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REVIEW

New insights into the genetics of spermatogenic failure: a review of the literature

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Abstract

Genetic anomalies are known to affect about 15% of infertile patients with azoospermia or severe oligozoospermia. Despite a throughout diagnostic work-up, in up to the 72% of the male partners of infertile couples, no etiological factor can be found; hence, the cause of infertility remains unclear. Recently, several novel genetic causes of spermatogenic failure (SPGF) have been described. The aim of this review was to collect all the available evidence of SPGF genetics, matching data from in-vitro and animal models with those in human beings to provide a comprehensive and updated overview of the genes capable of affecting spermatogenesis. By reviewing the literature, we provided a list of 60 candidate genes for SPGF. Their investigation by Next Generation Sequencing in large cohorts of patients with apparently idiopathic infertility would provide new interesting data about their racial- and ethnic-related prevalence in infertile patients, likely raising the diagnostic yields. We propose a phenotype-based approach to identify the genes to look for.

Introduction

Genetic anomalies are known to affect about 15% of infertile male patients and in particular those with azoospermia or severe oligozoospermia (Asero et al. 2014). At moment, the genetic diagnostic work-up of male infertility includes the screening of some candidate genes (whose list is progressively increasing) when a central hypogonadism is diagnosed, karyotype analysis, and/or Yq microdeletion in the presence of a primary testicular failure, *CFTR* gene evaluation for the diagnosis of congenital bilateral agenesia of the vas deferens when an obstructive form is suspected (Asero et al. 2014). This work flow has remained unchanged in the last 20 years. Worryingly, despite a throughout diagnostic work-up (including genetic testing), in up to 72% of the male partners of infertile couples no etiological factor can be found and the cause of infertility is elusive (Tüttelmann et al. 2018). Accordingly, a prospective single Centre study on 1737 patients with low sperm count has esteemed the rate of idiopathic oligozoospermia up to 75% (Punab et al. 2017).

Recently, much effort has been made in the attempt to identify novel candidate genes responsible for spermatogenic failure (SPGF) through genome-wide association studies (GWAS). As such, the number of reports of monogenic forms of SPGF is progressively increasing. Whether this genetic selection may impact on survival, as it appears for cancer (Voskarides 2018), has to be demonstrated.

Therefore, the aim of this review was to gather all the available data on the recently identified genetic causes of SPGF, including the clinical feature of the affected patients and the evidence coming up from in-vitro and animal studies, in the attempt to suggest a comprehensive and updated panel of genes to look for. To better understand the possible mechanisms through which such genes may act, the current knowledge on the genetic regulation of spermatogenesis is discussed below.

Physiology of spermatogenesis

Spermatogenesis is a 74 day-long process occurring in seminiferous tubules through which diploid cells develop into haploid mature spermatozoa. It includes three main

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phases: proliferation of spermatogonia, meiotic division of spermatocytes and changes in shape and nuclear content of spermatids (spermiogenesis). Such processes require intimate interaction between germ and somatic cells, such as Sertoli and peritubular myoid cells (Neto et al. 2016; Potter and Falco 2017).

Spermatogonial stem cells (SSCs) are undifferentiated spermatogonia defined by the ability to maintain the potential to self-renew. They differentiate into type A_{paired} and type $A_{aligned}$ spermatogonia which have loss the self-renewal. They latter divide into differentiating spermatogonia that include type $A_{1–4}$ and type B spermatogonia and this takes 16 days. Type B spermatogonia subsequently divide into primary spermatocyte in other 16 days (Chen and Liu 2015).

Several markers are known to be expressed in these cells and act in the regulation of their proliferation or differentiation. In particular, PAX7 and ID4 are expressed in mice SSCs, and among these, PAX7 is detectable also in human SSCs (Chen and Liu 2015). Furthermore, PLZF, a transcription factor required for SSCs self-renewal (Chen and Liu 2015) and SALL4, which removes PLZF from its targets (Liao et al. 2014) have been detected in human spermatogonia (Fischer et al. 2008; Vigueras-Villaseñor et al. 2015). Evidence in mice suggests that the competition PLZF/SALL4 may to be involved in the balance of quiescent and cycling SSCs/progenitor cells (Liao et al. 2014). In addition, POU5F1, c-Kit, PLAP, and AP2γ are required for gonocytes pluripotency in humans (Vigueras-Villaseñor et al. 2015).

Mice undifferentiated spermatogonia (SSCs, type A_{paired} and type $A_{aligned}$) express GFRA1, LIN28, NANOS2, NGN3, NANOS3, PLZF, SALL4, and CHD1proteins (Chen and Liu 2015). Among these, studies on human testicular tissue provide data for NANOS2 being expressed in prenatal germ cells and in spermatogonia, spermatocytes, and round spermatids of the adult testis (Kusz et al. 2009), NANOS3, detected in type A spermatogonia, primary spermatocytes, round and elongated spermatids (Julaton and Pera 2011), PLZF (Fischer et al. 2008), and SALL4 (Kohlhase et al. 2002).

Finally, SOHLH1 and SOHLH2 are selectively expressed in differentiating spermatogonia (Chen and Liu 2015) and coordinate their differentiation in the human (Suzuki et al. 2012). The transcriptional regulator DMRT1, localized in human spermatogonia and spermatocytes (Ying et al. 2007), has been found to induce *Sohlh1* expression in spermatogonia and to repress their commitment to meiosis (Matson et al. 2010).

Primary spermatocytes undergo to the first meiotic division (a 16 day-long process) and differentiate into secondary spermatocytes. The first meiotic division occurs through a complex series of key molecular events happening in prophase, such as programmed double-strand breaks (DSBs) (leptotene), pairing of homologue chromosomes (zygotene), and crossing over (CO) (pachytene) (Pawlowski and Cande 2005).

At first, centriole duplication, which is needed to ensure proper chromosome segregation, happens. It is regulated by Polo-like kinase 4 (PLK-4) (Harris et al. 2011). In mice, *Plk-4* expression is detected starting from pachytene spermatocyte stage and up to the end of spermatogenesis (Harris et al. 2011). Centrosome and spindle integrity, required for chromosome alignment, are ensured by the human augmin complex (Lawo et al. 2009). DSBs are induced by a specific DNA topoisomerase. In detail, SPO11β is the catalytic subunit of the DNA topoisomerase VI-like protein complex, that is indispensable for meiotic recombination (Robert et al. 2016). The human and the mouse SPO11β proteins share the 82% of amino acid identity. In mice, SPO11β is selectively expressed in pachitene spermatocytes when CO occurs (Shannon et al. 1999). After DSBs' formation, the single-strand DNA (ssDNA) is coated by the trimeric replication protein A (RPA) complex, which includes the RPA1, RPA2, and RPA3 subunits. It prevents ssDNA from degradation (Bochkareva et al. 2002).

