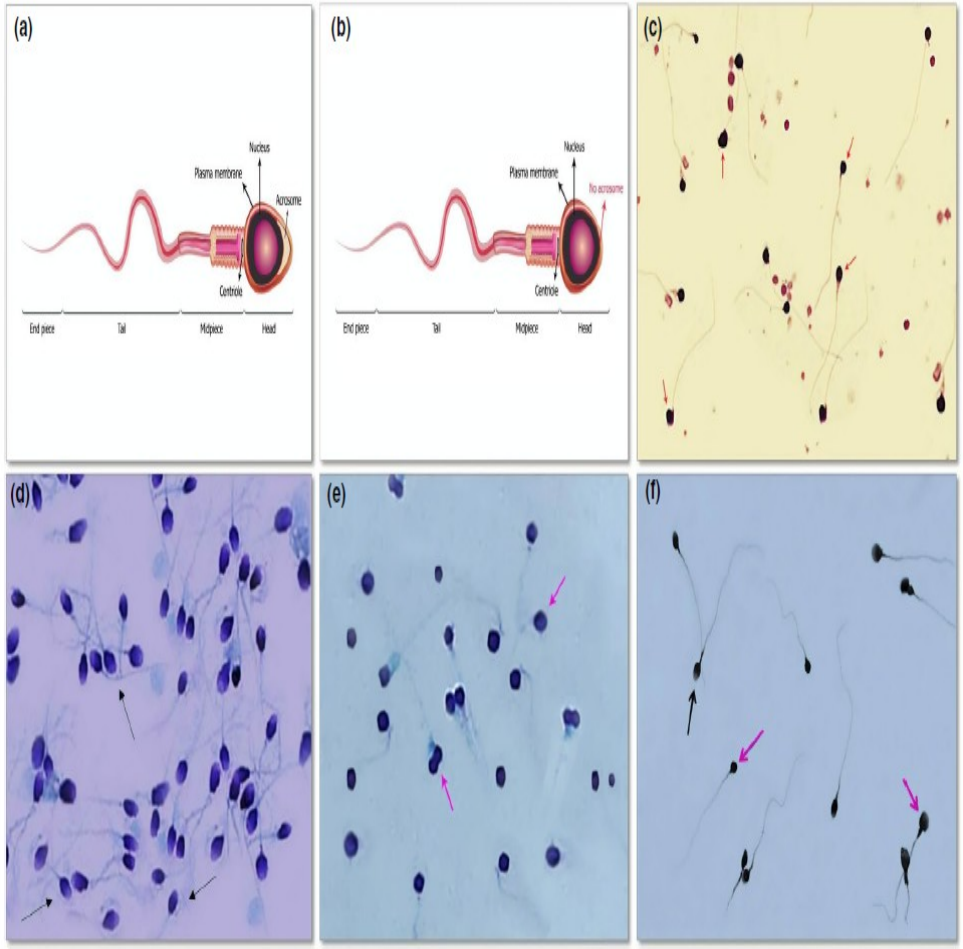
Macrozoospermia

Large- headed and multi flagellated spermatozoa

AURKC mutations are the only validated genetic causes of sperm macrocephaly

AURKC encodes a serine/threonine- protein kinase component of the chromosomal passenger complex in meiotic cells and is essential for correct meiotic chromosomal segregation

