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Report

Axonemal Dynein Intermediate-Chain Gene (*DNAI1*) Mutations Result in Situs Inversus and Primary Ciliary Dyskinesia (Kartagener Syndrome)

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Kartagener syndrome (KS) is a trilogy of symptoms (nasal polyps, bronchiectasis, and situs inversus totalis) that is associated with ultrastructural anomalies of cilia of epithelial cells covering the upper and lower respiratory tracts and spermatozoa flagellae. The axonemal dynein intermediate-chain gene 1 (*DNAI1*), which has been demonstrated to be responsible for a case of primary ciliary dyskinesia (PCD) without situs inversus, was screened for mutation in a series of 34 patients with KS. We identified compound heterozygous *DNAI1* gene defects in three independent patients and in two of their siblings who presented with PCD and situs solitus (i.e., normal position of inner organs). Strikingly, these five patients share one mutant allele (splice defect), which is identical to one of the mutant *DNAI1* alleles found in the patient with PCD, reported elsewhere. Finally, this study demonstrates a link between ciliary function and situs determination, since compound mutation heterozygosity in *DNAI1* results in PCD with situs solitus or situs inversus (KS).

Kartagener syndrome (KS [MIM 244400]) (Kartagener 1933) was initially described by Siewert (1904). The respiratory signs (nasal polyposis and bronchiectasis) that are part of the trilogy of symptoms are the long-term results of recurrent upper and lower respiratory tract infections that start early in life. A similar condition, referred to as immotile cilia syndrome (ICS) (*ICS1* [MIM 242650]) or later primary ciliary dyskinesia (PCD), is associated with the same respiratory symptoms. In both KS and PCD, respiratory infections are secondary to defective cilia that do not beat efficiently, impairing the drainage of inhaled particles and microbes to the oropharynx. KS and PCD are associated with anomalies of cilia structure—in particular, missing or abnormal dynein arms, abnormal radial spokes, and missing central pair of microtubules (Afzelius 2000). These anomalies may also be observed in the flagella of spermatozoa. The examination of cilia under an electron microscope is difficult, because biopsy specimens are often altered by recurrent infections. Furthermore, it is not always possible to distinguish primary from secondary ciliary alterations unless cells are cultured in a sequential monolayer/suspension system after biopsy (Jorissen and Willems 2000). Because PCD and KS could be observed in the same sibship and even in monozygotic twins (Noone et al. 1999), it was stated that KS was part of PCD and that laterality direction in PCD was randomized, resulting in 50% of patients with situs inversus and hence KS (Afzelius 2000). Nevertheless, there is no large-series study to confirm this hypothesis. Moreover, in two isolated populations of Polynesians, PCD is highly prevalent but not associated with situs inversus (Waite et al. 1981). In addition, a mouse mutant with hydrocephalus and anomalies of cilia and flagella does not exhibit situs inversus (Bryan 1977). This suggests that randomization of situs applies only to a subset of cases of PCD.

The first gene in which mutations were found to be associated with PCD was *DNAI1* (MIM 604366) (Pennarun et al. 1999) *DNAI1,* an axonemal dynein inter-

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mediate-chain gene that was isolated from *Chlamydomonas reinhardtii,* a unicellular alga with two flagella containing an axonemal structure similar to that of human respiratory cilia and sperm tails (Blair and Dutcher 1992; Vallee 1993; Porter 1996). Axonemal dyneins are found in ciliary and flagellar axonemes. The axonemal ultrastructure, which is highly conserved through evolution, is composed of nine outer-doublet microtubules that surround a central pair of microtubules. Two dynein arms—outer and inner—are bound to each peripheral microtubule doublet. Dynein arms are composed of several dynein heavy, intermediate, and light chains. Dynein heavy chains, the main component of dynein arms, are encoded by multiple genes in humans (Milisav et al. 1996; Vaughan et al. 1996; Chapelin et al. 1997; Neesen et al. 1997). An additional dynein heavy chain gene (*DNAH10*) and a pseudogene (*DNAH7p*) were recently reported, along with a classification and chromosomal mapping of known human dynein heavy chain genes (Maiti et al. 2000). These dynein arms are essential for ciliary and flagellar beating, which they generate through an ATP-dependent cycle of attachment-detachment to the adjacent microtubule doublet (Witman 1992; Shingyoji 1998). The dynein intermediate gene *DNAI1* is localized on 9p13-p21 and is composed of 20 exons encoding a 699–amino acid protein.