Pairing of homologous chromosomes requires the synaptonemal complex, a tripartite protein structure of bivalent chromosomes, whose assembly is indispensable for successful progression of the first meiotic division (Fraune et al. 2012). It is made up of two lateral and one central element and requires MEIOB, RAD51, and SPATA22 proteins (Xu et al. 2017). Early during leptotene stage, it is formed along each chromosome and is required for CO.

CO originates from the recombination of double-strand breaks (DSBs) of homologues chromosomes (Souquet et al. 2013), which needs DSBs repair. The complex RAD51/DMC1 is specific for meiotic DSBs repair (Neale and Keeney 2006). MEIOB and SPATA22 ensure RAD51/DMC1 complex stability (Souquet et al. 2013; Xu et al. 2017). Many other proteins seem to play a role in chromosome recombination, such as MSH4, MSH5, TEX11, TEX 15, MLH1/MLH3, SYCE, HSF2, HEI10, RNF212, and CNTD1 (Xu et al. 2017; Xing et al. 2005; Yang et al. 2008).

Once chromosomal recombination occurs, homologous chromosomes split up. This process is called segregation and needs that kinetochores attach to microtubules stemming from the same pole. Ensuing sister chromosomes segregation, daughter cells divide, but they remain connected through intercellular bridges (Greenbaum et al. 2006). The latter have been proposed to play a role in germ-cell communication, synchronization, and chromosome dosage compensation in haploid cells (Greenbaum et al. 2006). TEX14, a testis-specific protein sharing 64% of identity with the mouse homologue, localizes into the intercellular bridges of differentiating spermatogonia until their maturation into spermatozoa and seems to be required for their formation (Greenbaum et al. 2006).

Secondary spermatocytes then undergo to the second meiotic division (taking few hours) during which segregation of sister chromatids occurs (Muller et al. 2013). In addition, after chromatids segregation, cell division results in intercellular bridges (Greenbaum et al. 2006).

Later, spermiogenesis takes place. It is a 26-day-long process during which DNA packaging, acrosome biogenesis, midpiece formation, flagella organization, and cytoplasm expulsion occur. These events enable differentiation of round spermatids in mature spermatozoa (Tournaye et al. 2017). Molecular mechanisms occurring in spermiogenesis are largely unknown. Evidence suggests a role for DPY19L2 (Harbuz et al. 2011) and SIRT1 (Chao et al. 2017) in acrosome synthesis. Genes involved in human flagella and axonema organization have been previously reviewed (Ji et al. 2017).

The disruption of the fine and complex mechanisms regulating spermatogenesis may result in SPGF (Fig. 1).

Candidate genes

We classified candidate genes according to their location in autosomes or heterochromosomes. A complete list of genes thought to cause human SPGF is reported in Table 1. We discussed only the newly identified ones.

X-linked genes

TEX11(Xq13.1) is a conserved gene among vertebrates encoding for a 104 kDa protein that mediates protein–protein interactions. TEX11 is considered a meiosis-specific factor playing a role in DNA DSBs repair (Adelman et al. 2008) and showing the highest level of expression in zygotene spermatocytes and the lowest one in late leptotene spermatocytes (Blatch et al. 1999). In a cohort of azoospermic patients undergone to testis histology, mutations have been detected in the 15% (5/33) of patients with meiotic arrest and in none (0/63) with Sertoli cell only syndrome (SCOS). All patients with *TEX11* mutations had FSH and total testosterone (TT) within the normal range, aside of one patient with partial meiotic arrest [p.A698T (c.2092G>A)] showing few post meiotic cells and high FSH levels (28 IU/l) (Yatsenko et al. 2015). LH and testicular volumes (TV) were not reported (Yatsenko et al. 2015). *TEX11* mutations, most of which causing azoospermia, have already been reviewed (Sha et al. 2018a, b, c). Recently, a novel *TEX11* missense mutation [p.W856C (c.2653G>T)] has been described in two brothers with azoospermia due to meiotic arrest, having hormone values and a mean TV of about 15 ml (Sha et al. 2018a, b, c). These results confirm that *TEX11* is required for human meiosis. Its disruption in expression or function causes the SPGF X-linked, 2 (SPGFX2) (OMIM 309120).

