


# Molecular genetic mechanisms of teratozoospermia

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## Review Article

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## Summary

In recent years, the incidence of teratospermia has been increasing, and it has become a very important factor leading to male infertility. The research on the molecular mechanism of teratospermia is also progressing rapidly. This article briefly summarizes the clinical incidence of teratozoospermia, and makes a retrospective summary of related studies reported in recent years. Specifically discussing the relationship between gene status and spermatozoa, the review aims to provide the basis for the genetic diagnosis and gene therapy of teratozoospermia.

## 1. Introduction

According to the definition of the World Health Organization, infertility means that a couple cannot become pregnant naturally within 1 year after normal intercourse without contraception (Ford, 2010). Here, 10–15% of gestational-age couples in the world are infertile, and male infertility accounts for 50%. Teratozoospermia may be the main cause of male infertility (Coutton *et al.*, 2015). Teratozoospermia is a disease in which there a high proportion of abnormal sperm counts in semen, which greatly impairs male fertility and is a common cause of fertilization failure. It is characterized by defects in sperm morphology. The percentage of sperm with normal morphology is less than 4%, mainly divided into head, neck, middle, and/or tail defects (Yatsenko *et al.*, 2012). Abnormal sperm morphology can lead to decreased vitality and affect fertility (Sha *et al.*, 2017a).

The pathogenesis of teratozoospermia is still unclear, and it is generally believed to be related to factors such as inflammation, oxidative stress, obesity, and genetics. With the continuous improvement in research methods, studies have shown that sperm is regulated by genes in the process of formation. Gene deletion, mutation, and abnormal expression may all lead to the formation of abnormal sperm. Therefore, identifying the related genes that cause teratozoospermia and clarifying its mechanism of action have important practical significances for the occurrence, development, diagnosis, and treatment of teratozoospermia.

## 2. Overview of teratospermia

### 2.1 Definition of teratozoospermia

Sperm morphological defects can be divided into head defects, neck and mid-segment defects, main-segment defects, and excess residual cytoplasm.

Malformation of the sperm head includes globozoospermia, macrozoospermia, and needle spermatozoa:

- (1) Globozoospermia: Globozoospermia is described as the absence of an acrosomal cap in round-headed spermatozoa (Ghédér *et al.*, 2016). The main feature of this disease is that the round-headed sperm lacking acrosome cannot enter into the oocyte during fertilization (Ghédér *et al.*, 2019).
- (2) Macrozoospermia: Macrozoospermia is a rare sperm abnormality characterized by the presence of nearly 100% abnormal spermatozoa. This is a rare but serious genetic disease that causes male infertility due to an oversized irregular head, abnormal midpiece and acrosome, and multiple flagella in the ejaculate (Ray *et al.*, 2017).
- (3) Needle spermatozoa: In addition to the types of head deformities described above, there are also small head deformities, tapered heads, and irregular shapes (Dehghanpour *et al.*, 2017; Jiang *et al.*, 2019a).

**Table 1.** Classification of teratozoospermia for genetic abnormalities

Genetic abnormalities	Teratozoospermia						
	Malformation of the sperm head			Defective sperm neck and midsection	Malformation of the tail		
	Globozoospermia	Macrozoospermia	Needle spermatozoa		Acephalic spermatozoa	MMAF	DFS
Gene deletion	<i>PICK1, SIRT1, GOPC, GBA2, PCI, CREM, TH2A, TH2B, HRB, Csnk2a2</i>	<i>AURKC</i>	<i>SPATA6</i>	<i>SPATA6, ODF1, HOOK1, OAZ3, SPEM1</i>	<i>DNAH1, CFAP69</i>		
Gene mutation	<i>SPATA16, ZBP1, PRM</i>			<i>PRSS21, IFT88 Cntrob</i>	<i>CFAP43, CFAP44</i>		<i>CCNO, MCIDAS, CFAP298, CFAP300, DNAAF1, DNAAF2, DNAAF3, DNAAF4, DNAAF5, LRRC6, PIH1D3, SPAG1, ZMYND10, CCDC103, DNAH11, DNAH5, DNAH9, DNAI1, DNAI2, DNAL1, MNS1, NME8, TTC25, DNAH6, CCDC39, CCDC40, CCDC65, DRC1, GAS8, DNAJB13, RSPH1, RSPH3, RSPH4A, RSPH9, WDR66, STK36, HYDIN, GAS2L2, LRRC56</i>
Abnormal gene expression	<i>DPY19L2</i>			<i>SUN, GAT1</i>			
Abnormal gene duplication	<i>AR</i>						

Sperm tail deformities include sperm neck defects and tail deformities:

