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Novel *DNAH1* Mutation Loci Lead to Multiple Morphological Abnormalities of the Sperm Flagella and Literature Review

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The protein encoded by dynein axonemal heavy chain 1 (*DNAH1*) is a part of dynein, which regulates the function of cilia and sperm flagella. The mutant of *DNAH1* causes the deletion of inner dynein arm 3 in the flagellum, leading to multiple morphological abnormalities of the sperm flagella (MMAF) and severe asthenozoospermia. However, instead of asthenozoospermia and MMAF, the result caused by the mutation of *DNAH1* remains unknown. Here we report a male infertility patient with severe asthenozoospermia and teratozoospermia. We found two heterozygous mutations in *DNAH1* (c.6912C>A and c.7076G>T) and which were reported to be associated with MMAF for the first time. We next collected and analyzed 65 cases of *DNAH1* mutation and found that the proportion of short flagella is the largest, while the bent flagella account for the smallest, and the incidence of head deformity is not high in the sperm of these patients. Finally, we also analyzed 31 *DNAH1* mutation patients who were treated with intracytoplasmic sperm injection (ICSI) and achieved beneficial outcomes. We hope our research will be helpful in the diagnosis and treatment of male infertility caused by *DNAH1* mutation.

Keywords: Dyneins; Genes; Male infertility; Sperm tail

INTRODUCTION

Male infertility is a multifactorial pathological condition that affects approximately 7% of the male population [1]. Among all the factors leading to male infertility, genetic factors account for at least 15% of

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these patients [1]. In recent years, an increasing number of genes have been confirmed to be associated with male infertility [1]. However, due to the lack of evidence and clinical reports, the role of some of these genes is still not fully understood. Therefore, we report a clinical case of male infertility treated with multiple medications and two intracytoplasmic sperm injection (ICSI) for 8 years. During this period, this patient's sperm quality was declined, and did not achieve pregnancy. Genetic testing determined two mutation loci in the dynein axonemal heavy chain 1 (*DNAH1*) loci in the patient. Previous studies showed that *DNAH1* is related to multiple morphological abnormalities of the sperm flagella (MMAF) and results in male infertility [2-4]. Therefore, we collected and analyzed 65 cases of *DNAH1* mutations causing infertility from 6 search engines. Our results might provide new strategies for the diagnosis and treatment of male infertility caused by *DNAH1* mutations.

MATERIALS AND METHODS

1. Case report

This is a case for a 43-year-old male who suffered from infertility for eight years. Several consecutive semen analyses showed that the patients had severe asthenozoospermia, moderate/severe oligozoospermia, teratozoospermia. His chromosome presented 46XY, the development of secondary sexual characteristics was normal, and he had no family history of genetic diseases (both brothers had given birth naturally). This patient was diagnosed without symptoms related to primary ciliary dyskinesia (PCD), such as chronic lung disease, chronic sinusitis and hearing impairment. He received several drugs during the treatment, such as Vitamin E Soft Capsules (Zhejiang Medicine Co., Ltd., Shaoxing, Zhejiang, China), Coenzyme Q10 Capsules (Eisai China Inc. Shanghai, China), Zinc Gluconate (Aonuo [China] Pharmaceutical Co., Ltd, Baoding, Heibei, China), Aescuven Forte (Cesra Arzneimittel GmbH & Co.KG, Baden, Germany), Levocarnitine Oral Solution (Northeast Pharmaceutical Group Shenyang No.1 Pharmaceutical Co., Ltd., Shenyang, Liaoning, China) for at least five years. However, his sperm quality did not improve, and the sperm concentration tended to decrease (Fig. 1). The abnormal semen results of the patient were shown in Supplement File 1, Extension 1, 2 (examination standards according to the WHO laboratory manual for the examination and processing of human semen-5th ed [5]). Subsequently, we observed rare motile sperm extracted by testicular sperm extraction (TESE) in January 2017 (Supplement File 1, Extension 3).

Other routine tests showed no significant abnormalities. Ultrasonic examination (Supplement File 1, Extension 4), immunological tests (serum anti-sperm antibody, semen leukocytes, tray agglutination test, sperm immobilization test), sex hormone tests (Supplement File 1, Extension 5), and microbiological analyses (ureaplasma urealyticum, chlamydia trachomatis, herpes virus) related to infertility were not abnormal.