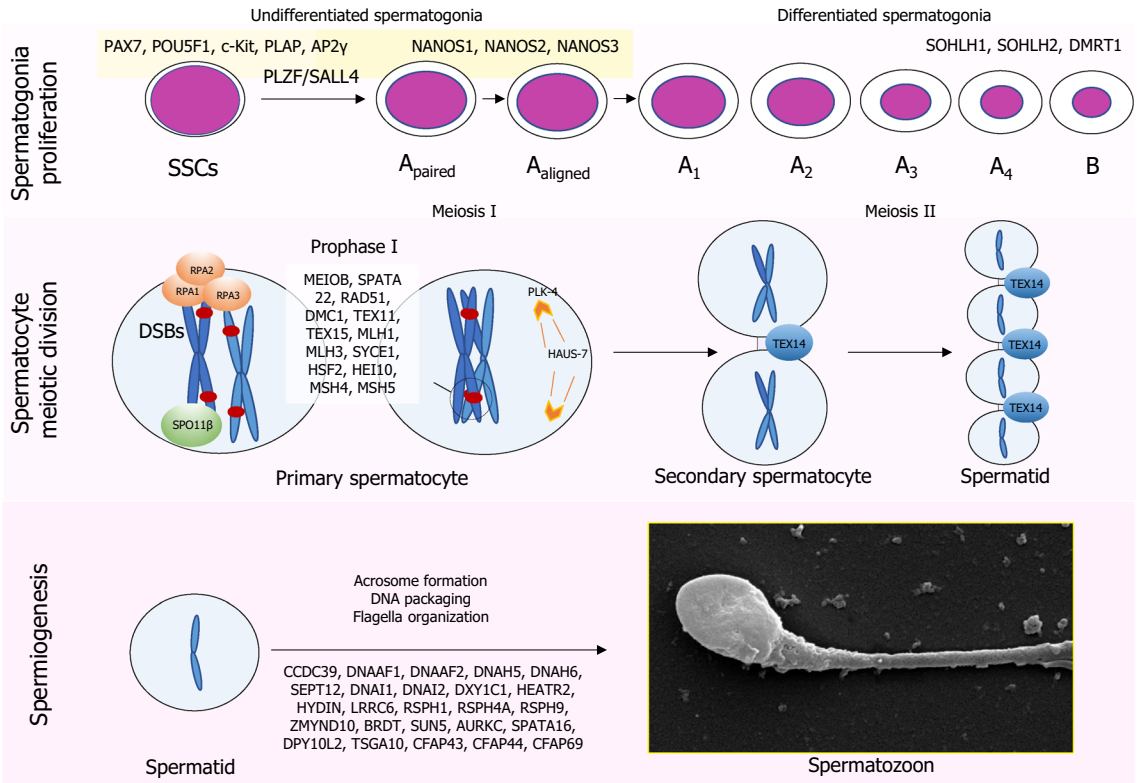

Fig. 1 Genes involved in human spermatogenesis

Table 1 Genes involved in human spermatogenic failure

Gene name	Full name	MIM number	Infertility phenotype	Cytogenetic location	References
AK7	*Adenylate kinase 7*	615364	Flagella abnormalities	14q32.2	Lores et al. (2018)
AURKC	*Aurora kinase C*	603495	Macrozoospermia	19q13.43	Ben Khelifa et al. (2011)
BRDT	*Bromodomain, testis-specific*	602144	Acephalic spermatozoa	1p22.1	Li et al. (2017)
CATSPER1	*Cation channel, sperm-associated, 1*	606389	Oligozoospermia	11q13.1	Avenarius et al. (2009)
CCDC39	*Coiled-coil domain-containing protein 39*	613798	Oligoasthenozoospermia, Flagella abnormalities	3q26.33	Ji et al. (2017)
CEP135	*Centrosomal protein, 135 KD*	611423	Flagella abnormalities	4q12	Sha et al. (2017a, b), Tang et al. (2017), Coutton et al. (2018)
CFAP43	*Cilia- and flagella- associated protein 43*	617558	Flagella abnormalities	10q25.1	Sha et al. (2017a, b), Tang et al. (2017), Coutton et al. (2018)
CFAP44	*Cilia- and flagella- associated protein 44*	617559	Flagella abnormalities	3q13.2	Sha et al. (2017a, b)
CFAP69	*Cilia- and flagella- associated protein 69*	617949	Flagella abnormalities	7q21.13	Dong et al. (2018)
DAZ1	*Deleted in azoospermia 1*	400003	NOA	Yq11.223	Foresta et al. (1999), Mozdarani et al. (2018)
DAZ2	*Deleted in azoospermia 2*	400026	NOA	Yq11.223	Foresta et al. (1999), Mozdarani et al. (2018)
DAZ3	*Deleted in azoospermia 3*	400027	NOA	Yq11.23	Foresta et al. (1999), Mozdarani et al. (2018)
DAZ4	*Deleted in azoospermia 4*		NOA	Yq11.223	Foresta et al. (1999), Mozdarani et al. (2018)
DBY (DDX3Y)	*Dead/H Box 3, Y-linked*	400010	NOA (Spermatocytes maturation arrest)	Yq11.221	Foresta et al. (2000)
DMC1	*Disrupted meiotic Cdna 1, yeast, homolog of*	602721	NOA	22q13.1	He et al. (2018)
DMRT1	*Doublesex- and MAB3-related transcription factor 1*	602424	NOA	9p24.3	Lopes et al. (2013), Tewes et al. (2014), Tüttelmann et al. (2018)
DNAAF1	*Dynein, axonemal, assembly factor 1*	613190	Flagella abnormalities	16q24.1	Ji et al. (2017)
DNAAF2	*Dynein, axonemal, assembly factor 2*	612517	Asthenozoospermia, Flagella abnormalities	14q21.3	Ji et al. (2017)
DNAAF3	*Dynein, axonemal, assembly factor 3*	614566	Flagella abnormalities	19q13.42	Ji et al. (2017)
DNAH1	*Dynein, axonemal, heavy chain 1*	603332	Flagella abnormalities	3p21.1	Ben Khelifa et al. (2014), Amiri-Yekta et al. (2016), Wang et al. (2017), Tang et al. (2017)
DNAH5	*Dynein, axonemal, heavy chain 5*	603335	Asthenozoospermia, flagella abnormalities	5p15.2	Ji et al. (2017)
DNAH6	*Dynein, axonemal, heavy chain 6*	603336	NOA (spermatocytes maturation arrest) Globozoospermia, acephalic spermatozoa	2p11.2	Gershoni et al. (2017), Li et al. (2018a, b)
DNAI1	*Dynein, axonemal, intermediate chain 1*	604366	Asthenozoospermia, flagella abnormalities	9p13-p21	Ji et al. (2017)
DNAI2	*Dynein, axonemal, intermediate chain 2*	605483	Flagella abnormalities	17q25	Ji et al. (2017)
DNAJB13	*DNAJ/HSP40 homolg, subfamily B, member 13*	610263	Flagella abnormalities	11q13.4	El Khouri et al. (2016)

Table 1 (continued)

Gene name	Full name	MIM number	Infertility phenotype	Cytogenetic location	References
DPY19L2	*DPY19-like 2*	613893	Globozoospermia	12q14.2	Koscinski et al. (2011), Harbuz et al. (2011), Ellnati et al. (2012)
DYX1C1 (DNAAF4)	*Dynein axonemal assembly factor 4*	608706	Asthenozoospermia, flagella abnormalities	15q21.3	Ji et al. (2017)
FANCM	*FANCM gene*	609644	NOA	14q21.2	Kasak et al. (2018), Yin et al. (2018)
FSIP2	*Fibrous sheath-interacting protein 2*	615796	Flagella abnormalities	2q32.1	Martinez et al. (2018)
HAUS7	*Haus Augmin-like complex, subunit 7*	300540	Oligozoospermia	Xq28	Li et al. (2018a, b)
HEATR2 (DNAAF5)	*Heat repeat-containing protein 2*	614864	Flagella abnormalities	7p22.3	Ji et al. (2017)
HSF2	*Heat shock-transcription factor 2*	140581	NOA (spermatocytes maturation arrest)	6q22.31	Mou et al. (2013)
HYDIN	*Hydrocephalus-inducing, mouse, homolog of*	610812	Asthenozoospermia	16q22.2	Ji et al. (2017)
KLHL10	*Kelch-like 10*	608778	Oligozoospermia	17q21.2	Yatsenko et al. (2006)
LRRC6	*Leucine-rich repeat-containing protein 6*	614930	Asthenozoospermia, Flagella abnormalities	8q24.22	Ji et al. (2017)
MEIOB	*Meiosis-specific protein with OB domains*	617670	NOA (spermatocytes maturation arrest)	16p13.3	Gershoni et al. (2017)
NR5A1	*Nuclear receptor subfamily 5, group A, member 1*	184757	NOA (spermatocytes maturation arrest), Oligozoospermia	9q33.3	Bashamboo et al. (2010), Ferlin et al. (2015)
PIH1D3	*PIH1 domain-containing protein 3*	300933	Flagella abnormalities	Xq22.3	Paff et al. (2017)
PLK-4	*Polo-like kinase 4*	605031	NOA	4q28.1	Miyamoto et al. (2016)
RSPH1	*Radial spoke head 1, Chlamydomonas, homolog of*	609314	Flagella abnormalities	21q22.3	Ji et al. (2017)
RSPH4A	*Radial spoke head 4A, Chlamydomonas, homolog of*	612647	Flagella abnormalities	6q22.1	Ji et al. (2017)
RSPH9	*Radial spoke head 9, Chlamydomonas, homolog of*	612648	Flagella abnormalities	6p21.2	Ji et al. (2017)
SEPT12	*Septin 12*	611562	OAT	16p13.3	Kuo et al. (2012)
SLC26A8	*Solute carrier family 26 (sulfate transporter), member 8*	608480	Asthenozoospermia	6p21.31	Dirami et al. (2013)
SOHLH1	*Spermatogenesis- and oogenesis- specific basic helix–loop–helix protein 1*	610224	NOA	9q34.3	Choi et al. (2010), Nakamura et al. (2017)
SPATA 16	*Spermatogenesis-associated protein 16*	609856	Globozoospermia	3q26.31	Dam et al. (2007)
SPINK2	*Serine protease inhibitor, Kazal-type, 2*	605753	NOA, OAT	4q12	Kherraf et al. (2017)
SUN5	*SAD1 and UNC84 domain-containing protein 5*	613942	Acephalic spermatozoa	20q11.21	Zhu et al. (2016)
SYCE1	*Synaptonemal complex central element protein 1*	611486	NOA	10q26.3	Maor-Sagie et al. (2015), Huang et al. (2015)