- (1) Acephalic spermatozoa: Acephalic spermatozoa is a common type of teratozoospermia in humans and one of the causes of mammalian sterility (Martínez-Rodríguez *et al.*, 2015).
- (2) Malformation of the tail:
  - (i) Multiple morphological abnormalities of the flagella (MMAF): MMAF is defined as the presence of sperm in ejaculation with abnormal morphology of the flagella, for example, a flagellate, short, curved, coiled, and irregular flagella. Up to 20% of MMAF cases have a genetic origin (Ben Khelifa *et al.*, 2014).
  - (ii) Dysplasia of the fibrous sheath (DFS): DFS refers to the 'short-tail' or 'stump' defect of the flagella of the hairs. It is characterized by male infertility and abnormally shaped flagella (Dávila Garza and Patrizio, 2013).
  - (iii) Primary ciliary dyskinesia (PCD): PCD, also called 'Kartagener's syndrome', belongs to a heterogeneous group of hereditary autosomal-recessive inherited diseases, which are characterized by reduced or no activity of cilia (Sironen *et al.*, 2020).

## 2.2 Clinical effect of teratozoospermia

### 2.2.1 The effect of teratospermia on infertility

Teratozoospermia can cause infertility due to abnormal sperm structure, and most teratozoospermia are caused by abnormal head acrosomes. One study (Liu *et al.*, 2003) found that the zona pellucida-induced acrosome reaction was significantly positively correlated with morphologically normal sperm. The sperm-zona pellucida binding rate was significantly reduced in teratozoospermia

patients (Liu and Baker, 2003). Malformed sperm will affect the structure of glycosyl and glycosyl-binding proteins on the surface of sperm, and affect the ability of sperm to fix to the zona pellucida, so that sperm cannot penetrate the zona pellucida and egg membrane to achieve fertilization.

### 2.2.2 The effect of teratozoospermia on abortion

A recent study (Rondanino *et al.*, 2015) showed that abnormal sperm morphology and chromosomal abnormalities in patients with decapitation sperm syndrome (lack of tail and only head) would directly affect ICSI pregnancy failure.

## 3. Research on related genes of teratozoospermia

The aetiology of teratozoospermia is complex and closely related to many factors. Large numbers of studies have shown that there is a close relationship between genetic abnormalities and teratozoospermia. Some evidence has suggested that genetic factors, such as gene mutation, gene deletion, and abnormal gene expression, can cause various special types of teratozoospermia, which are summarized in the following sections. Abnormalities of spermatozoa gene are listed in Table 1.

### 3.1 Gene deletion

#### 3.1.1 Globozoospermia

**3.1.1.1 PICK1 gene.** The human *PICK1* gene is located on chromosome 22 and contains 13 exons, encoding a 415 amino acid protein (Liu *et al.*, 2010; Modarres *et al.*, 2016). The PICK1 protein contains a PDZ (PSD-95, Dlg, and ZO1) domain and a Bin, amphiphysin, and Rvs (BAR) domain (He *et al.*, 2015), and is important for protein and vesicle trafficking. It is highly expressed in round spermatids and localizes to the vesicles between the Golgi apparatus and the acrosomes (Xiao *et al.*, 2009). The lipid binding of

the PICK1 BAR domain is positively regulated by the PDZ domain and negatively regulated by the C-terminal acid domain. A homozygous missense mutation (G198A) in the C-terminal domain, which destroys a *PvuII* site, eventually resulted in round-headed sperm formation (Liu *et al.*, 2010; Modarres *et al.*, 2016). In addition, PICK1 participates in vesicle transport between the Golgi apparatus and the acrosome, and the PDZ domain regulates the transport process. Deletion of PICK1 affects the transport of precursor particles, which indirectly leads to insufficient fusion of precursor particles, in turn affecting acrosome formation. Alternatively, the lack of PICK1 may cause membrane proteins to mismatch into precursor particles (Xiao *et al.*, 2009; He *et al.*, 2015).

**3.1.1.2 SIRT1 gene.** Sirtuins are a family of NAD<sup>+</sup>-dependent enzymes (Haigis and Sinclair, 2010). Mammals possess seven Sir2 type genes (SirT), namely *Sirt1* to *Sirt7* (Verdin *et al.*, 2010). In a study using mice, deletion mutations in the *Sirt1* gene disrupted the sperm cell LC3 and Atg7 deacetylation, affecting the redistribution of LC3 from the nucleus to the cytoplasm and activation of autophagy. The deletion of *Sirt1* prevents LC3 from being recruited to Golgi-derived vesicles.