Given that the pathophysiology of KS seems close to that of PCD, one could speculate that each gene involved in PCD may be a good candidate to be investigated in KS and that each gene involved in KS may be a good candidate to be investigated in PCD. Alternatively, two distinct genes could underlie KS and PCD. Since the patient with compound mutations in *DNAI1* had PCD without situs inversus, we undertook to screen a series of patients with KS for mutations in *DNAI1.*

In the present report, we studied 34 independent patients with KS. Blood samples were obtained after informed consent. To search for mutations in *DNAI1,* the 20 exons of the gene were amplified by PCR with intronic primers, according to the method described by Pennarun (1999). Amplified fragments were electrophoresed by SSCP at 7°C and at 20°C, except for exon 13 amplicon, which was digested with *Afl*III prior to migration, on a 10% acrylamide gel (acrylamide/bisacrylamide: 29/1) with TBE 1× buffer at 16 mA per gel, for 2 h 30 min to 6 h (depending on the size of each

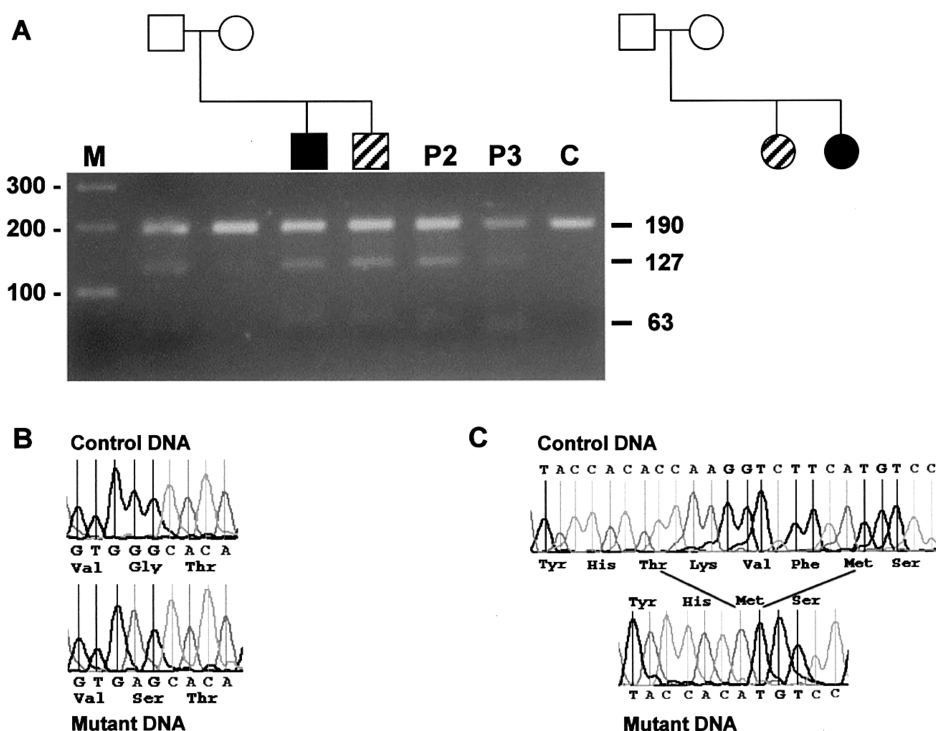

Figure 1 *A,* Pedigree tree of the families of patients 1 and 2. Below symbols of the family tree of patient 1 is the agarose gel of exon 1 amplicons after digestion with *Hpa*I. On the left-hand side, the size marker: a 100-bp ladder. Bars on the right-hand side indicate the position of obtained bands (190, 127, and 63 bp). Band 190 bp is the uncut amplicon; bands 127 and 63 bp are the cut bands when there is a T insertion in the splicing site. Blackened symbols indicate patients with KS; oblique stripes indicate patients with PCD. P2 and P3 indicate patients 2 and 3 of this study. *B,* Electrophoregram of the normal and missense mutations of patient 1. *C,* Electrophoregram of the normal and the 12-bp deletion observed in patient 3. Both abnormal electrophoregrams were obtained after cloning the amplicons.

fragment). When bandshifts were identified, the corresponding PCR products were cloned in a pGEM-T vector system (Promega) and five or more clones were sequenced in both directions.