The patient underwent the ICSI twice in 2016 and 2017 separately for a total of 3 ICSI cycles, and both failed to conceive due to embryonic dysplasia (Supplement File 1, Extension 6, 7). The patient's wife was a 32-years-old (2016) female, G0P0, with regular menstruation (28 days cycle, lasting 7 days, medium volume). She had no obvious medical conditions that affected her fertility.

The genetic test report (GRCH37/hg19) showed that the patient had two base mutations (c.6912C>A and c.7076G>T) in the *DNAH1* (MIM No.603332) on chromosome 3, according to the American College of Medical Genetics and Genomics (ACMG) [6] (Supplement File 1, Extension 8). *DNAH1* is the pathogenic gene for PCD 37 (OMIM: 617577)/Spermatogenic Failure 18 (OMIM: 617576). The disease is an autosomal recessive disease. However, since the patient's father had died, it was impossible to determine whether the two mutation sites were on the allele.

This patient also had a *KISS1R* heterozygous mutation (c.875G>A), an autosomal recessive gene associated

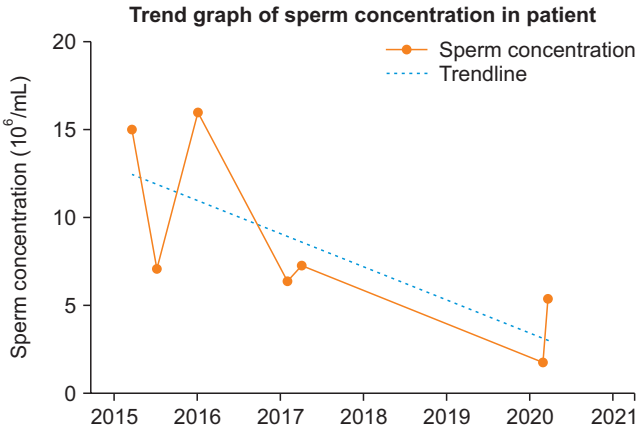

Fig. 1. Changes in sperm concentration in the patient.

with central precocious/hypogonadotropic hypogonadism with an ACMG marker of "unsure significance". This patient did not show symptoms associated with the KISS1R mutation.

To increase our understanding of *DNAH1*, we reviewed and searched the relevant literature, and our search strategy and results are reported below.

2. Search strategy and inclusion/exclusion criteria

The subject term ("DNAH1" OR "dynein, axonemal, heavy chain 1, human") on PubMed, Web of Science, Embase, ScienceDirect, FMRS, and CNKI was searched and collected all the cases of *DNAH1* mutations causing male infertility.

Case exclusion criteria: (1) Single patient's semen test results were not listed; (2) Single *DNAH1* mutation site with no indication of whether it is pure or heterozygous; (3) Cases with homozygote or compound heterozygote mutations in other genes affect semen quality; (4) Inclusion criteria in the literature include filtering for sperm concentration and vitality.

3. Ethics statement

The ethics committee of our hospital considers that this study is only a statistical collection of medical record information and does not involve actual specimens, so ethics committee approval is not required. We have obtained informed consent from the patients.

RESULTS

The search strategy yielded 204 studies. Of these, 23 papers (123 cases, combined with the case report above) contained cases of male infertility due to *DNAH1* mutations (Supplement File 2) [2-4,7-26], involving 89 mutant loci (the highest mutation frequency of c.11726_11727del). Sixty-five cases were obtained after screening by case exclusion criteria (Table 1). All included cases presented with male infertility, with no other PCD-related symptoms.

1. Sperm concentration and vitality statistics

Statistically, 34 patients suffer from oligozoospermia (sperm concentration <15×10^6/mL), accounting for 52.31% (total=65) (Fig. 2A); 20 patients were diagnosed necrozoospermia (vitality<58%), accounting for 68.97%, of which vitality=0% accounted for 24.1% (total=29) (Fig. 2B).