**3.1.1.3 GOPC gene.** GOPC (Golgi-associated PDZ- and coiled-coil motif-containing protein) is abundantly found in the *trans*-Golgi region in round spermatids (Suzuki-Toyota *et al.*, 2007; Yatsenko *et al.*, 2012). In mice, GOPC collaborates with PICK1 to participate in vesicle transport in acrosomes. Both *Pick1*-knockout and *Gopc*-knockout mice show acrosome fragmentation during spermiogenesis (Jiang *et al.*, 2019b). GOPC interacts with CCDC62 in mouse testes and is regulated by CCDC62. Upon deletion of the *Gopc* gene in the mouse, vesicles are transported from the Golgi apparatus and the acrosome in the sperm disappear completely (Li *et al.*, 2017). These findings indicated that GOPC plays an important role in vesicle transport and acrosome fusion. It is also involved in the formation of abnormal sperms (Yao *et al.*, 2002; Wang *et al.*, 2014).

**3.1.1.4 GBA2 gene.** The *GBA2* gene (12.36 kb) is located on the human chromosome 9p13.3, and encodes  $\beta$ -glucosidase. *GBA2* is the only enzyme known to have true  $\beta$ -glucosidase activity in the endoplasmic reticulum (ER). Studies have shown that lipid transport is inhibited in round-headed sperm in mice lacking *GBA2* (Roy and Lin *et al.*, 2006). The round-headed spermatozoa produced by such mice have abnormal acrosomes and show the accumulation of glycosylceramide, which may prevent acrosome formation (Walden *et al.*, 2007).

**3.1.1.5 PCI gene.** The *PCI* (serpin peptidase inhibitor; 11.73 kb) gene is located on human chromosome 14q32.1, and encodes a serine protease inhibitor. In contrast with serine protease, *PCI* is a serine protease inhibitor (serpin), including protein C (PC) and plasminogen activators (Odet *et al.*, 2004). Male mice lacking *PCI* are unable to resist proteolytic activity, and unrestricted proteolytic activity may directly or indirectly disrupt the Sertoli cell barrier (Uhrin *et al.*, 2000). Sperm acrosomes are also destroyed in the absence of *PCI* (Elisen *et al.*, 1998).

**3.1.1.6 CREM gene.** The *CREM* (cyclic AMP responsive element modulator) gene is located at chromosome 10p11.21, and has a length of 86.12 kb (Liu *et al.*, 2013). The *CREM* protein is thought to be important for mammalian spermatogenesis (Kramer *et al.*, 1991). All male mice lacking the *CREM* protein are infertile,

because sperm do not complete the differentiation process normally (Blendy *et al.*, 1996; Krausz and Sassone-Corsi, 2005), leaving the sperm at the round sperm stage (Krausz and Sassone-Corsi, 2005).

**3.1.1.7 TH2A and TH2B genes.** *TH2A* (393 bp) and *TH2B* (470 bp) (testicular histone H2A and H2B, respectively) genes are both located on rat 17p11. *TH2A* and *TH2B* are highly expressed during spermatogenesis and play a vital role in the change of chromatin structure during spermatogenesis; they induce an open chromatin structure (Huynh *et al.*, 2016). During spermatogenesis, chromatin in round spermatozoa condenses because most of the histones are replaced by transition proteins and then by PRM. Studies have shown that disruption of *Th2a* and *Th2b* can lead to sperm defects, especially affecting the two steps involved in the normal release of adhesin between meiosis I and meiosis II and histone replacement during spermatogenesis, leading to changes in sperm morphology (Shinagawa *et al.*, 2015).

**3.1.1.8 HRB gene.** *HRB* is an HIV-1 Rev binding/interacting protein and an important cofactor in the Rev export pathway (Kierszenbaum *et al.*, 2004). Studies have shown that the *Hrb* gene is expressed in large amounts during spermatogenesis. The transformation of the *Hrb* gene-deficient round spermatids into testicular spermatozoa (spermatogenesis) is significantly disrupted. The resulting mutant microtubules do not have elongated spermatids, and only contain round-headed sperm cells that lack acrosome structure (Kang-Decker *et al.*, 2001). At the same time, *HRB* interacts with the EPS15 homology domain (EH) protein and, as part of the EH network, it plays an important role in vesicle classification. If their sperm lacks acrosomes, defects such as multiple tails, amorphous heads, and multiple nuclei appear (Kopp *et al.*, 2007).

**3.1.1.9 Csnk2a2 gene.** *Csnk2a2* is considered to be one of the pathogenic genes associated with round-headed sperm (Pirrello *et al.*, 2005). The *Csnk2a2* gene is located on mouse chromosome 8, and the human homolog is located on 16q21. This gene belongs to the casein kinase II gene family, which encodes a protein that is associated with the nuclear matrix during the later stages of spermatogenesis. Studies have found that *Csnk2a2* is preferentially expressed in the late stage of spermatogenesis. Homozygous mice with the *Csnk2a2* gene deletion are infertile due to oligospermia and round-headed spermatozoa, and their sperm acrosomes often detach from the sperm nucleus and disappear during spermatogenesis. Currently, the heterodimeric partner *Csnk2b* of the *Csnk2a2* gene is also considered to be a candidate gene for balospermia.