Table 1 (continued)

Gene name	Full name	MIM number	Infertility phenotype	Cytogenetic location	References
SYCP3	*Synaptonemal complex protein 3*	604754	NOA	12q23.2	Stouffs et al. (2005a, b)
TAF4B	*TAF4B RNA polymerase II, TATA Box-binding protein-associated factor*	601689	NOA, oligozoospermia	18q11.2	Ayhan et al. (2014)
TDRD6	*Tudor domain-containing protein 6*	611200	OAT	6p12.3	Sha et al. (2018a, b, c)
TEX11	*Testis-expressed gene 11*	300311	NOA (spermatocytes maturation arrest)	Xq13.1	Yatsenko et al. (2015), Sha et al. (2018a, b, c)
TEX14	*Testis-expressed gene 14*	605792	NOA	17q22	Gershoni et al. (2017)
TEX15	*Testis-expressed gene 15*	605795	NOA	8q12	Okutman et al. (2015), Colombo et al. (2017)
TSGA10	*Testis-specific protein 10*	607166	Acephalic spermatozoa	2q11.2	Sha et al. (2018a, b, c)
USP26	*Ubiquitin-specific protease 26*	300309	NOA	Xq26.2	Ma et al. (2016)
WDR66	*WD repeat-containing protein 66*	618146	Flagella abnormalities	12q24.31	Kherraf et al. (2018)
ZMYND10	*Zing finger mind-containing protein 10*	607070	Flagella abnormalities	3q21.31	Ji et al. (2017)
ZMYND15	*Zing finger mind-containing protein 15*	614312	NOA (spermatocytes maturation arrest)	17p13.2	Ayhan et al. (2014)

NOA non-obstructive azoospermia, *OAT* oligoasthenoteratozoospermia

HAUS7(Xq28) encodes for a component of the human augmin complex, a 8-subunit compound ensuring centrosome and spindle integrity, critical structures for chromosome alignment and separation during mitosis and meiosis (Lawo et al. 2009). The hemizygous variant c.G386T, p.G129V (a highly pathogenic mutation by in silico analysis) has recently been described in two brothers with severe oligozoospermia. They had normal hormone values. TV were not reported (Li et al. 2018a, b).

USP26(Xq26.2) encodes for the ubiquitin-specific protease 26, a testis-specific expressed protein belonging to the family of deubiquitinating enzymes (Wosnitzer et al. 2014). In mice, this protein localizes in blood–testis barrier and near the Sertoli-germ-cell interface (Lin et al. 2011a, b). Stouff and colleagues described three *USP26* variants (c494T-C, p.L165S, c.370_371insACA, c.1423C-T, p.H475Y) in 8/111 (7.2%) patients with SCOS (Stouff et al. 2005a, b). However, among these, two (494T-C and 370_371insACA) were present with significant frequencies in sub-Saharian African and South and East Asian population, including fertile men (Ravel et al. 2006), and therefore, they do not seem to affect spermatogenesis. The c.1082G-A, p.R344W *USP26* transition has been firstly detected in two Han Chinese azoospermic men with arrest at the spermatocyte stage (Ma et al. 2016). The study included a cohort of 776 NOA patients and 709 fertile men. The mutation was not detected in any of controls. Co-immunoprecipitation analysis demonstrated a decreased deubiquitinating activity of the R344W variant and its incapacity to bind the androgen receptor (AR). The authors concluded that this variant may play a role in human SPGF through a disruption in AR function (Ma et al. 2016).

Y-linked genes

DBY(or *DDX3Y*)(Yq11.221) encodes for a conserved RNA DDX3 helicase specifically expressed in pre-meiotic spermatogonial cells, which acts in RNA unwinding, annealing and remodeling of ribonucleoprotein complexes (for review, see Kotov et al. 2017). It maps within the AZFa region, whose deletion causes SCOS. Studies indicate that *DBY*expression is required for human fetal germ-cell proliferation (Kotov et al. 2017). To investigate the role of DBY in the AZFa microdeletion phenotype, Ramathal and coworker developed a line of pluripotent stem cells lacking the AZFa and complemented with *DBY*. These cells were transplanted in mice seminiferous tubules, resulting in the rescuing of spermatogenesis, in contrast with the findings in the AZFa-deleted cell line used as control (Ramathal et al. 2015). These findings strongly support the role of the lack of *DBY* in the determination of the phenotype of patients with AZFa deletion. Accordingly, *DBY* deletions have been identified in patients with SCOS or severe hypospermatogenesis (Foresta et al. 2000).

USP9Y(Yq11.221) encodes for the ubiquitin-specific protease 9 and maps inside the AZFa region. Despite mutations and deletions in this gene have been reported in azoospermic patients (Sun et al. 1999; Foresta et al. 2000), a 513,594-bp deletion in the AZFa region encompassing the *USP9Y* gene has been described in a normozoospermic men, his brother, and father (Luddi et al. 2009). Therefore, it does not seem to be required for normal sperm production.