Three independent patients with KS were found to have mutations in the *DNAI1* gene. Patient 1 has a brother who has recurrent upper and lower respiratory tract infections and sterility without situs inversus (fig. 1*A*). Repeated spermograms of his brother demonstrated immotile spermatozoa flagellae. Both brothers also presented ureteral lithiasis, an anomaly that is not usually reported in patients with PCD or KS. The cilia of the brother show absent or truncated outer dynein arms (fig. 2), but no biopsy from patient 1 was available. Both individuals were heterozygous for a common loss-of-function mutation identified in Pennarun's patient: a T insertion at position 3 of the intron 1 donor site that results in absence of splicing and peptide truncation. This mutation was confirmed by digesting the amplicon with *Hpa*I (fig. 1*A*). In addition to this mutation, patient 1 and his brother had a transition in exon 16 at position 1543 (G→A) that resulted in a glycine to serine transposition at position 515 (fig. 1*B*). This glycine is highly conserved in both sea urchin IC2 and *Chlamydomonas* IC78 (Pennarun et al. 1999) and is a potential N-myristoylation site (*G*TEEGK) (PROSITE, Database of Protein Families and Domains). Moreover, testing parental DNA demonstrated that the splicing error was inherited from the father and the missense mutation from the mother (fig. 1*A*).

Both patient 2 and her sister (fig. 1*A*) (who has PCD without situs inversus) have the same compound mutations as patient 1; both also had children. Patient 3, who has no other affected sibling, has situs inversus totalis, chronic sinusitis, bronchitis, recurrent otitis, and aplasia of frontal sinus. She refused to have a nasal or bronchial biopsy. She has compound *DNAI1* gene defects. One gene defect is the same splice defect as observed in patients 1 and 2. The other mutation is a 12-bp deletion (fig. 1*C*), which results in truncation of DNAI1 by four amino acids in the fourth WD domain. This deletion removes a phenylalanine at position 556, which is conserved between sea urchin IC2, *Chlamydomonas* IC78, and human DNAI1.

To confirm that the missense and deletion mutations were causative, we tested 200 normal chromosomes by SSCP analysis and *Sty*I digestion, respectively (the 12-bp deletion removes a *Sty*I site). None showed the same pattern of migration as the DNA of patients.

The T insertion in intron 1 is a highly prevalent *DNAI1* mutation, since it represents four of eight mutant alleles so far reported in patients with PCD and KS. This observation suggests that the patients with *DNAI1* splice defect were related. Nevertheless, we were unable to demonstrate a familial relationship between these patients who originated from different geographic areas. To test for a founder effect, we searched for polymorphisms in the vicinity of this splice defect. We found no variation in the 5′ untranslated sequence or in the intronic sequence of the amplicon; however, we detected a variant in the coding sequence of exon 1: a G→T transversion at position +22 that changes the encoded amino acid from alanine to serine and suppresses a *Nla*IV restriction site. This variation was considered to be a polymorphism, since this alanine residue is not conserved between human, sea urchin, and *Chlamydomonas*. Moreover, this transversion was found in several control DNAs. Unfortunately, this polymorphism was uninformative in this study, since patients 1, 2, and 3 were all homozygous G/G.

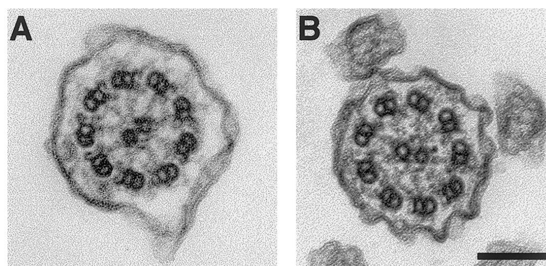

Figure 2 Electron-microscopic specimen of a normal case (*A*) and of the brother of patient 1 (*B*). The outer dynein arms are shortened or missing. Bar: 0.1 μm. Tracheal biopsies were fixed with 2.5% glutaraldehyde in 0.1M cacodylate buffer, pH 7.4, postfixed 1 h at 4°C in 1% osmium tetroxyde in 0.1 M cacodylate, and, after 1 h impregnation in 2% aqueous uranyl acetate, embedded in Epon. Ultrathin sections were stained with uranyl acetate and lead citrate and were examined at 80 KV with a JEOL 2000EX electron microscope.

In this series, 31 (91%) of 34 patients with KS had no mutations, which strongly suggests that KS is, like PCD (Pennarun et al. 1999), a heterogeneous condition. This hypothesis was confirmed by showing, by means of both SSCP and DNA sequencing, that two of the nine patients with consanguineous parents were heterozygous at one or both of the polymorphic sites, described elsewhere, in exon 11 of *DNAI1* (Pennarun et al. 1999). Furthermore, in three pairs of affected siblings with nonconsanguineous parents, two had discordant genotypes at this locus. These data demonstrate KS heterogeneity, because it is very unlikely that four recombination events would have occurred in this small sample within a gene of 62 kb (Centre de Ressources INFOBIOGEN).

