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## REVIEW

Male Fertility

# Management of primary ciliary dyskinesia/Kartagener's syndrome in infertile male patients and current progress in defining the underlying genetic mechanism

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Kartagener's syndrome (KS) is an autosomal recessive genetic disease accounting for approximately 50% of the cases of primary ciliary dyskinesia (PCD). As it is accompanied by many complications, PCD/KS severely affects the patient's quality of life. Therapeutic approaches for PCD/KS aim to enhance prevention, facilitate rapid definitive diagnosis, avoid misdiagnosis, maintain active treatment, control infection and postpone the development of lesions. In male patients, sperm flagella may show impairment in or complete absence of the ability to swing, which ultimately results in male infertility. Assisted reproductive technology will certainly benefit such patients. For PCD/KS patients with completely immotile sperm, intracytoplasmic sperm injection may be very important and even indispensable. Considering the number of PCD/KS susceptibility genes and mutations that are being identified, more extensive genetic screening is indispensable in patients with these diseases. Moreover, further studies into the potential molecular mechanisms of these diseases are required. In this review, we summarize the available information on various aspects of this disease in order to delineate the therapeutic objectives more clearly, and clarify the efficacy of assisted reproductive technology as a means of treatment for patients with PCD/KS-associated infertility.

*Asian Journal of Andrology* (2014) 16, (101–106); doi: 10.4103/1008-682X.122192; published online: 16 December 2013

**Keywords:** assisted reproductive technology; clinical diagnosis and treatment; genetic mechanism; Kartagener's syndrome; male fertility, primary ciliary dyskinesia

## INTRODUCTION

In 1933, Kartagener for the first time reported four patients with 'sinusitis-bronchiectasis-*situs inversus* syndrome' and emphasized that this 'clinical triad' was a special kind of congenital syndrome with familial and hereditary characteristics. Therefore, the syndrome presenting all three symptoms was named complete Kartagener's Syndrome (KS). Another term, incomplete KS, was used to describe cases that did not involve *situs inversus*.<sup>1-3</sup>

A previous study has revealed some defects of the ciliary dynein arm in the airway epithelial cells of KS patients.<sup>4</sup> These defects may be related to the decreased mucosal scavenging capability and the absence of ciliary motility in KS. In 1988, Rossman and Newhouse<sup>5</sup> suggested a more appropriate nomenclature for this condition, i.e. primary ciliary dyskinesia (PCD). Generally, PCD encompasses all congenital ciliary dysfunctions, and the term 'KS' can still be used for describing the syndrome accompanied by *situs inversus*. KS is an autosomal recessive genetic disease accounting for approximately 50% of the cases of PCD. It is one of the most serious subtypes of PCD as it is caused by simultaneous abnormal ciliary function in several parts of the organism.<sup>6-8</sup>

In this review, we first discuss the incidence and various clinical manifestations of PCD/KS. Then, we present the probable molecular mechanism underlying this disease by summarizing the information on the known predisposing genes and the recent progress made in this

field. Next, we summarize the diagnostic and therapeutic approaches employed for PCD/KS on the basis of its partially understood pathoetiology. Throughout these sections, we have discussed several complications associated with PCD/KS, including the causal link between PCD/KS and male infertility, and we briefly point out appropriate treatment approaches for these complications.

## INCIDENCE AND CLINICAL MANIFESTATIONS OF PRIMARY CILIARY DYSKINESIA/ KARTAGENER'S SYNDROME

KS is a rare clinical disease. Its overall incidence is approximately 1/40 000, and it occurs in about 1% of cases of bronchiectasis and 20% of cases of *situs inversus*. The general age of onset is 10–29 year, and most of the patients are school-aged children or adolescents younger than 15 years of age. However, there is no significant difference in the incidence between males and females.<sup>2,9</sup>