Genes on autosomes

MEIOB(16p13.3) is an evolutionary conserved protein among vertebrates containing single-strand DNA (ssDNA)-binding sites (Souquet et al. 2013). In mice, its D383 single residue seems to be indispensable for MEIOB, SPATA 22, and PRA interaction (Xu et al. 2017). *Meiob*-deficientmice do not form CO in germ cells and are infertile due to a meiotic arrest (Souquet et al. 2013; Luo et al. 2013). In line with these findings, the homozygosity for a missense mutation of the evolutionary conserved asparagine 64 (N64I) of MEIOB protein (belonging to the RPA1-binding domain) has been reported in patients with NOA. The analysis has been carried out in four brothers having azoospermia. Hormonal data and TV were available only in three of them. Two brothers had FSH and TV with the normal range. The last one had the right TV measuring 5 ml, the left 15 ml and his FSH levels were 13.5 IU/l. Histologic analysis (available only in one brother) showed complete spermatocyte maturation arrest (Gershoni et al. 2017). These results suggest that *MEIOB* is required for meiosis I and that its mutation is associated with complete spermatocyte maturation arrest in humans. *MEIOB* gene mutations are thought to be responsible for SPGF 22 (OMIM 617706).

TEX 14(17q22) encodes for a testis-specific protein of 1497 aminoacidic residues, which is highly conserved among mammals. It includes an ankyrin repeated domain and a protein kinase-C domain. It localizes in germ-cell intercellular bridges (Greenbaum et al. 2006) and acts in the inactivation of germ-cell division (Kim et al. 2015). In *Tex 14*$^{-/-}$ mice, spermatogenesis halts before the achievement of the first meiotic division (Greenbaum et al. 2006). In addition, a 51-bp (bp) exonic insertion in *TEX 14* (resulting in a truncated protein) has been reported to cause maturation arrest at early meiotic phase of spermatogenesis in pigs (Sironen et al. 2011). A 10 bp deletion in *TEX 14* (exon 16: 2668-2678del), resulting in a truncated protein, has recently been reported in two azoospermic brothers. In accordance with the findings in animals, histologic section showed spermatogonia in all the tubules and few spermatocyte cells, thus suggesting that also in humans, TEX 14 may be required for the early phase of the first meiotic division. Hormonal findings and TV were reported only in one brother, showing normal TV (29 ml, bilaterally) and FSH levels of 12.2 U/l (Gershoni et al. 2017). LH and TT values were within the normal range. *TEX 14* mutations cause the SPGF 23 (OMIM 617707).

DNAH6(2p11.2) is a poorly characterized gene encoding for a testis-specific expressed protein (belonging to the dynein family proteins) that has very recently been identified in the neck region of spermatozoa (Li et al. 2018a, b). Although its role in spermatogenesis is unknown, the homozygosity for the H3471Q missense mutation has been identified in two azoospermic brothers showing complete spermatocyte maturation arrest. They displayed normal FSH serum levels and borderline TV (right TV measured 8 and 10 ml, respectively, left TV measured 15 ml in both patients). One patient had an history positive for right cryptorchidism. LH and TT values were in the normal range. The other members of the family were carries of the mutation but did not show NOA. At the light of such findings, this gene has been hypothesized to play a role in rapid prophase movements (Gershoni et al. 2017). Furthermore, compound heterozygous variants in *DNAH6* have been described in a patient with globozoospermia and acephalic spermatozoa (Li et al. 2018a, b).

NR5A1(9q33.3), also called *steroidogenic factor*, encodes for a transcription factor involved in the expression and regulation of genes known to play a role in steroidogenesis, sexual differentiation, and reproduction. Its mutations have been associated with a wide spectrum of phenotypes, such as 46,XY partial and complete gonadal dysgenesis with or without adrenal failure, hypospadias, micropenis and anorchia, and 46,XX primary ovarian insufficiency (Lin et al. 2008; Lourenco et al. 2009).

Among a cohort of infertile patients, *NR5A1* mutations have been identified in the 3.9% (4/103) azoospermic or cryptozoospermic patients, in the 4.3% (2/48) of the patients with severe oligozoospermia (sperm concentration < 1 million/ml), and in the 2% (1/50) of the patients with moderate oligozoospermia (sperm concentration from 1 to 10 million/ml). No mutations have been reported in fertile and normozoospermic men or in patients with mild oligozoospermia (sperm count > 10 million/ml) (Bashamboo et al. 2010). Similar findings have been reported also elsewhere (Ferlin et al. 2015).

In contrast with these results, no *NR5A1* mutation has been found in a cohort of 414 Indian patients with NOA (Sudhakar et al. 2018). From the histologic point of view, *NR5A1* missense mutations result in SCOS, severe hypospermatogenesis or partial spermatocyte arrest in NOA patients (Bashamboo et al. 2010; Ferlin et al. 2015). Considering all cases reported, azoospermic patients with *NR5A1* mutations more frequently display high FSH levels (> 10.7 UI/ml) and may exhibit also high LH levels but normal TT values. The mean TV has been reported ranging from 7 to 12.2 ml (Bashamboo et al. 2010; Ferlin et al.

2015). The point mutations p.Arg191Cys (c.571C>T), p.Gly212Ser (c.634G>A), and p.Asp238Asn (c.712G>A) have been described in patients with severe oligozoospermia (< 1 million/ml) and high FSH serum levels. p.Gly123Ala (c.368G>C)/p.Pro129Leu (c.386C>T) have been detected in patients with moderate oligozoospermia (1–10 million/ml) and normal FSH levels (Bashamboo et al. 2010). Currently, *NR5A1* mutations cause the SPGF 8 (OMIM 613957).

SOHLH1(9q34.3) encodes for the spermatogenesis- and oogenesis-specific basic helix–loop–helix protein 1, which is involved in spermatogonia differentiation with the *SOHLH2* (13q13.3) as well, likely by the regulation of genes involved in SSC pluripotency maintenance (Suzuki et al. 2012). The heterozygosis for the c.346-1G-A splice site mutation has been reported in two of 96 Korean (Choi et al. 2010) and in two of 40 Japanese (Nakamura et al. 2017) NOA patients. No *SOHLH2* mutation in human SPGF has been reported so far.

Nanos gene encodes for a translational regulator of specific mRNA involved in Drosophila germ-cell development. *Nanos 2* and *Nanos 3* play a role in mice spermatogenesis. The human orthologous *NANOS 1*(10q26.11) seems to be involved in germ-cell development. Indeed, the heterozygosis for the deletion of two single aminoacidic residues (p.Ser78del or p.Ala173del) has been identified in Polish azoospermic patients with low TV (6–10 ml) and high FSH (15.4–18.2 IU/l) levels. The histologic feature, available only in one patient, showed SCOS (Kusz-Zamelczyket al. 2013). Furthermore, the *NANOS1* missense mutations pArg246His and Arg276Tyr have been reported in patients with severe oligozoospermia (Kusz-Zamelczyk et al. 2013). Mutations of this gene cause the SPGF 12 (OMIM 615413).