2. Sperm morphology statistics

Morphological analysis showed that the proportion

Table 1. Sperm concentration and vitality status of currently reported *DNAH1* deficiency patients

Author (reference)	Sperm concentration 10^6/mL	Vitality %
Sha et al (2017) [2], (2019) [7]	12.64±4.79 (n=12)	1.48±2.64 (n=12)
Wang et al (2017) [3], Wang (2017) [8]	19.03±7.59 (n=4)	61.38±8.23 (n=4)
Yang et al (2018) [4]	11.21±14.34 (n=2)	None
Ben Khelifa et al (2014) [9], Wambergue et al (2016) [10]	26.23±17.45 (n=6)	43.67±19.86 (n=3)
Amiri-Yekta et al (2016) [11]	25.33±8.82 (n=6)	79.33±16.22 (n=6)
Yu et al (2021) [12]	12.67±14.97 (n=12)	None
Jiang et al (2021) [13]	1.8 (n=1)	1 (n=1)
Hu et al (2021) [14]	16.33 (n=1)	None
Zaman (2020) [15]	10±8.89 (n=3)	None
Zhu (2019) [16]	16.08±7.47 (n=2)	None
Yang (2016) [17]	10.94±5.36 (n=10)	32±7.21 (n=3)
Zhi (2019) [18]	34.75±5 (n=4)	None
Oud et al (2021) [19]	20 (n=1)	None
Current study	8.44 (n=1)	None
Total	16.64±11.86 (n=65)	33.36±33.74 (n=29)

Values are presented as mean±standard deviation or mean only.
n: number of cases.
Some cases had multiple semen examination results or a range. The average of the maximum and minimum of the range or multiple results were included. A case of sperm concentration of "<1" was calculated as 1. Data that cannot be calculated are excluded (statistics with SPSS 26.0; IBM Corp., Armonk, NY, USA).

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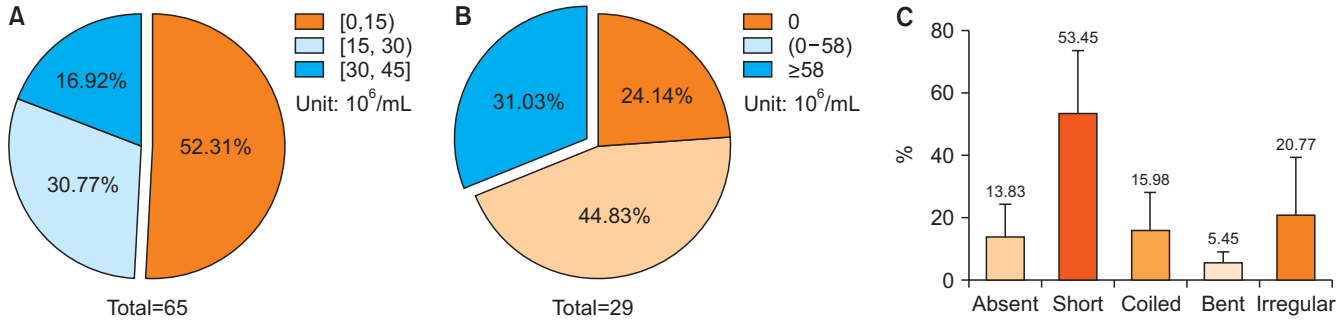

Fig. 2. (A) Percentage of different sperm concentrations. (B) Percentage of discrepancy vitality. (C) Sperm flagella defect type statistics.

of short flagella is the highest (53.45%±19.94%, multiple comparisons, $p<0.01$), the proportion of bent flagella is small (5.45%±3.3%, multiple comparisons, $p<0.05$) (Fig. 2C). Short flagella exceeded 40% in 78.95% of patients and only one case (3.13%) had bent flagella exceeding 10%. Both short flagella >40% and bent flagella <10% were present in 71.88% (n=32) of patients. Only a few sperm showed head abnormalities (9.91%±9.31%, n=18) and multiple morphological abnormalities (8.17%±4.57%, n=13).

3. Effectiveness of ICSI in the treatment of infertility caused by *DNAH1* mutations

30 patients with infertility caused by *DNAH1* mutations treated with ICSI were reported. Wambergue et al [10] performed ICSI for 6 couples with *DNAH1* defects and all obtained embryos, 4 of which delivered successfully. The total fertilization, pregnancy and delivery rates showed no statistical difference with patients without the mutation [10]. Yu et al [12] performed ICSI on 4 patients with *DNAH1* mutations and their partners, and all of them successfully obtained embryos. Two couples performed embryo transfer, 1 delivered successfully, and the other suffered an early miscarriage [12]. Sha et al [7] sperformed ICSI on 12 *DNAH1* patients, 8 of them were clinically pregnant and 1 had a miscarriage. Wu et al performed ICSI on 8 patients, and the clinical pregnancy rate (% per embryo transfer) was 53.8% (7/13) [25,26]. Combined with the cases in the case report above, the embryonic implantation and clinical pregnancy rates were 30.26% (23/76) and 61.90% (13/21), respectively (Supplement File 3).