Cilia are widely present in a variety of tissues and organs, such as the organs of the respiratory tract, paranasal sinuses, Eustachian tube, middle ear, oviduct, spermaductus, flagella of the sperm tail, brain and spinal cord ependyma. Therefore, clinical PCD/KS may not merely exhibit the typical 'clinical triad', but may often be accompanied by a variety of malformations or complications. The most common complications include congenital heart disease, hydrocephalus, cleft palate, bilateral cervical ribs, anal atresia, urethral crack and duplex

kidney. In addition, PCD/KS may be complicated by pulmonary heart disease,<sup>10</sup> acute mesangial proliferative glomerulonephritis,<sup>11</sup> renal cell adenocarcinoma,<sup>12</sup> central giant cell granuloma,<sup>13</sup> mediastinal tumor,<sup>14</sup> amyotrophic lateral sclerosis,<sup>15</sup> pulmonary hypertension/pulmonary capillary hemangioma,<sup>16</sup> diffuse bronchiolitis,<sup>17</sup> rheumatoid arthritis,<sup>18</sup> congenital glaucoma/cataracts, nearsightedness, membranous pupil, olfactory defects, serous mucinous otitis,<sup>19</sup> hearing loss, conductive deafness, nephrogenic bone defects,<sup>20</sup> pulmonary infundibular stenosis, chronic kidney failure,<sup>21</sup> reproductive tract abnormalities, testicular seminoma,<sup>22</sup> mental retardation, schizophrenia,<sup>23,24</sup> neonatal respiratory distress<sup>25-27</sup> and so on. Ciliary dysfunction in the oviduct or endometrium may lead to an increasing risk of ectopic pregnancy or infertility in women.<sup>3,28,29</sup> Sperm flagellum is also a type of cilia. Therefore, abnormal ciliary structure may lead to the reduction or loss of the ability of the flagellum to swing, ultimately causing male infertility.

### PATHOPHYSIOLOGY AND THE ROLE OF GENETIC FACTORS

The normal ultrastructural arrangement of cilia shows a typical '9 + 2' pattern: in cross-section, two central and nine pairs of peripheral microtubules can be observed by electron microscopy. All these units are linked by the following three structures. (i) A nexin link, viz., an elastic bridge linking consecutive microtubules, which plays a role in stabilizing the axoneme. (ii) Dynein arms, which allow the nine pairs of microtubules to slide against each other, resulting in a swing of the flagellum. The outer dynein arm (ODA) and the inner dynein arm (IDA) extend from the peripheral microtubules, which are connected by nexin links. (iii) Radiating spokes, which connect central microtubules with peripheral microtubules and change the distance between the peripheral microtubules and the center sheath so as to prevent excessive bending of the flagellum. Together, these structures play an important role in maintaining the overall structure of the flagellum.

A variety of structural defects inside the cilia have been found in patients with PCD/KS by electron microscopy. These defects involve abnormal radiating spokes, microtubular structure, ODA/IDA and so on. These defects are always consistent with the morphological performance of the stunted cilia, including abnormalities of the number (including absence) or structure (such as heterotopia, shortening) of the units mentioned above.<sup>30,31</sup> Currently, the known defects of cilia can be broadly divided into the following categories: (i) abnormalities of dynein arms, which occur most commonly<sup>32</sup> and include partial or complete absence of ODA/IDA,<sup>33</sup> (ii) abnormalities of radiating spokes, including the absence of spokes or centrotheca or deviated central microtubules, (iii) inappropriate directionality of cilia because of the partial or complete absence of the central microtubules<sup>33</sup> and (iv) abnormal number of peripheral microtubules. Atypical structures such as 8 + 1, 8 + 2, 8 + 3 or 7 + 2 have been observed on cross-section in some parts of histology. As more and more types of defects are found, more scientific classifications are being explored.<sup>34</sup> These defects of stunted cilia are usually the genotype determined characteristics of the patients, but secondary local anomalies caused by inflammation also cannot be ruled out completely in some cases.

During normal embryonic and fetal life, the rotation of various organs is specifically directed and determined by certain genetic factors. In this process, cilia facilitate the correct orientation of viscera sinus in the embryo by swinging in a certain direction. However, in the presence of ciliary disorders, this directional rotation may become random, which may result in malrotation of various organs. Partial or complete *situs inversus* may result in this manner.<sup>35</sup> In addition, congenital

systemic structural and functional abnormalities of cilia always result in defective ciliary clearing function, causing the retention of secretions or bacteria. Inflammation may also be initiated by blockage of the sinus apertures. Persistent or recurrent infections cause bronchiectasis or sinusitis, thus forming part of the pathological basis of KS.