TAF4B(17p13.2), also called *TAFII105*, encodes for a protein of 862 amino acidic residues, belonging to the family of TATA box-binding proteins (TAFs). Gathering with the TATA-binding protein (TBP), TAFs form the TFIID complex, that is involved in the initiation of gene transcription by RNA polymerase II. TAF4B is predominantly expressed in testis (Freiman et al. 2001). Although its exact role in spermatogenesis is unclear, *Taf4b*-null male mice became infertile by 3 months, due to an impaired gonocytes proliferation (Falender et al. 2005).

In humans, the nonsense mutation TAF4B p.R611X has been observed in four brothers, three with azoospermia, and one with oligozoospermia (6 million/ml) (Ayhan et al. 2014). This mutation results in a truncated protein of 252 residues, lacking the histone fold domain (residues 653–702) (which increases the DNA-binding activity of TAFs) and the TAF12 interaction domain (residues 830–862) (that promotes the interaction with TAF12). FSH levels of affected men were increased (its values have not been reported). TV and testis histology are not available (Ayhan et al. 2014). *TAF4B* is involved in SPGF 13 (OMIM 601689).

ZMYND15(17p13.2) encodes for a testis-specific histone deacetylase-dependent transcriptional repressor which has been suggested to control normal temporal expression of haploid cell genes (e.g., *Prm1, Tnp1, Spem1*, and *Catsper3*) during spermatogenesis.

In mice, its inactivation results in late spermatids depletion (Yan et al. 2010). Testis histology from azoospermic patients with a nonsense *ZMYND15* mutation (p.K507Sfs*3) showed maturation arrest at the spermatid stage. Many primary and secondary spermatocytes and very few spermatids were observed (Ayhan et al. 2014). This mutation resulted in a truncated protein lacking the Pro-rich domain which is essential for the binding of signal transduction and cytoskeleton proteins (Kay et al. 2000).

The mutation has been identified in three azoospermic brothers. Only in one, TESA resulted in twins. FSH levels of affected men were increased. TVs were not available. These findings suggest that, in humans, *ZMYND15* may play a role in meiosis II, which is required for spermatid differentiation. Finally, its expression in testis of azoospermic patients has recently been shown to predict a successful sperm retrieval among patients with NOA (Hashemi et al. 2018). *ZMYND15* mutations are responsible for SPGF 14 (OMIM 615842).

SYCP3(12q23.2) encodes for the synaptonemal complex protein 3, which has a key role in the first meiotic division (Fraune et al. 2012). In mice, a null mutation of *Sycp3* causes azoospermia with meiotic arrest (Yuan et al. 2000).

A deletion (643delA) of *SYCP3* resulting in a truncated protein has been described in 11% (2/19) azoospermic patients with maturation arrest and in no fertile controls (0/75). FSH and TV values have not been reported (Miyamoto et al. 2003). Such prevalence may reasonably be overestimated, since in a subsequent study, no *SYCP3* mutations have been reported among a cohort of 58 patients with azoospermia and maturation arrest (Stouffs et al. 2005a, b). This gene is currently believed to be responsible for SPGF 4 (OMIM 270960).

HSF2(6q22.31) encodes for a protein belonging to the HSFs family, which activates target genes under stress conditions. In mice, *Hsf2* has been shown to interact with the promoter region of the *hsp70i* gene. Its blocking reduced cell survival (Xing et al. 2005). *Hsf2*-null mice showed structural defects in the synaptonemal complex of pachytene spermatocytes and developing spermatocytes were eliminated via apoptosis (Kallio et al. 2002). In humans, three synonymous mutations and five missense mutations of HSF2 have been identified in azoospermic patients with maturation arrest at the spermatocyte stage. FSH and TV levels of azoospermic patients with an *HSF2* mutation have not been reported (Mou et al. 2013).

SYCE1(10q26.3) encodes for the synaptonemal complex central element protein 1, a testis-specific 329-aminoacidic protein, which is essential during meiotic prophase I (Fraune

et al. 2012). In *Syce*-null mice, meiosis is arrested at prophase I (Bolcun-Filas et al. 2009).

The homozygosis for a splice site mutation resulting in a premature stop codon has been identified in two azoospermic brothers of Iranian–Jewish origin with spermatocytes maturation arrest. No abnormalities in FSH serum levels and TV were found (Maor-Sagie et al. 2015). Furthermore, the homozygosis for a 134-kb deletion on chromosome 10 encompassing the *SYCE* gene has been described in three Chinese patients with spermatocyte maturation arrest. The heterozygosis for this deletion was observed both in patients with NOA and in fertile controls (Huang et al. 2015). These findings support a role for *SYCE* disrupted function in the pathogenesis of NOA in humans. Accordingly, its mutations cause SPGF 15 (OMIM 616950).

TEX15(8p12) encodes for a testis-specific protein of 2.785-aminoacidic residues playing a role in DNA DSBs repair (Yang et al. 2008). Male (but not female) *Tex15*-null mice have early meiotic arrest (Yang et al. 2008).

A nonsense mutation (c.2130T>G, p.Y710*) leading to a premature stop codon has been described in patients with azoospermia (Okutman et al. 2015). Their testicular histology showed maturation arrest at the primary spermatocyte stage. The mean TV was 10–12 ml. FSH serum levels are not available. The compound heterozygosis for a nonsense mutation (c.2419A>T, p.Lys807*) and a single-nucleotide deletion (c.3040delT, p.Ser1014Leufs*5) leading to premature stop codons has been identified in two brothers with NOA and high FSH (16.7 and 14.1 IU/l; respectively), high LH (12.5 and 11.3 IU/l), and borderline-low TT (3.1 and 3.5 ng/ml) levels. The other family members carrying the single mutation were fertile (Colombo et al. 2017). *TEX 15* gene is currently believed to be responsible for SPGF 25 (OMIM 605795).

PLK-4(4p28.1) seem to play a role in germ-cell maintenance. In mice, its point mutation causes germ-cell loss (Harris et al. 2011). In humans, among 81 patients with histologically documented SCOS and different serum FSH levels, a heterozygous 13 bp deletion in the Ser/Thr domain of PLK4 was identified in one patient (Miyamoto et al. 2016).

DMRT1(9p24.3) encodes for a testis-specific transcription factor playing a role in testis differentiation. Deletions of the 9p chromosome including DMRT1 are well known associated with the 9p deletion syndrome and XY gonadal dysgenesis (Vinci et al. 2007). Smaller deletions (Lopes et al. 2013) and mutations (Tüttelmann et al. 2018) of this gene have been identified in NOA patients (Tüttelmann et al. 2018) without XY gonadal dysgenesis.