### 3.1.2 Macrozoospermia

**3.1.2.1 AURKC gene.** The *AURKC* (Aurora Kinase C) gene is located on 19q13.3-qter. It contains seven exon sequences and is highly expressed in the testes (Jedidi *et al.*, 2018). Human *AURKC* and mouse *AURKC* have 82.1% amino acid identity in the kinase domain, 68.8% amino acid identity in the N-terminal domain, and only 26.7% identity in the C-terminal domain. This difference in amino acid content indicates specific differences between the species (Quartuccio and Schindler, 2015). A 1-bp deletion in the *AURKC* gene (c.144delC) interferes with the CPC positioning and results in a metaphase chromosomal misalignment. This deletion produces a frameshift that causes a change from leucine to tryptophan codon at amino acid 49.

The 22 missense residues after the frameshift are translation stop codons that cause protein truncation and block meiosis, resulting in the appearance of tetraploids and a large number of flagella (Chianese *et al.*, 2015; Fellmeth *et al.*, 2016; Ray *et al.*, 2017). Studies have shown that, in the cohort of patients with megaspermia, the frequency of the *AURKC* mutation was 78.6% (11/14); the c.144delC mutant accounted for 91% of the mutant alleles, and the rest were p.Y248 (Ounis *et al.*, 2015).

### 3.1.3 Needle spermatozoa

**3.1.3.1 SPATA6 gene.** The *SPATA6* gene is an evolutionarily conserved testis-specific gene and also a spermatogenesis-related gene. The *SPATA6* gene consists of 15 exons, encoding a protein of 488 amino acid residues. It encodes the proteins required for the formation of the segmented column and the head, two major structures of the sperm junction that are essential for connecting the developing flagella to the head during late spermatogenesis. It is specifically expressed in haploid germ cells, and *SPATA6* deletion may lead to needle spermatozoa or azoospermia. Yu *et al.* (2009) studied the mouse animal model of headless sperm; proteomic results found that the *SPATA6* gene was involved in the transport of myosin microfilaments and, to some extent, affected the function of motor proteins in sperm cell myosin. Thereby affecting the transformation of sperm cells into sperm with normal shape and function, and finally generating needle sperm or headless sperm.

### 3.1.4 Acephalic spermatozoa

**3.1.4.1 SPATA6 gene.** The *SPATA6* gene deletion impairs the construction of segmented columns based on myosin-based microfilament transport. Partial or complete lack of segmented columns during the development of connectors that extend sperm cells or cause sperm to become part of a segmented column results in headless sperm (Shang *et al.*, 2018; Abu-Halima *et al.*, 2019; Sujit *et al.*, 2020).

**3.1.4.2 ODF1 gene.** The *ODF1* (dense outer fibre of sperm tail 1) gene is located on human chromosome 8q22.3, with a total length of 9.40 kb. In mice, the *Odf1* gene is a single-copy gene located in the B2–C region of chromosome 15. *ODF1* has been assigned as a small heat shock protein (sHSP), leading it to be renamed HSPB10 (Yang *et al.*, 2014). *ODF1* defects lead to abnormal spermatogenesis, with some developmental defects in the implant plate and thin-layered fibres (Hetherington *et al.*, 2017). The protein complex consisting of the core proteins *ODF2/ODF1/CCDC42* forms a rigid scaffold that is essential for the formation of the connector and sperm tail. In the absence of any of these proteins, the rigid scaffold is destroyed, resulting in the failure of the formation of the connection complex and the sperm tail, resulting in sperm deformity (Tapia Contreras and Hoyer-Fender, 2019).

**3.1.4.3 HOOK1 gene.** The *HOOK1* (Hook homolog 1) gene is located on human chromosome 1p32.1, it contains 22 exons, and is 61.52 kb in length. In the sperm of the *azh* mutant mice, the deletion of two exons in the *Hook1* gene leads to the production of truncated proteins that can affect the intra-manchette transport processes, resulting in abnormal sperm heads, detached tails, and aberrant manchette positioning (Zhou *et al.*, 2009; Schwarz *et al.*, 2017; Tapia Contreras and Hoyer-Fender, 2019).

**3.1.4.4 OAZ3 gene.** *OAZt/OAZ3* is a member of the ornithine decarboxylase anti-enzyme family and is only expressed in the haploid germ cells of the testis. The *OAZ3* gene contains five exons

and four introns, and the sequence of the exons is the same as the cDNA sequence (Ike *et al.*, 2002). Sperm head–tail separation was observed in *Oaz3*-knockout mice. It is speculated that a lack of *Oaz3* may cause the accumulation of amines, which affects the structure of sperm junctions (Tokuhiro *et al.*, 2009). By studying the protein p12 expressed by *Oaz3* in rats, it was found that p12 plays a role in signal transduction by regulating protein phosphatase and may play a role in the assembly of the head–tail-coupling apparatus (HTCA), without the p12 head–tail connection being fragile. The ultrastructure of the separated head and tail appeared normal. Fractures occurred on the base plate and the struts, indicating that the connector was fragile (Ruan *et al.*, 2011).