The pathophysiology of PCD/KS is based on poor ciliary movement, which results from genetic defects of ciliary function.<sup>36,37</sup> Cilia contain a variety of structural proteins or regulatory proteins, and even only the axoneme is composed of more than 130 types of polypeptides; hence, hundreds of genes control these proteins. Theoretically, any mutation of related genes may eventually lead to the formation of dysfunctional cilia, which also reflects the genetic heterogeneity of PCD/KS patients.<sup>38,39</sup> For this reason, in the decades following recognition of PCD/KS as a clinical entity, many molecular genetic approaches have been applied for the following purposes: (i) to screen and identify candidate genes associated with the disease; (ii) to localize the candidate region of the PCD/KS-related genes in the genome;<sup>40-42</sup> and (iii) to investigate the relationships between the functions of these genes (including their mutations) and the different phenotypes of PCD/KS patients.<sup>43</sup>

The axonemal dynein intermediate chain gene, *DNAI1* (located on chromosome 9p12-21), and the axonemal dynein heavy chain gene, *DNAH5* (located on chromosome 5p15-14), are two of the best studied genes in PCD/KS. Mutations in these genes may result in absence of ODA, leading to abnormalities of ciliary ultrastructure and motor function.<sup>31,44-47</sup> A number of studies have shown the relationship between genetic mutation and PCD/KS phenotypes, thus driving the investigation of the underlying pathologic mechanism. Guichard *et al.*<sup>48</sup> performed mutation screening of *DNAI1* in 34 KS patients; they identified gene defects in *DNAI1* in three independent patients, and the family members of two of these patients also suffered from PCD without *situs inversus viscerum*. This study demonstrated the association between ciliary function and the localization of organs. In 2002, Ibanez-Tallon *et al.*<sup>49</sup> established a model of *Dnah5* defects in mice. After insertional mutagenesis, these animals presented with a variety of PCD exosyndromes, particularly hydrocephalus. Moreover, the absence of ODA in these animals could be clearly observed under electron microscopy. These results indicated that mutation of *Dnah5* was one of the major factors leading to PCD and provided direct evidence for the pathogenesis of hydrocephalus.

Besides *DNAI1* and *DNAH5*, other similar genes have been identified and studied in recent years. Dynein intermediate chain 2 (*DNAI2*) may be a candidate gene for PCD/KS according to a report by Pennarun *et al.*<sup>50</sup> It comprises 14 exons, is located on 17q25, and is highly expressed in the trachea and testes. In 2001, the complete cDNA and genomic sequences of axonemal beta heavy chain dynein (*DNAH9*) were first reported by Bartoloni *et al.*<sup>51</sup> In 2002, the same group reported that mutations in axonemal heavy chain dynein type 11 (*DNAH11*) may lead to PCD/KS-related symptoms. They also pointed out that KS may be related to paternal uniparental disomy of chromosome 7.<sup>8</sup> In 2008, Schwabe *et al.*<sup>52</sup> confirmed this view, but emphasized the possibility of retaining normal axonemal ultrastructure and male fertility when nonsense mutations in *DNAH11* occurred. In 2011, Mazor *et al.*<sup>53</sup> reported a homozygous point mutation of axonemal dynein light chain 1 (*DNALI1*), viz. NM\_031427.3: c.449A>G; p.Asn 150Ser. The occurrence of this mutation reduced the stability of DNALI1 and altered the correlation between this protein and the dynein heavy chain/microtubule. PCD may consequently result with absent or substantially shortened ODA. After identifying mutations in *DNAAF3* (also known as *PF22*), Mitchison *et al.*<sup>54</sup> suggested that *DNAAF3* plays an

important role in the pre-assembly of the dynein complex prior to the formation of cilia. The packing of an active cilia-dynein complex in the cytoplasm may follow a conserved, step-wise process, which is similar to the findings for some other pre-assembled proteins, such as DNAAF2 (also known as PF13 or KTU) and DNAAF1 (also known ODA7 or LRRC50).<sup>54,55</sup>