SEPT12(16p13.3) encodes for a testis-specific GTB-binding protein, which concentrates in the acrosome in the first step of spermiogenesis (Lin et al. 2011a, b). The heterozygosity for a transition mutation (c.584G>A/p.Asp197Asn) interfering with GTP binding has been described in a patient with a severe oligoasthenozoospermia. FSH and TV values have not been reported (Kuo et al. 2012). *SEPT12* gene is the hallmark of SPGF10 (OMIM 611562).

KLHL10(17q21.2) encodes for an evolutionary conserved protein exclusively expressed in spermatids. The c.647A>C (Q216P) (p.Gln216Pro) and the c.937G>A (A313T) p.Ala313Thr missense mutations, both affecting KLHL10 homodimerization, have been identified in patients with mild and moderate oligozoospermia. FSH and TV values have not been reported (Yatsenko et al. 2006). *KLHL10* gene is the hallmark of SPGF 10 (OMIM 608778).

CATSPER1(11q13.1) encodes for a protein which mediates calcium entry into spermatozoa. The c.539-540insT (p.Lys180LysfsX8) and c.948-949insATGGC (p.Asp317MetfsX18) mutations, which are predicted to lead to frameshifts and premature stop codons, have been described in patients with oligozoospermia. Their FSH and TV values have not been reported (Avenarius et al. 2009). *CATSPER1*is responsible for SPGF 7 (OMIM 612997).

A complete and updated list of genes is available in Table 1.

Racial disparities

Genetic basis of racial disparity has emerged as a significant unexpected aspect of medical diagnosis. Several studies have addressed the role of racial and ethnic differences in female reproductive potential (Butts et al. 2010). In men, due to genetic inheritance, specific polymorphisms and/or genetic variations of genes influencing spermatogenesis may gather together in some ethnic groups more than in others. On this account, the *SPO11* gene (OMIM 605114) C631T polymorphism predisposes to male infertility in Chinese, but not in Iranian people (Ren et al. 2017). Similarly, *MEI1* gene (OMIM 608797) C1791A and C2397T polymorphisms associate with azoospermia in European American but not in Israeli and Japanese (Sato et al. 2006). Limited to the evidence coming from cohort studies, *NR5A1* mutations might occur with a higher frequency in Caucasian compared to Indian men (Bashamboo et al. 2010; Ferlin et al. 2015; Sudhakar et al. 2018). In addition, *SOHLH1* variants have been described in Asiatic countries (Choi et al. 2010; Nakamura et al. 2017), but no other ethnic groups have been analyzed as far. *SYCE* mutations have also been reported in Iranian–Jewish men and Chinese patients (Maor-Sagie et al. 2015; Huang et al. 2015). Finally, studies indicate two *USP26* variants as frequently occurring among sub-Saharian African and South and East Asian population, including fertile men (Ravel et al. 2006). Therefore, it is recommended to extend the evaluation of the key genes hypothesized to be responsible of SPGF (Table 1) to large cohorts of different race and ethnicity, including fertile men. This may shed light

into the understanding of the impact of racial disparities in male infertility, prevalence of genetic SPGF, and the real pathogenic role of the investigate genes.

Population origin of gene responsible for SPGF as well as gene variants is reported in the Supplementary Table 1.

Cryptorchidism and mini-puberty: genetic background and impact on spermatogenesis

Cryptorchidism often associates with SPGF (Kalfa et al. 2019). The reason of such association might be the insufficient testosterone secretion during mini-puberty in cryptorchidic children (Živković and Fratrić 2014). Studies indicate that the GnRH-induced raise in LH and testosterone levels induce the maturation of gonocytes into type A spermatogonia during mini-puberty. The lack of secretion of these hormones disrupts both type A spermatogonia differentiation and Sertoli cell proliferation. Mini-puberty modulates Sertoli cell gene expression. Indeed, GnRH administration in testis negative for type A spermatogonia at the histologic levels increases *FASLG* and *GDNF* expression, thus possibly promoting Sertoli cell proliferation and germ-cell self-renewal (Gegenschatz-Schmid et al. 2018).

Genetic factors, as well as intra-uterine environment, play a role in the pathogenesis of cryptorchidism and in the modulation of its prevalence due to genetic–environment interaction. Accordingly, the prevalence of cryptorchidism is higher in patients with a familiar history positive for cryptorchidism compared to those with a negative one (Urh et al. 2018). Nevertheless, the specific genetic abnormality causing cryptorchidism is rarely identified. Table 2 provides a list

Table 2 Genes involved in cryptorchidism

Homo sapiens	Isolated cryptorchidism	*INSL3* (146738), *RXFP2* (606655), *AR* (313700), *HOXA10* (142957), *SF1* (601516), *AXIN1* (603816), *VAMP7* (300053), *OTX1* (600036), *UPF2* (605529), *NUCB2* (608020), *FGFR1* (136350), *FGFR3* (134934), *FGF1* (131220), *FGF2* (134920), *FGF4* (164980), *FGF5* (165190), *FGF6* (134921), *FGF7* (148180), *FGF8* (600483), *FGF9* (600921), *FGF10* (602115), *FGF11* (601514), *FGF12* (601513), *FGF13* (300070), *FGF14* (601515), *FGF16* (300827), *FGF17* (603725), *FGF18* (603726), *FGF19* (603891), *FGF20* (605558), *FGF21* (609436), *FGF22* (605831), *FGF23* (605380)
	Cryptorchidism associated with germ cell testicular tumor	*RBFOX1* (605104), *RBFOX3* (616999), *ADAMTSL1* (609198), *CNTN4* (607280), *CSMD1* (608397), *DNAH11* (603339), *ERG* (165080), *FHIT* (601153), *PTPRD* (601598), *BMP7* (112267), *TGFBR3* (600742)
	Syndromic cryptorchidism	Aarskog–Scott syndrome: *FGD1* (300546) Beckwith–Widemann syndrome: *CDKN1C* (130650), *ICR1* (616186) BRESEK/BRESHECK syndrome: *MBTPS2* (300294) CAKUT syndrome: *GFRA1* (601496), *RET* (164761) Cardiofaciocutaneous syndrome: *BRAF* (164757), *MAP2K2* (601263) Carpenter syndrome: *MEGF6* (604266) Carpenter syndrome: *RAB23* (606144) CHARGE syndrome: *CHD7* (608892) Costello syndrome: *HRAS* (190020) HJCYS syndrome: *NOTCH2* (600279) Kallmann syndrome: *ANOS1* (300836), *CHD7* (608892), *PROK2* (607002), *PROKR2* (607123), *SEMA3A* (603961) KBG syndrome: *ANKRD11* (611192) Leopard syndrome: *PTPN11* (176876), *RAF1* (164760) Martsolf syndrome: *RAB3GAP2* (609275) MDP syndrome: *POLD1* (174761) Meier–Gorlin syndrome: *CDT1* (605525), *ORC1* (601902), *ORC6* (607213) MEND syndrome: *EBP* (300205) Noonan syndrome: *KRAS* (190070), *PTPN11* (176876), *RAF1* (164760), *RIT1* (615355), *SOS1* (182530) OCRL syndrome: *OCRL* (300535) OKS syndrome: *MED12* (300188) Persistent Müllerian duct syndrome: *AMH* (600957) Popliteal pterygium syndrome: *IRF6* (607199) Prune Belly syndrome: *CHRM3* (118494) Smith–Fineman–Myers syndrome: *ATRX* (300032) Sotos syndrome: *NSD1* (606681)
Mice and rat models	Isolated cryptorchidism	*B-catenin, Ptgds, Hoxa11, Wt1, Adamts 16, Desrt, GnRH, GnRHr, LHr, Erα, P450arom, Cgrp*