In conclusion, we have demonstrated that mutation in *DNAI1* may result in KS, thus establishing the first molecular basis for KS. Moreover, this work confirms the attractive hypothesis that, in some patients with PCD, the proper body asymmetry is the result of random determination of left-right asymmetry, since in two sibships compound heterozygous mutations resulted in

PCD with or without left-right inversion. This is also the first molecular demonstration of autosomal recessive inheritance of lateralization defects. Before *DNAI1,* other genes have been shown to be associated with laterality disturbances in humans: *ZIC3* (Gebbia et al. 1997), *LEFTY A* (Kosaki et al. 1999*a*), *ACVR2B* (Kosaki et al. 1999*b*), and *CFC1* (Bamford et al. 2000). However, in the autosomal genes (*LEFTY A, ACVR2B,* and *CFC1*), no patients with compound mutations were found, which suggests that the inheritance mode is not recessive, as in the case of *DNAI1,* but is di- or trigenic.

This work, although refuting the hypothesis that two closely linked loci may be involved in KS and in PCD, confirms the link between abnormal ciliary function and situs determination (Afzelius 1999). A link between cilia motility and lateralization determination was already provided by mouse mutants defective in genes required for cilia growth (*Hfh4*) (Chen et al. 1998; Brody et al. 2000) or beating (*Kif3B* and *Kif3A*) (Nonaka et al. 1998; Takeda et al. 1999). Nodal cells of the mouse embryo have a unique cilium at their apical pole. This cilium does not actually beat but displays an anticlockwise vortex movement. Nonaka et al. (1998) showed elegantly, by adding a dye to the extraembryonic fluid, that cilia rotation induces a leftward directional flow to this extraembryonic fluid, potentially concentrating on the left side and depleting on the right side, which are critical factors that would initiate the cascade of molecular events leading to normal lateralization (Nonaka et al. 1998). If this vortexing movement is absent, as it is in *Kif3A*- and *Kif3B*-deficient mice (Nonaka et al. 1998; Takeda et al. 1999), there is presumably no left-right gradient of signaling factors, and hence laterality is randomized. In support of this hypothesis, Okada et al. (1999) showed that the mouse mutants *iv* (Supp et al. 1997, 1999) and *inv* (Mochizuki et al. 1998; Morgan et al. 1998), which present laterality defects, do not display a normal nodal cilia motility. Curiously, the *iv* mutation is located in the *lrd* (left right dynein) gene, which encodes a dynein-heavy–chain gene, although homozygous mice do not express any respiratory symptoms.

In contrast with *Kif3A* and *Kif3B* mouse mutants, which present severe developmental anomalies, the *Hfh4* mutant mouse has randomized laterality, hydrocephalus, and growth retardation but survives up to 12 wk after birth. Interestingly, Hfh4 -/- mice have nodal cilia; it is not known, however, whether these cilia are functional (Brody et al. 2000). Because *Kif3A*- and *Kif3B*-deficient mice die before ciliogenesis of airway epithelial cells, it is also not known whether these mutants have normal ciliary growth and motility. These data suggest that *Hfh4* is a candidate gene to be considered in cases of human PCD. Indeed, the human ortholog gene *HFH4,* recently renamed *FOXJ1* (MIM 602291), was screened in a series of human patients with PCD, and no mutations were identified; however, it was not specified whether any patients had ciliary aplasia (Maiti et al. 2000). Aplasia of cilia accounts for ~4% of PCD (Jorissen et al. 2000), and it would be worthwhile repeating *FOXJ1* screening in patients with bona fide ciliary aplasia, a condition that is best evidenced after in vitro culture of respiratory epithelial cells (Jorissen et al. 2000).

DNAI1 maps to 9p13-p21, even though this chromosomal region was not detected as potentially harboring a gene implicated, by linkage analysis, in PCD (Blouin et al. 2000). It confirms that it is difficult to detect linkage in such a highly heterogeneous autosomal recessive condition. In the two cases in which electron microscopy was available, *DNAI1* mutations were associated with abnormal outer dynein arms. Nevertheless, this anomaly is not specific to this gene defect, since Pennarun et al. (1999) excluded *DNAI1* mutations in two patients with PCD from consanguineous families who had abnormal outer dynein arms.

In this report, we have provided evidence for the high prevalence of a splicing defect in the four independent cases of compound heterozygous *DNAI1* gene defects so far reported. Further studies are required to confirm this high prevalence and to conclude whether the underlying molecular mechanism is the result of a founder effect or a recurrent mutation event.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Centre de Ressources INFOBIOGEN, http://www.infobiogen.fr/srs/ (accession number AL359088)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for KS [MIM 244400], ICS1 [MIM 242650], and *DNAI1* [MIM 604366])

PROSITE, Database of Protein Families and Domains, http://www.expasy.ch/prosite

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