**3.1.4.5 SPEM1 gene.** *SPEM1* (spermatid maturation 1) is one of the spermiogenesis-essential genes and is exclusively expressed in the testis. *Spem1*-knockout mice display a ‘head-bent-back’ phenotype and show cytoplasmic droplet-like remnants translocated to the junction between the head and the neck (Bao *et al.*, 2010). In the absence of *SPEM1*, many proteins originally degraded by the ubiquitin-proteasome system may be retained, resulting in abnormal sperm cell development and cytoplasmic abnormalities in the later stages (Bao *et al.*, 2010).

### 3.1.5 MMAF

**3.1.5.1 DNAH1 gene.** *DNAH1* (MIM #603332) was the first gene formally identified in humans with mutations that caused an MMAF phenotype and male sterility (Touré *et al.*, 2021). *DNAH1* encodes for inner-arm heavy-chain dynein, which is an axonemal component. This component is needed in spermatozoa to form the inner dynein arms, which are distributed as three molecular complexes in groups of 3–2–2 in three different types of inner arms IDA1–IDA3. The absence of *DNAH1* eliminates the anchoring sites of radial spokes 3, which results in weakened adhesion of the two central singlet microtubules, leading to MMAF and dysplasia of the fibrous sheath (DFS) (Sha *et al.*, 2017b).

**3.1.5.2 CFAP69 gene.** *CFAP69* (formerly known as c7orf63; GenBank: NM\_001039706) is located on chromosome 7 and contains 23 exons encoding a predicted 941-amino acid protein (A5D8W1) (Dong *et al.*, 2018). This gene encodes the protein of cilia and flagella-associated protein 69, which contains a WD repeat domain (He *et al.*, 2019). *Cfap69* gene deletion causes MMAF in mice. Furthermore, it was shown that *CFAP69* may be involved in sperm tail biogenesis and CPC assembly through flagellin transport (Nsota Mbango *et al.*, 2019).

## 3.2 Gene mutation

### 3.2.1 Globozoospermia

**3.2.1.1 SPATA16 gene.** *SPATA16* (spermatogenesis-associated 16, also known as NYD-SP12) is located on chromosome 3q26.32 and is composed of 11 exons encoding a highly conserved protein of 569 amino acids, which contains a tetratricopeptide repeat (TPR [MIM 602259]) domain (Dam *et al.*, 2007; Jedidi *et al.*, 2018). *SPATA16* is localized in the Golgi apparatus and proacrosomal granules (Karaca *et al.*, 2014). It is involved in the transport of proacrosomal granules to the acrosome in the round and elongated spermatids, thereby playing an essential role in acrosome formation during spermatogenesis (Chianese *et al.*, 2015; Bracke *et al.*, 2018). *SPATA16* gene mutation has been demonstrated to show autosomal-recessive inheritance 10. The deletion of its exons

due to gene mutation can destroy the TPR domain, leading to interference with protein–protein interaction and aberrant meiosis, finally resulting in globozoospermia (Dam *et al.*, 2007; Ghédir *et al.*, 2019).

**3.2.1.2 ZBPB1 gene.** *ZBPB1* (zona pellucida binding protein 1/sp38) is localized to the acrosomal membrane (Yatsenko *et al.*, 2012). In mice, *Zbp1* is 184 kb long, has eight exon configurations and is located on chromosome 11 (Lin *et al.*, 2007). The zona pellucida binding protein gene knockout (*Zbp12/2*) shows that an acrosomal protein (IAM38/Sp38/ZBPB1) can play a critical architectural role during acrosomal formation (Yu *et al.*, 2009). In mice, the sperm containing the *ZBPB1* gene knockout shows acrosome fragmentation, disrupted Sertoli–spermatid junctions, and defective sperm head morphology (Liu *et al.*, 2010). This feature is similar to that observed in human teratozoospermia. Studies have shown that abnormal head morphology may be due to a lack of functional ZBPB1 protein or due to the negative effects of the mutant ZBPB1 protein and other acrosome proteins required for sperm head formation (Yatsenko *et al.*, 2012).