DISCUSSION

1. *DNAH1* mutations cause severe asthenozoospermia and MMAF

The patient mentioned in the case report may have severe asthenozoospermia caused by abnormal sperm flagella structure caused by *DNAH1* mutation.

Cilia/flagella protrude from the surface of almost all eukaryotic cells and have many various roles in human physiology [27]. In humans, ciliary motility is responsible for diverse biological processes, including symmetry breaking during embryogenesis, the circulation of cerebrospinal fluid in the brain, mucociliary clearance in innate defense, and the swimming of spermatozoa [28]. Cilia and sperm flagella have a common origin and share the common structural element, the internal cytoskeletal structure called axoneme, which is highly conserved throughout evolution. The axoneme contains 9 microtubules doublets (MTDs), 2 central pairs (CPs) ("9+2" pattern), some axoneme dynein, radial spoke (RS), nexin-dynein regulatory complex, and many other components that drive and regulate the movement of cilia or flagella (Fig. 3) [29].

Dynein is one of the three families of the cytoskeletal motor protein. They have been shown to drive intracellular transport towards the minus ends of microtubules and convert the chemical energy in adenosine triphosphate (ATP) into mechanical energy for movement [30,31]. The motion of dynein is generated by a conserved motor structural domain which contains a ring-shaped head with six AAA structural domains [32]. Dynein includes cytoplasmic dynein and axonemal dynein. Among them, axonemal dynein is connected to MTDs within the cilia, and it provides power for the beating of motile cilia [30,33]. Dynein is a microtubule-related motor protein complex composed of several heavy chains (HCs), light chains, and intermediate chains. HC is a massive protein of 4,500 residues [33], surround dynein as force-producing subunits [34]. The HC has ATP hydrolysis and ATP-sensitive microtubule-binding sites and is responsible for converting chemical energy into directed mechani-