Apart from axoneme-related genes, several other candidate genes for PCD/KS have been screened for mutations and studied in order to clarify their physiological functions.<sup>56-59</sup> DNA polymerase lambda (Pol lambda, also known as Pol beta 2), a member of the DNA polymerase X family, has 32% homology with DNA Pol beta at the amino acid level. In 2002, Kobayashi *et al.*<sup>60</sup> prepared Pol lambda<sup>(-/-)</sup> knockout mice utilizing homologous recombination technology. The embryonic development of these mice appeared to be normal; however, most of them showed hydrocephalus with characteristic lateral ventricle expansion, resulting in high postnatal mortality. The surviving individuals always suffered from chronic purulent sinusitis accompanied by visceral translocation; males were sterile because of motionless sperm. Normal offspring could be produced through intracytoplasmic sperm injection (ICSI), suggesting that meiosis was not affected, but ultrastructural analysis showed that the IDA of the ependymal cells and respiratory epithelial cells were not intact, which may be the basis of the disease. Zariwala *et al.*<sup>61</sup> identified *Dpcd* as a candidate gene for PCD. In 2002, Pennarun *et al.*<sup>62</sup> isolated human *PF20* and screened this gene in five patients with abnormal ciliary structure. Human PF20 showed homology to *Chlamydomonas* PF20. Furthermore, adenylate kinase 7 (AK7) provides energy for the beating of cilia via conversion of adenylic acids (2ADP = ATP + AMP). In 2010, Milara *et al.*<sup>63</sup> measured AK7 expression by real-time PCR and western blotting and investigated its effect on the ciliary beat frequency by siRNA experiments. They also evaluated the motility and ultrastructure of cilia in 29 PCD/KS patients and 26 healthy people, and found that the expression of AK7 was related to ciliary beat frequency, which may be a cause of ciliary dysfunction in PCD/KS patients. A study by Mata *et al.*<sup>64</sup> in 2012 also found two mutations on AK7 in PCD/KS patients; viz., a previously reported single-nucleotide polymorphism (rs 2369679) and a novel mutation, c.1214insT, which may also be associated with PCD/KS.

In 2011, Geremek *et al.*<sup>65</sup> generated genome-wide gene expression profiles using bronchial extractions from a PCD patient and identified many genes highly related to PCD by employing a quality-threshold clustering algorithm. Of the 372 genes identified, 164 were known, strongly suggesting that the remaining 208 may be new cilia-related genes, which provides a number of candidates for investigation in PCD/KS. However, it is likely that not all mutations in these genes will cause abnormal ciliary movement, which indirectly reflects the intrinsically complex link between genetic variation and morbid phenotype.<sup>66-68</sup>

## DIAGNOSIS

In practice, the clinical diagnosis of PCD/KS is not difficult. The main clinical manifestations of the condition include recurrent chronic cough, sputum, nasal congestion, nasal discharge, hemoptysis and other symptoms of respiratory infections.<sup>3,69</sup> The incidence of PCD/KS among the offspring of consanguineous marriages is about 20%–30%; the incidence is especially pronounced in Caucasians. PCD is a congenital, clinically and ultrastructurally heterogeneous disease due to abnormal structure and/or function of cilia, and KS is an autosomal recessive genetic disease accounting for approximately 50% of the cases of PCD. It may recur in the same generation or show an inter-generational familial hereditary tendency.<sup>70</sup> Accordingly, the parents of patients may have a consanguineous or inter-generational marital history and the

patients' brothers or sisters may also suffer from PCD/KS. Therefore, the acquisition of detailed, relevant information is crucial.<sup>71</sup>

Imaging investigation is one of the important methods in the diagnosis of KS.<sup>72</sup> In order to confirm whether bronchiectasis or sinusitis, both of which are important clues for the diagnosis of KS, are present, some auxiliary examination of the chest or sinuses may be needed, depending on the clinical manifestations. Imaging diagnosis of bronchiectasis and sinusitis is relatively easy because these are common diseases. Dextrocardia is the main basis for imaging diagnosis of PCD/KS, because it is the most essential sign of the syndrome. Dextrocardia may be associated with the reversal of the S-shaped heart tube during embryonic development, and it is easily discovered by tube of radiography.