**3.2.1.3 PRM genes.** Protamines (PRMs) are arginine-rich and cysteine-rich small basic proteins that play a role in packaging paternal genomes. PRMs are conserved in some species and are only found in mature spermatozoa (Aydos *et al.*, 2018). Humans and mice have three different protamine genes: *Prm1*, *Prm2*, and *Prm3*. In mice, PRM1 is an arginine- and cysteine-rich protein of 50 amino acids, whereas PRM2 is rich in histidine and contains 106 amino acids (Takeda *et al.*, 2016). The *PRM1* and *PRM2* genes are located on chromosome 16p13.2, spanning a 28.5-kb region, and play a critical role in spermatid differentiation (Tüttelmann *et al.*, 2010; Ganguly *et al.*, 2013). Both genes contain a single intron. In the process of spermatogenesis, the compaction of sperm chromatin requires testicular-specific nuclear proteins called transition proteins and PRM. The transition proteins convert sperm nuclear proteins from histones to PRM. Deletion or mutation of the *PRM* gene results in protamine deficiency in the sperm nucleus. As a result, sperms appear as round-headed sperms or show other head morphological abnormalities. In addition, abnormal ratios of protamine P1 and P2 can also cause abnormal morphology of the sperm head (Steger *et al.*, 2002; Ravel *et al.*, 2007; Tüttelmann *et al.*, 2010; Ganguly *et al.*, 2013; Utsuno *et al.*, 2014).

### 3.2.2 Acephalic spermatozoa

**3.2.2.1 PRSS21 gene.** Serine proteases play an important role in sperm production, maturation, and functional capacity. Several lines of evidence have suggested that one or more trypsin-like serine proteases are essential for successful fertilization in mammals (Swegen *et al.*, 2019). PRSS21 (also known as testosterone, esp-1, trypsinase 4, and TESP5) is a trypsin-like protease that is abundantly expressed by male germ cells and sperm. *PRSS21* is a unique gene family in the homologous region of the chromosome and is located at 16p13.3 on the human chromosome and on chromosome 17 in mice (Netzel-Arnett *et al.*, 2009). PRSS21 plays an important role in guiding the maturation of sperm cells in the epididymis and the process of sperm fertilization. A sperm lacking PRSS21 shows the characteristics of decreased motility, angulation, and fragility of the sperm neck (Liu *et al.*, 2019). In a study on bull sperm, the *PRSS21* (serine protease 21) gene, along with *TEX14*, was found to be involved in the production of male gametes. This process encodes a cell surface-anchored serine protease called

testis protein, which is expressed in large quantities in the pre-meiotic stage. However, sperm lacking PRSS21 showed some defects during epididymal transport (Stafuzza *et al.*, 2020). Prss21-mutant mouse sperm showed an increased tendency to go out. PRSS21 is highly expressed on the surface of round and elongated sperm in the testis in both humans and mice, and remains associated with sperm tails throughout the epididymal tract. PRSS21 deficiency produces headless sperm and hairpin-like structures (Dehghanpour *et al.*, 2017).

**3.2.2.2 IFT88 gene.** IFT88 (intraflagellar transport protein 88) is a core anterograde or type B trafficking protein. It can transport proteins to the tip of primary cilia, so it plays a vital role in the assembly process of cilia (Coveney *et al.*, 2018). Studies have shown that IFT88 is localized in precursor vesicles, and that there is a complete actin-based Va-Rab27a/Rab27b vesicle transport system in *Ift88*-mutant mouse, which may facilitate acrosome–acrosome and tail development. In the presence of a normal *Ift88*, the development of the acrosome–acrosome enzyme complex was not significantly disrupted in the mutant. Although the actin-based transport system can partially offset the defects of the microtubule-based transport system and the IFT88 protein, this compensation cannot prevent sperm from forming abnormal heads. Similar to myosin Va and Rab27/Rab27b, GMAP210 and IFT88 also seem to be involved in HTCA and tail transport (Kierszenbaum *et al.*, 2011b). Therefore, the *Ift88* gene can participate in the development of the sperm acrosome, HTCA and tail. If *Ift88* is mutated, the mouse sperm head will be abnormal and the sperm will have no tail (Pandey *et al.*, 2019).

**3.2.2.3 Centrob gene.** Centrobin (also known as NIP2 or LIP8) is a centrosome component and the corresponding gene is designated *Centrob* (Entrez Gene ID: 303240; Rat Genome Database ID: 1307488) (Ogungbenro *et al.*, 2018). The hd mutation in WHD rats was induced by retroviral element mutagenesis into intron 10 of the *Centrob* gene on rat chromosome 10. The transcription of the hd allele produces exons containing retrotransposon origin. For multiple mRNA species, these exons cause truncated centrin proteins at the C-terminus. Centrin-truncated proteins may interfere with the shape of sperm heads, HTCA organization and anchoring, and sperm tail development (Liska *et al.*, 2009).