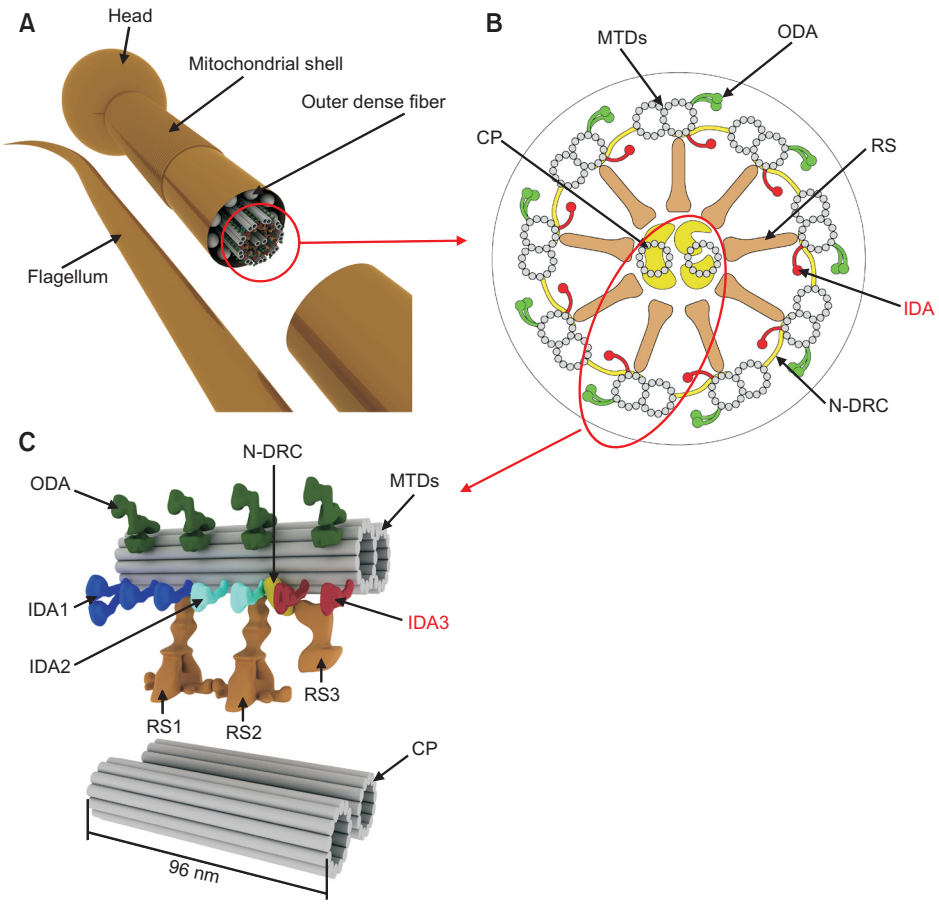

Fig. 3. Schematic diagram of the ultrastructure of the sperm flagella. (A) Sperm. (B) Internal cross-section of sperm flagella. (C) Dynein and its related structures. The dark blue, light blue, and red parts are IDA1, IDA2, and IDA3, respectively, in a 3-3-2 arrangement. The red text in (B) is IDA, including IDA1, 2 and 3, and the red text in (C) is IDA3, which is the expression site of *DNAH1*. The green, brown, grey, and yellow parts are ODA, RS, MTDS or CP, and N-DRC, respectively. The defect of *DNAH1* results in a deletion of IDA3, which becomes a 3-2-1 structure and leads to the loss of CP. Dynein and its related structures repeat every 96 nm. IDA: inner dynein arm, ODA: outer dyneim arm, RS: radial spoke, MTDs: microtubular doublets, CP: central pair, N-DRC: nexin-dynein regulatory complex, *DNAH1*: dynein axonemal heavy chain 1.

cal forces exerted on the microtubule surface [35]. Axonemal dynein is divided into outer dynein arm (ODA) and inner dynein arm (IDA). The ODA repeats every 24 nm [36], and seven different IDAs are repeated within the 96 nm range [37,38]. ODAs are responsible for providing acceleration power, and IDAs are involved in bending motion [29,39].

DNAH1 has 80 exons and is expressed in tissues such as the testis [40,41]. Seven IDAs are repeated in 96 nm with three different types (IDA1, IDA2, and IDA3) arranged in 3-2-2 groups (Fig. 3C). *DNAH1* is a component of IDA3. *DNAH1* mutations can cause the missing one head of the IDA3, leading to a 3-2-1 globular head arrangement [9,41]. ODA is not affected by *DNAH1* deletion [11]. The absence of *DNAH1* removes the anchoring site of the RS 3, which results in a disorganized microstructure with missing CP, resulting in a 9-0 structure [9].

The structural defect of axoneme dynein is the leading cause of PCD [42,43] and male infertility [44,45]. PCD, a rare autosomal recessive genetic disease with an incidence between 1/10000 and 1/15000 [46-48], is characterized by extensive genetic heterogeneity and clinical variabilities, such as chronic lung disease (bronchiectasis), chronic sinusitis, hearing impairment, situs inversus in 50% patients, and infertility [46]. The triad of bronchiectasis, chronic sinusitis, and situs inversus are called Kartagener syndrome, a subgroup of PCD [49]. PCD patients' sperm is usually immobile with various ultrastructural defects of the sperm flagella, such as absences of the dynein arms, microtubular translocations, and RSs [50]. PCD patients often lack ODAs or IDAs in the sperm flagella and cilia. Compared to the loss of individual IDAs, the loss of ODAs results in more severe ciliary motility defects [28]. Studies showed that Chlamydomonas mutants lacking some IDAs have almost regular beating frequency, but the amplitude of flagellar beating has changed [39]. At present, the correlation between IDAs and PCD still needs to be testified by more researches [51]. Over 40 genes, including *DNAH5*, *DNAH11*, *DNAI1*, were demonstrated to be associated with PCD, and more genes continue to be discovered [46]. Although there is a view that *DNAH1* may be the causative gene of PCD, there

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is still a lack of sufficient evidence [52-54].

Although *DNAH1* is expressed in both sperm flagella and cilia, there are some differences between flagella and cilia [50]. Clinically, it was shown that most patients with *DNAH1* mutations might only exhibit symptoms of infertility and no other PCD-related symptoms. Ben Khelifa et al [9] called this disease MMAF. MMAF may be a phenotypic variation of the classical forms of PCD [50]. Patients present with primary infertility characterized by a mosaic of flagellar abnormalities, including absent, short, coiled, bent, and irregular flagella [9].