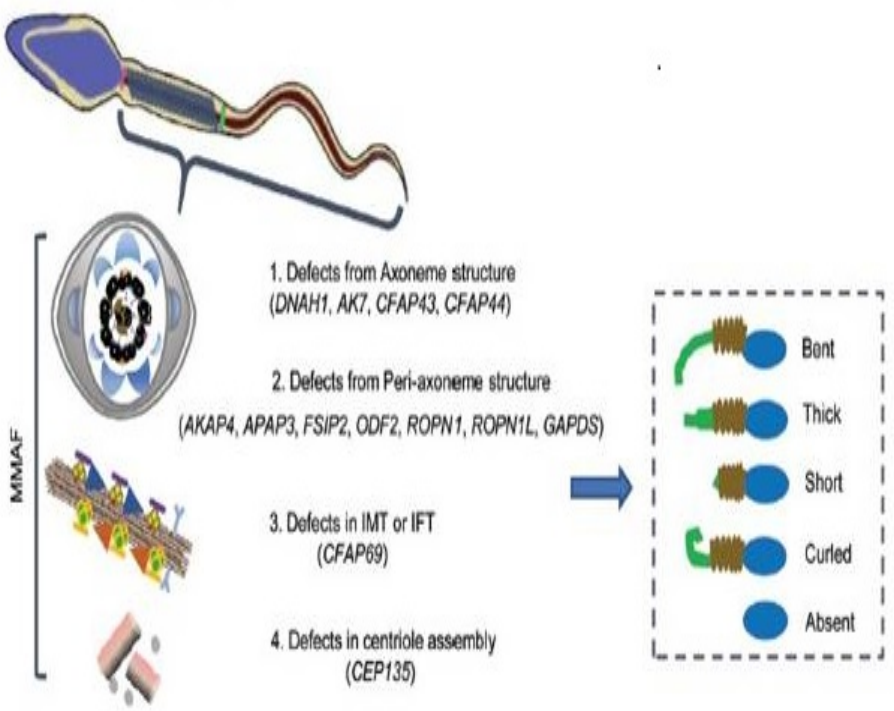
Globozoospermia



Globozoospermia is affecting 0.1% of infertile men, and is characterized by the production of **round- headed, acrosome- less spermatozoa** that are unable to fertilize the oocyte, as **no acrosome reaction** can occur

Genes:
DPY19L2, PICK1, ,SPATA16, ZPBP

Multiple morphological abnormalities of the sperm flagella (MMAF)



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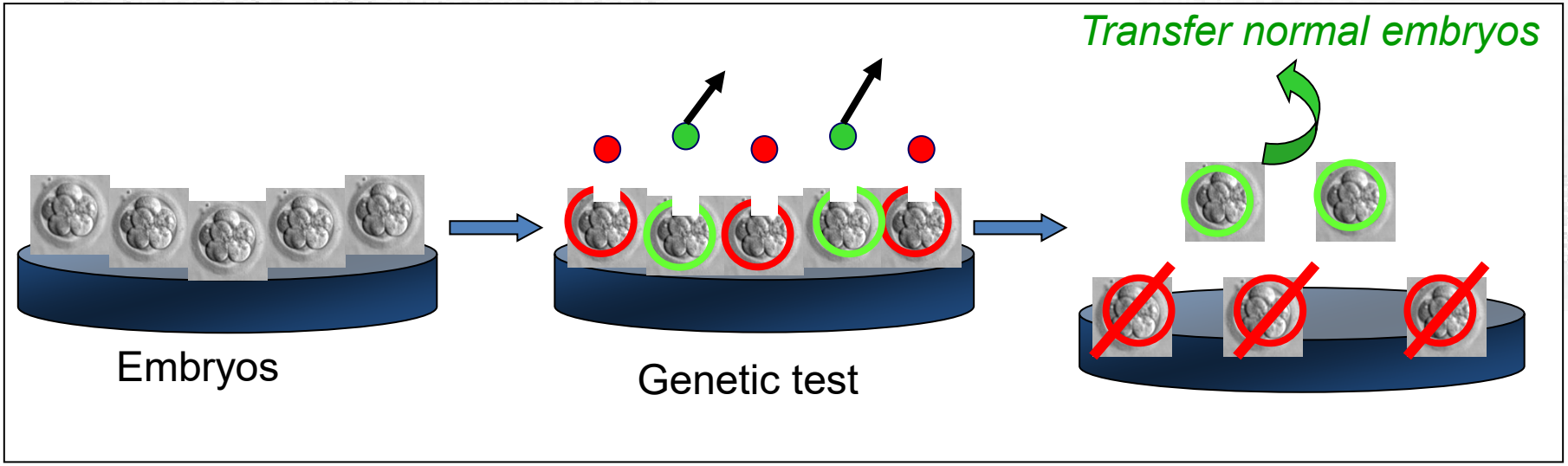
Asthenoteratozoospermia resulting from a mosaic of morphological abnormalities concerning the sperm flagella, including absent, coiled, bent, angulated, irregular, or short flagella

Mutations in **DNAH1** seem to be responsible for 25%

Genetic diseases in Urology which needs PGD (preimplantation genetic diagnosis)

Genetic diseases in Urology which needs PGD



1. ADPKD
2. VHL disease
3. Alport syndrome

Summary & Conclusion

1. Karyotype anaysis: NOA, Multiple abortion, RIF
   Y Chromosome deletion test: NOA, sperm<1mil/ml

2. Objectives of Genetic screening
   -> Diagnosis, prognosis before m-TESE, personalizing tx

3. Gene mutation causing infertility should be screened before IVF-ICSI -> Treatment
   IVF-ICSI with artificial oocyte activation, IVF-ICSI + PGD
   Pharmacogenetics (Personalized hormone therapy)

Thank You!