### 3.2.3 MMAF

**3.2.3.1 CFAP43 and CFAP44 genes.** The *CFAP43* gene has 37 exons and encodes a protein of 1665 amino acids. The *CFAP44* gene has 35 exons and encodes a protein of 1854 amino acids. Both genes contain WD repeat domains and are mainly expressed in humans (Sha *et al.*, 2019). Mice models lacking the *CFAP43* and *CFAP44* orthologous proteins showed male sterility and an MMAF phenotype similar to that observed in humans. Gene changes in *CFAP43* and *CFAP44* can result in abnormalities in cilia and flagella (Touré *et al.*, 2021) and *CFAP43* and *CFAP44* mutations induce severe axonemal disorganization (Coutton *et al.*, 2018).

### 3.2.4 PCD gene

Different PCD gene mutations lead to the loss of the inner dynein arms of the cilia due to the disorder of the microtubule structure, or the lack of outer and inner dynein arms. Multiple genes have been associated with PCD, including *CCNO*, *MCIDAS*, *CFAP298*, *CFAP300*, *DNAAF1*, *DNAAF2*, *DNAAF3*, *DNAAF4*, *DNAAF5*, *LRRC6*, *PIH1D3*, *SPAG1*, *ZMYND10*, *CCDC103*, *DNAH11*, *DNAH5*, *DNAH9*, *DNAI1*, *DNAI2*, *DNAL1*, *MNS1*,

*NME8*, *TTC25*, *DNAH6*, *CCDC39*, *CCDC40*, *CCDC65*, *DRC1*, *GAS8*, *DNAJB13*, *RSPH1*, *RSPH3*, *RSPH4A*, *RSPH9*, *WDR66*, *STK36*, *HYDIN*, *GAS2L2*, and *LRRC56* (Sironen *et al.*, 2020).

### 3.3 Abnormal gene expression

#### 3.3.1 Globozoospermia

**3.3.1.1 DPY19L2 gene.** DPY19L2 is a testis-specific protein with nine transmembrane domains. The corresponding gene is located on chromosome 12q14.2, has 22 exons, two flanking low copy repeat (LCR) sequences, and an identity of 96.5% (Elinati *et al.*, 2012). Four LCRs are localized at the end of DPY19L2. These repeats are ~25 and 9 kb at the 3'-end and 62 and 77 kb at the 5'-end of DPY19L2, respectively (Ghazavi *et al.*, 2019). In contrast with SPATA16 (Koscinski *et al.*, 2011), the DPY19L2 mutation may disrupt only the spermiogenesis process and not germ cell proliferation and meiosis. There is evidence that the lack of DPY19L2 leads to a lack of related proteins, resulting in the instability of the connection between the dense nuclear layer and the roof and the nuclear membrane in sperms. Furthermore, the acrosome and the manchette fail to be linked to the nucleus, leading to the disruption of vesicular trafficking, failure of sperm nuclear shaping, and eventually the elimination of the unbound acrosomal vesicle (Chianese *et al.*, 2015). The loss of the acrosome occurs in the final stage of sperm formation (Ounis *et al.*, 2015). Therefore, a lack of DPY19L2 affects the formation of the sperm acrosome and hinders sperm head elongation (Modarres *et al.*, 2016).

#### 3.3.2 Acephalic spermatozoa

**3.3.2.1 SUN gene.** In mammals, the SUN-domain proteins are characterized by a conserved C-terminal region of ~175 amino acids and the presence of at least one transmembrane domain (Yang and Adham *et al.*, 2018). At least five SUN-domain proteins have been reported, and three of these genes in mice have been named *Sun1*, *Sun2*, and *Sun3*. Two other SUN-domain proteins were originally named rat sperm-associated antigen 4 (SPAG4) and SPAG4-like (SPAG4L), and then later named *Sun4* and *Sun5* (Shang *et al.*, 2017). *Spag4* is mainly present in the testis and pancreas, and specifically expresses SPAG4 (SUN4) in the testis. It is expressed in the sperm and axons and interacts with external dense fibrin 1 during sperm head formation and rat sperm tail elongation. In *Spag4*-deficient mice, the function of the LINC complex was impaired. Furthermore, the absence of SPAG4 inhibits the formation of the HTCA, eventually resulting in the production of headless sperm (Kierszenbaum *et al.*, 2011a; Zhu *et al.*, 2018; Li *et al.*, 2019; Yeh *et al.*, 2019). SUN5 is a transmembrane protein with 379 amino acids located in the inner membrane (INM). It consists of a C-terminal N-terminal nucleoplasmic region, a transmembrane helix, a coiled-coil region, and a SUN domain. SUN5 is synthesized in the ER, then transported to the Golgi apparatus, reaches the nuclear envelope (NE), attaches to the INM, and finally moves to the junction between the head and the tail of the sperm. During sperm division, most of the head remains in the seminiferous epithelium when it separates from the flagella (Zhu *et al.*, 2018; Li *et al.*, 2019). In the absence of SUN5, effective anchoring is lost in the last step of spermatogenesis, due to which the last part of the sperm cytoplasm cannot be removed in time, and the top of the sperm will carry part of the cytoplasm. Moreover, flagella cannot be anchored properly, mitochondrial sheaths cannot be aligned properly, and axon assembly is affected. Typical cytoplasmic droplets can be found in normal ejaculated

sperm or headless sperm (Pasch *et al.*, 2015; Zhu *et al.*, 2016; Elkhatib *et al.*, 2017; Shang *et al.*, 2018).