Mouse dynamin heavy chain 7 (*MDHC7*) is the mouse orthologue to the human gene, *DNAH1*. *MDHC7-/-* mice exhibit deletion of the ATP binding site (P1-loop domain) of IDA [41]. Disruption of the *MDHC7* gene result in asthenozoospermia and reduce cilia beating frequency without severe defects in the axonemal structure [55]. *MDHC7-/-* mice have severely lower sperm velocities than wild-type mice, with velocities not exceeding 100 μm/s. The sperms that were utterly unable to make forward progress were up to 99% or more, and these severely weakened sperm exhibited rapid (~15 Hz) low-amplitude vibrations of the midpiece region [56]. *MDHC7*-deficient sperm were entirely unable to penetrate media of elevated viscosity (25–4,000 cP) and could not enter the oviduct from the uterus [52]. However, a small minority (generally ~1%) could swim progressively, and their flagellar activity was impaired but not severely [56]. Both female and male *MDHC7+/-* mice were normal and fertile, and fertility in *MDHC7-/-* females were not affected. Furthermore, there was no increase in embryonic or postnatal lethality in *MDHC7-/-* and *MDHC7+/-* [55]. All 30 *MDHC7-/-* male mice in Neesen et al's study did not obtain offspring [55]. However, the clinical significance of *DNAH1* mutations in humans is unclear due to the scarcity of patients and the lack of rigorous controlled clinical trials.

2. Association of *DNAH1* mutations with sperm concentration and vitality

About 15% of couples did not achieve pregnancy within 1 year. Male infertility-related factors, often accompanied by abnormal semen parameters, were found in half of the involuntary childless couples [57,58]. There are no authoritative statistics on the prevalence of oligozoospermia and necrozoospermia in the population, but it can be expected that both should be below 15%, which is an enormous disparity from 52.31% and 68.97%. None of the cases were filtered for sperm concentration and vitality in the selected literature, and it is reasonable to suspect that *DNAH1* mutations may be significantly associated with the development of oligozoospermia and necrozoospermia. However, this conclusion is not rigorous and partially conflicts with the current mouse study. In *MDHC7-/-*mice, there were 62% of completely immobile sperm, but no significant sperm reduction was shown [55]. Unfortunately, we did not find second *DNAH1*-related literature involving sperm concentration.

At present, most reports on *DNAH1* are cross-sectional studies. This patient is the first reported treatment of infertility caused by a *DNAH1* mutation for up to eight years. Patients had persistent decreases in sperm concentration over the past five years and had poor TESE results. However, more evidence on whether the sperm concentration will change with age is needed.

3. Morphological characteristics of sperm with *DNAH1* mutation

We found that spermatozoa from patients with *DNAH1* mutations exhibited distinctive features: a high percentage of short flagella, a low percentage of bent flagella and head malformations, which contribute to the initial clinical screening. Clinically, we may consider the possibility of *DNAH1* mutation in patients presenting a higher percentage of short flagella (>30%) and a lower rate of bent flagella (<10%).

4. Patients with *DNAH1* compound heterozygous mutations have the possibility of natural pregnancy

In Sha et al's study [2], we found that a person (P12's father) with heterozygous mutations at two *DNAH1* loci (c.5766-2A>G and c.10630G>T) may have successfully reproduced naturally. P12 has shorter or coiled sperm tails and very low or almost absent *DNAH1* expression compared with healthy people. So P12 should be a compound heterozygous mutation patient with two mutant loci from each of his parents (Fig. 4). P12 and his parents have two identical *DNAH1* heterozygous mutations. Therefore, the father of P12 should also be a *DNAH1* compound heterozygous mutation patient. P12 was born before 1987 (the article was published in 2017 and the paper shows P12 as 30 years