In addition to imaging investigation, biopsies of the nasal or airway mucosa may contribute to the diagnosis of PCD/KS. However, artificial secondary ciliary damage must be avoided by obtaining the biopsy materials from the relatively healthy parts of the patient in a stable state. A culture of ciliated epithelial cells may also be required.<sup>73,74</sup> If ultrastructural defects inside the cilia are observed under scanning electron microscopy or transmission electron microscopy, and if these defects have the morphological appearance of ciliary dysplasia, PCD can be diagnosed.<sup>75</sup> The cilia of patients with other mucous clearance defects have no ultrastructural defects, but do demonstrate decreased oscillatory frequency or abnormal arrangement patterns in their internal structure.<sup>76</sup> Given that the clinical manifestations of these patients may not be obvious or typical, some noninvasive examinations should be considered, such as a saccharin experiment or the measurement of nitric oxide concentrations in exhaled nasal air.<sup>31,76-79</sup> For instance, if the concentration of nasal nitric oxide is substantially lower than control values, PCD/KS is more likely to be positively diagnosed.<sup>73</sup> Another technique, the pulmonary radioaerosol mucociliary clearance test has also shown excellent sensitivity and specificity in the diagnosis of PCD/KS.<sup>74,80,81</sup>

Genetic diagnosis is another approach for assisting diagnosis of PCD/KS, but it is not yet popularly applied in the clinical setting.<sup>77,82,83</sup> In 2007, Morillas *et al.*<sup>29</sup> developed a clinical genetics analytical method that used *DNAI1* and *DNAH5* and involved a total of nine exons; the most common mutations in these two genes could be detected using this method, thereby promoting genetic diagnosis of PCD/KS. Given that the number of PCD/KS susceptibility genes and mutations that are being identified continues to increase, more extensive genetic screening should be performed in PCD/KS patients in the future.

It is important that incomplete and wrong diagnoses, such as diagnoses of ordinary sinusitis, pneumonia, asthma and tuberculosis, are avoided as much as possible; there are few specific indications during the early onset of PCD/KS, and several atypical presentations may occur. Bronchiectasis, for example, is an important indication of PCD. For a more definite diagnosis, some known causes of bronchiectasis, such as fibrosis, primary immunodeficiency, antitrypsin deficiency and some connective tissue diseases, must be ruled out. For adult patients, PCD can almost be ruled out if no bronchiectasis can be observed through high-resolution CT.<sup>84</sup>

## TREATMENT

McManus *et al.*<sup>85</sup> described faster development of respiratory symptoms before the age of 25 years, which worsens more slowly after this age. Therefore, treatment for PCD/KS should be initiated as early as possible, although there is currently no cure. For the treatment of bronchiectasis, the use of anti-infective therapies that promote discharge of secretions is indispensable. Since severe bronchiectasis may adversely affect



the prognosis of the disease, pneumonoresection may be applied to treat local bronchiectasis without other visceral injury. For sinusitis, intranasal corticosteroids can be used in addition to drainage methods, and sensitive antibiotics should be cautiously adopted according to the results obtained in the culture of secretions. If conservative treatment is ineffective or if severe nasal polyps are accompanied by sinusitis, nasal endoscopic surgery can be considered. Effective treatment of sinusitis may relieve progression of bronchial and lung disease. Given the serious consequences that usually result from lung damage caused by repeated infections, such as respiratory insufficiency, pulmonary heart disease and heart failure; the therapeutic objectives for PCD/KS are to enhance prevention, facilitate prompt definitive diagnosis, avoid misdiagnosis, ensure active treatment, control infection and postpone development of lesions.<sup>72,86–89</sup> Adherence to these objectives will usually ensure a good prognosis.<sup>90</sup>