**3.3.2.2 GAT1 gene.** *GAT1* ( $\gamma$ -aminobutyric acid transporter I) is located on human chromosome 3p25.3 and the full length of the gene is 46.52 kb. *GAT1* is the primary neuronal transport protein in the rodent brain among the four *GAT*'s (*GAT1*–*GAT4*) (Hu *et al.*, 2004). The testis and sperm of transgenic mice overexpressing *GAT1* were significantly abnormal. In human sperm, GABA can induce an acrosomal reaction (Zhang *et al.*, 2009).

### 3.4 Abnormal gene duplication

#### 3.4.1 Globozoospermia

**3.4.1.1 AR gene.** The AR protein (androgen receptor) mediates androgen action by determining male sexual differentiation, initiation and promotion of spermatogenesis, and the growth of accessory sex organs (Bhanmeechao *et al.*, 2018). The AR gene is a single-copy sequence composed of eight exons located on chromosome Xq11–12 (Milatiner *et al.*, 2004). The AR gene contains two polymorphic trinucleotide repeat loci: [CAG]*n*, which encodes a polyglutamine bundle, and [GGC]*n*, which encodes a polyglycine bundle. Both loci are located in exon 1, and the *trans*-activation domain of the exon encoding the receptor protein contains a CAG repeat that is translated into polyglutamine. Glutamine repeats are polymorphic, with normal individuals showing 9–36 repeats. A CAG repeat length of 49 in AR was positively correlated with teratozoospermia (Tut *et al.*, 1997).

### 3.5 Clinical application of gene detection of spermatozoa deformity

Different teratozoospermia patients have genetic differences. De Braekeleer *et al.* (2015) reviewed the literature and showed that more than 90% of sperm with megacephalospermia were aneuploid, mainly diploid; Ounis *et al.* (2015) found a homozygous aurora in Algerian megacephalospermia patients. The mutation rate of the kinase C gene (*AURKC*) was 79%; 18 typical infertile patients with macrocephaly in Morocco were all homozygous for the c.144delC mutation in the *AURKC* gene (El Kerch *et al.*, 2011), so the *AURKC* gene detection is recommended for patients with macrocephaly. The proportion of male infertility caused by round-headed spermatozoa was less than 0.1% (Perrin *et al.*, 2013), and several studies support that *DPY19L2* deletion is the main reason, accounting for 19% of patients (Koscinski *et al.*, 2011; Elinati *et al.*, 2012; Zhu *et al.*, 2013). Homozygous deletion of *DPY19L2* blocks sperm head elongation and acrosome formation. The incidence of homozygous *DPY19L2* in patients with round-headed spermatozoa is 100%. Zhu *et al.* (2013) reported 15 genetically independent Chinese patients with round-headed spermatozoa, four were homozygous for the *DPY19L2* deletion, five were heterozygous for a point mutation, one was heterozygous for one allele deletion, and the other was heterozygous for one allele. One allele had no mutation; 60% of patients had biallelic *DPY19L2* sequence variants. Therefore, *DPY19L2* should be sequenced for diagnosis in patients with round-headed spermatozoa. In addition, the *SPATA6* gene has been implicated in spiculospermia; *Cntrob* is a new candidate gene for the currently unexplained genotype of easily decapitated sperm syndrome in humans.

Gene abnormality is an important cause of teratozoospermia, but in the actual clinical diagnosis, the diagnosis at the gene level

is still lacking. At present, the genetic research that causes sperm deformity is still in theory. The relationship between the genes and their upstream and downstream genes is not clear. In addition, it is not entirely clear whether the genes that cause deformed sperm act by regulating other genes to cause sperm deformities or directly through proteins.

#### 4. Summary and outlook

Spermatogenesis is a complex process. Although there have been many reports of sperm abnormalities, many mechanisms remain unclear, and clinical applications are still in the developmental stage. Studying the molecular genetics of abnormal sperm can help guide clinicians toward more effective treatments for their patients. With the deepening of research, the molecular mechanism of teratozoospermia will become more and more clear, which will help the gene diagnosis and gene therapy of teratozoospermia in the clinic.

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