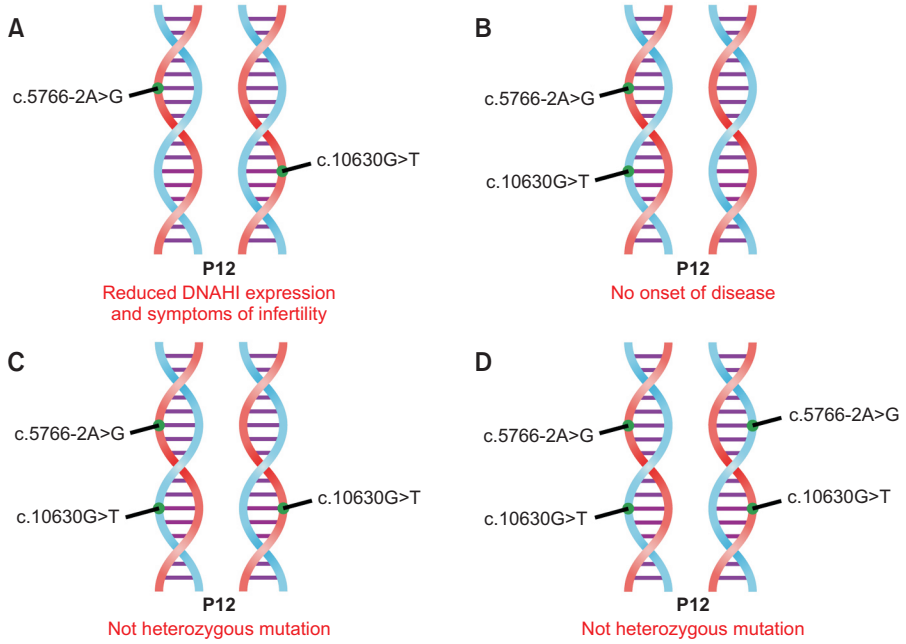

Fig. 4. The two *DNAH1* mutation loci in patient P12 are only likely to be on alleles. (A) When the two mutant loci c.5766-2A>G and c.10630G>T are on two alleles, P12 will exhibit symptoms of MMAF and both mutations are heterozygous. (B) When the two mutant loci c.5766-2A>G and c.10630G>T are on one chromosome, although both mutations are heterozygous, P12 will not exhibit symptoms of MMAF. (C, D) When one or both of the two mutant loci c.5766-2A>G and c.10630G>T are on both alleles, P12 will exhibit symptoms of MMAF, but one or both of these two mutations will be homozygous mutations rather than two heterozygous mutations. So P12 can only be the case of A, the compound heterozygous mutation. Similarly, the father of P12 could only be a compound heterozygous mutation. MMAF: multiple morphological abnormalities of the sperm flagella.

old), while the first *in vitro* fertilization in China was performed in 1988 [59] and the world's first ICSI procedure was performed in 1992 [60]. So, the parents of P12 must have conceived naturally. Therefore, we can conclude that there is a possibility that patients with *DNAH1* compound heterozygous mutations could have a natural pregnancy. We speculate that there may be two possibilities: (1) Individuals with *DNAH1* mutations may show intermediate asthenozoospermia and low levels of morphological anomalies [9]; (2) Patients with *DNAH1* mutations will have very few swimming sperm [55,56], which also has a chance to lead pregnancy.

5. ICSI can be used to treat infertility due to *DNAH1* mutations, but it is unclear whether *DNAH1* mutations will have an impact on ICSI treatment success

The outcome of ICSI in the treatment of MMAF has not yet been determined [61-63]. A total of 30 patients with infertility caused by *DNAH1* mutations were reported to be treated with ICSI with good results. However, due to the small number of cases, more evidence is still needed for support. In *in vitro* experiments in mice, *MDHC7-/-* sperm could fertilize, but a reduced number of 8-cell stage embryos were obtained [55]. Whether patients with *DNAH1* mutations have a lower success rate of ICSI treatment remains to be further confirmed.

CONCLUSIONS

The c.6912C>A and c.7076G>T mutations in *DNAH1* may lead to asthenozoospermia and MMAF. We cannot draw any definite conclusions from the available data, but the possibility that *DNAH1* might affect spermatogenesis and survival cannot be fully excluded. Patients with *DNAH1* mutations have a high percentage of short flagella and less frequently have significantly elevated bent flagella. ICSI is effective in treating *DNAH1* mutations, but it is unclear whether *DNAH1* mutations affect the success rate of ICSI. Patients with *DNAH1* compound heterozygous mutations might have the possibility of natural pregnancy.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: BJZ, YDY, XJY. Data curation: BJZ, SYX, LD, BLZ, DAC. Formal analysis: BJZ, XPH. Funding acquisition: XJY. Methodology: BJZ, SYX, XJY, PHZ. Project administration: XJY. Resources: XJY. Supervision: XJY. Validation: GSL, XJY, DGC. Visualization: BJZ, SYX. Writing – original draft: BJZ, SYX, LD, BLZ, XPH, GSL, YDY, DAC. Writing – review & editing: PHZ, XJY, DGC.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.210119.

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