The sperm of infertile male patients with PCD/KS are usually immotile to varying degrees, or are even completely static and manifest defective morphology. Afflicted men generally have immotile ejaculated sperm and have almost no chance of achieving a spontaneous pregnancy. For these PCD/KS patients, assisted reproductive technology, including *in vitro* fertilization and ICSI, should be considered. *In vitro* fertilization could be a treatment option for patients when sperm motility is retained.<sup>91</sup> However, ICSI is currently the only treatment option for most PCD/KS patients. ICSI overcomes the factors related to impaired motility and bypasses the natural processes for fertilization. A number of reports have confirmed that it is possible to obtain healthy offspring in PCD/KS patients with the help of ICSI technique.<sup>92–103</sup>

The sperm for ICSI could be obtained from ejaculate, epididymis or testis. Although some authors reported successful pregnancies using sperm from ejaculate,<sup>95,104</sup> it has been demonstrated that fertilization is improved with immotile testicular spermatozoa.<sup>92</sup> Until a better understanding of genetic control of PCD/KS is achieved, successful ICSI treatment will depend on sperm motility and should be individualized.<sup>100</sup> When using immotile sperm, differentiation between live and dead sperm is critical for the success of ICSI.<sup>105</sup> Some practical methods have been developed to differentiate and improve sperm motility. The hypoosmotic swelling test is widely used for identification of viable spermatozoa in a pool of immotile spermatozoa for ICSI.<sup>102,104</sup> A noncontact diode laser assessment for sperm viability may be a useful alternative, especially in cases where the hypoosmotic swelling test is not informative.<sup>106</sup> A new sperm-screening method based on SYBR-14/propidium iodide flow cytometry has recently been reported.<sup>107</sup> To improve their motility, sperm with greater potential for fertilization may be obtained from ejaculated semen if patients undergo multiple ejaculations before providing the sample for *in vitro* fertilization/ICSI.<sup>108</sup> In addition, the velocity of sperm can be stimulated by treatment with pentoxifylline, a phosphodiesterase inhibitor. Employing this approach, a successful pregnancy and live delivery has been achieved.<sup>109</sup>

To date, it has been demonstrated that ICSI is an effective treatment modality for PCD/KS patients even with severest forms of male factor infertility.<sup>95</sup> However, it should be noted that the fertility of PCD/KS patients can still not be compared with that of the normal population,<sup>28,110</sup> even though there have been many positive reports. In addition, clinical practitioners should be aware that the low fertility in male PCD/KS patients may involve a high incidence of aneuploid sperm, which is related to primary flagellum abnormalities.<sup>111</sup> Although the reported pregnancies and offspring are mostly normal and healthy,<sup>95,97–103</sup> it should be noted that the defects not only cause impaired fertility, but also increase the risk of genetic defects in the offspring. Therefore, genetic counseling may be mandatory for couples pursuing assisted reproductive

technology and genetic assessment of sperm is highly recommended prior to clinical action.<sup>110</sup> To avoid undesirable cycles of treatment with a high possibility of failure or inheritance of genetic diseases, use of a semen donor may be a better option for some patients with severe defects.

In summary, PCD/KS severely affects the quality of life of patients, and the male infertility resulting from the disease is a major concern. More rapid, accurate, effective and economic means of diagnosis as well as treatments will hopefully be developed in the near future. The popularity of assisted reproductive technology will certainly benefit infertile couples affected by this disease. However, full understanding of the underlying molecular mechanisms of PCD/KS will require further studies.

## AUTHOR CONTRIBUTIONS

YWS and LD drafted the manuscript, and PL revised it critically for important intellectual content. All authors have read and approved the final manuscript.

## COMPETING INTERESTS

All authors declare no competing interests.

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**How to cite this article:** Sha YW, Ding L, Li P. Management of primary ciliary dyskinesia/Kartagener's syndrome in infertile male patients and current progress in defining the underlying genetic mechanism. *Asian J Androl* 2013 Dec 16. doi: 10.4103/1008-682X.122192. [Epub ahead of print]