Gene (MIM number)

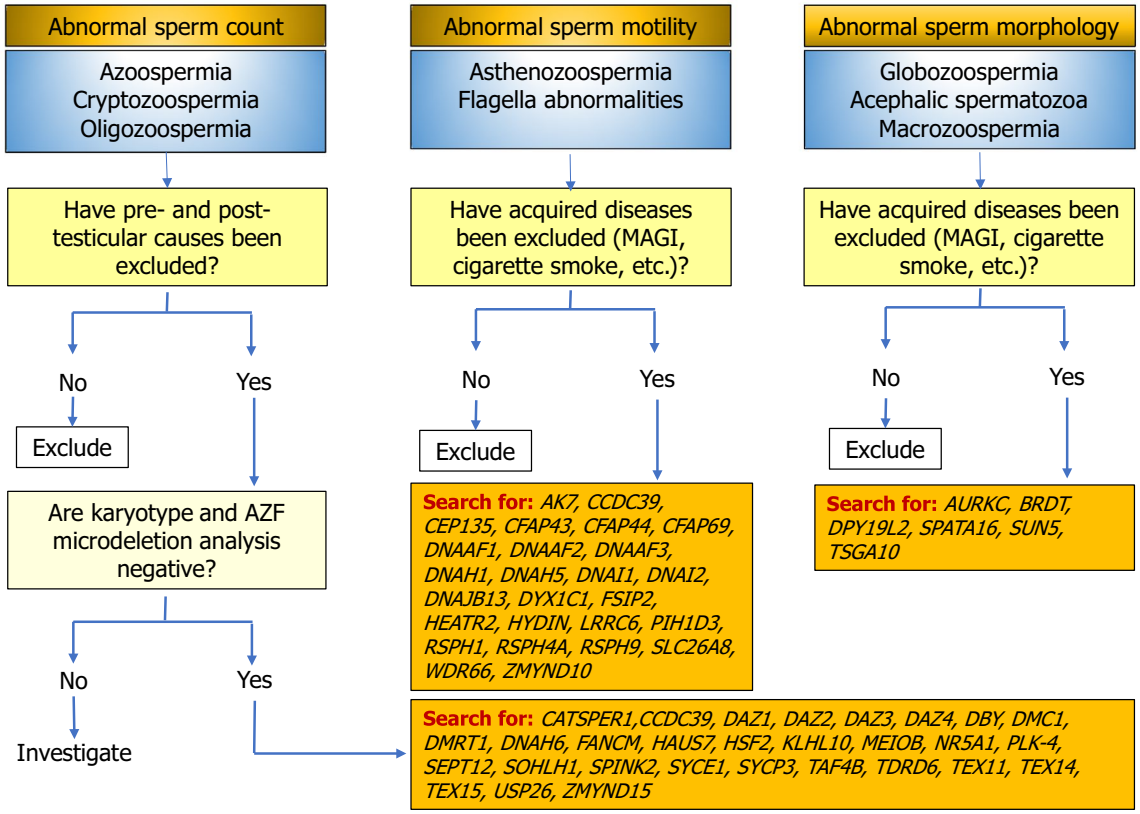

Fig. 2 Genetic work-up for spermatogenetic failure

of the currently known genes responsible for isolated cryptorchidism, associated with germ-cell tumors or syndromic forms. It further shows those genes identified in mice and rat models, which may represent candidate ones for the human being (Urh et al. 2018; Wang et al. 2018; Kalfa et al. 2019).

Despite the association between cryptorchidism and SPGF (Kalfa et al. 2019), there is a lack of knowledge on the possible implication of these genes (Table 2) in human SPGF. To overcome this, such genes might be encompassed in the list of those to search for in patients with SPGF.

Conclusion and future perspectives

In conclusion, male infertility is a widespread disease and it has been esteemed up to 75% the rate of idiopathic oligozoospermia (Punab et al. 2017). Genetic diagnostic work-up is usually suggested in case of azoospermia and severe oligozoospermia, having these forms a greater probability to hide a genetic abnormality compared to the other less severe sperm parameter abnormalities (Asero et al. 2014).

In recent years, mutations of several genes have been firstly identified in men with SPGF. Preliminary data seem to support that looking for mutations of such candidate genes in patients with unexplained azoospermia or severe oligozoospermia would improve patient care (Tüttelmann et al. 2018). Indeed, the analysis of *TEX11, NR5A1*, and *DMRT1* genes in 80 patients with non-obstructive azoospermia (NOA), normal karyotype, and no Yq microdeletions resulted in the discovery of likely etiopathogenic mutations in 4 patients (accounting for the 5% of the whole cohort), thus increasing the diagnostic rate up to 25% (Tüttelmann et al. 2018). On this account, the detection of a broaden diagnostic panel of genes in patients with apparently idiopathic NOA or severe oligozoospermia may increase the probability to achieve a diagnosis.

By reviewing the literature, we provided a list of 60 candidate genes for SPGF (Table 1). Their investigation by NGS in large cohorts of patients with apparently idiopathic infertility would provide new interesting data about their prevalence in infertile patients (also according with race and ethnicity), likely raising the diagnostic yields (Tüttelmann et al. 2018). The assessment of mutations in candidate genes might be performed on the basis of the clinical phenotype (Fig. 2). Furthermore, hopefully multicenter, studies are needed.

Author contributions RC: conception and design of the study, data acquisition, analysis and interpretation of data, drafting and writing

of the article, and final approval of the manuscript. RAC: data acquisition, analysis and interpretation of data, and final approval of the manuscript. YD: data acquisition, analysis and interpretation of data, and final approval of the manuscript. SLV: data acquisition, analysis and interpretation of data, and final approval of the manuscript. AEC: conception and design of the study, analysis and interpretation of data, critical final revision of the manuscript, and final approval of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interests in this study.

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