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Paternal Isodisomy of Chromosome 7 Associated with Complete Situs Inversus and Immotile Cilia

To the Editor:

Uniparental disomy (UPD) refers to the inheritance of two homologous chromosomes from one parent, in a diploid individual. Heterodisomy is the inheritance of both parental homologues, whereas isodisomy implies the inheritance of two copies of a single parental homologue (Engel 1980). Uniparental inheritance of a human autosome in a cytogenetically normal individual was first recognized by Spence et al. (1988), on the basis

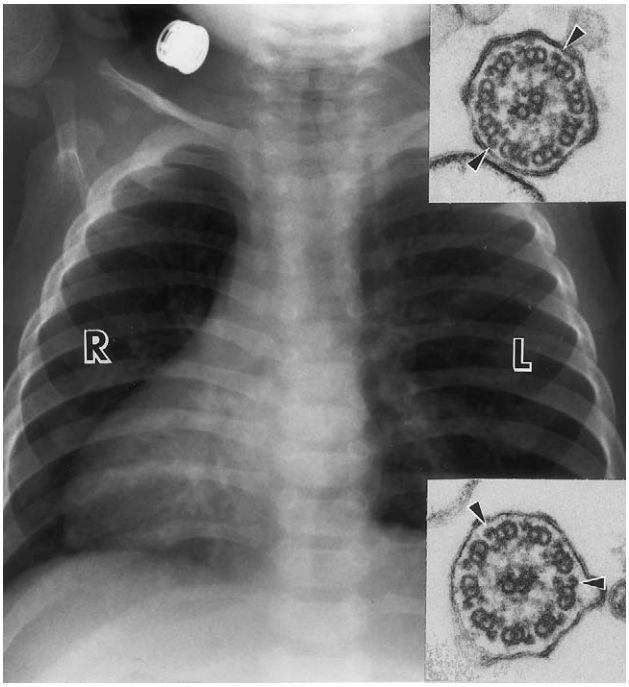

Figure 1 Complete situs inversus. A chest X-ray demonstrates the laterality defect manifested as dextrocardia and visceral situs inversus. The ultrastructural appearance of bronchial cilia is shown in the insets. Note normal axonemal structure with typical 9 + 2 doublet microtubular configuration. Arrowheads indicate normal inner and outer dynein arms (transmission electron microscopy).

of the failure to detect a paternal allele in the course of genotyping a patient with cystic fibrosis (CF; MIM 219700).

Patient CC was born at 34 wk gestation to a 20-year-old Hispanic mother after an uncomplicated pregnancy. His birth weight was 2,540 g and the newborn physical exam was reported as normal. The family history was unremarkable, and there was no known consanguinity. He developed respiratory distress at 10 d of age, and a chest X-ray and echocardiogram demonstrated dextrocardia with a structurally normal heart (fig. 1). An abdominal ultrasound demonstrated visceral situs inversus with a structurally normal spleen. At 6 mo of age, the child was growth retarded with signs of significant respiratory disease. A tracheal aspirate grew *Pseudomonas aerugenosa* and *Staphylococcus aureus,* and a sweat chloride test confirmed the clinical diagnosis of CF. Because of the presence of situs inversus and severe lung disease, a bronchial biopsy was performed to evaluate ciliary function. The respiratory mucosal brushings were obtained by the endoscopist, transported in isotonic saline, and immediately examined by the pathologist. The endoscopist was instructed to avoid mucosal areas with acute and/or chronic inflammatory changes, such as erosions, ulcerations, or hyperemia, and to sample only those areas that appear clinically normal. Microscopic examination for ciliary motility was performed by use of dark-field microscopy with the cytologic material diluted with saline (Rutland and Cole 1980, 1981). An exhaustive search with numerous wet preparation slides was performed. No normal ciliary motion was observed, despite the lack of an inflammatory infiltrate. Electron microscopy of the sample demonstrated structurally normal cilia (fig. 1, *inset*).

A peripheral lymphocyte karyotype was normal. DNA testing showed the patient to be homozygous for the ΔF508 CFTR (*c*ystic *f*ibrosis *t*ransmembrane-conductance *r*egulator) mutation, with his mother lacking any detectable alteration. To further define the mode of inheritance, DNA was extracted from lymphoblasts of the patient and his mother; a sample from the father was not available for study. PCR amplification was carried

Table 1

DNA Markers and Results of Genotyping

Chromosome and Marker[a]	Location	Alleles		Heterozygosity
		Mother	Patient	
7:				
D7S531[b]	7pter-p15	2,3	1,1	.77
D7S481	7pter-p15	1,2	2,2	.84
D7S507[b]	7pter-p15	1,2	3,3	.89
D7S488[b]	7p21-p15	1,2	3,3	.83
D7S673[b]	7	1,2	3,3	.86
D7S526[b]	7p21-p15	1,2	3,3	.71
D7S485[b]	7p15	2,2	1,1	.78
Elastin	7q11.23	1,2	1,1	.63
D7S849	7p11-q21	1,2	2,2	.57
D7S440	7q	1,1	1,1	.73
D7S492	7q15-q22	1,2	1,1	.76
D7S501	7q31	1,1	1,1	.81
D7S471[b]	7	1,3	2,2	.83
D7S650	7q	1,1	1,1	.85
D7S640[b]	7q	2,3	1,1	.85
D7S495	7q31-q35	1,2	1,1	.81
D7S636	7	2,3	1,1	.90
D7S483[b]	7q31-qter	1,2	3,3	.82
D7S550[b]	7q31-qter	2,3	1,1	.83
D7S489	7p15-q22	1,2	1,1	.38
D7S467	7q35-q36	1,1	1,1	.93
Other:				
D1S249		1,2	2,3	.87
D9S195		1,1	1,2	.74
D9S67		2,2	1,2	.64
D10S187		1,2	1,1	.83
D10S211		1,2	2,3	.83
D14S67		2,3	1,2	.87
D14S68		2,2	1,2	.88
D16S406		1,1	1,1	.83
D17S806		1,3	1,2	.90
D21S1255		1,2	1,2	.80

[a] Twenty one polymorphic loci were examined for evidence of UPD for chromosome 7, and 10 markers from other chromosomes were used to examine maternity.

[b] Demonstrated uniparental isodisomy.

out under standard conditions for the di- and trinucleotide repeat loci listed in table 1 (Gyapay et al. 1994), by use of a Perkin-Elmer 480 device and polyacrylamide electrophoresis. A total of 21 loci along the length of chromosome 7 were used to demonstrate paternal isodisomy for the chromosome. The patient was homozygous at all 21 loci, with 10 of the markers being fully informative for paternal inheritance. To establish that maternity is correct, 10 highly polymorphic markers (6–16 alleles for each) for autosomal loci other than chromosome 7 were tested. The patient shared at least one allele at each locus with his mother, indicating a high likelihood (>99%) of maternity.

To address the possibility of a second independent etiology for situs abnormalities, the patient's DNA was examined for deletions within the critical region of the X-linked heterotaxy locus in Xq26.2 (MIM 306955; Casey et al. 1993), and the coding region of a recently identified gene that when altered leads to heterotaxy (Gebbia et al. 1997) was sequenced. Males with X-linked heterotaxy typically have complex heart anomalies in addition to visceral situs ambiguous (Casey et al. 1993), a feature lacking in this patient. Sporadic cases of heterotaxy have been described with submicroscopic deletions within this critical region (Ferrero et al. 1997). A total of nine sequence-tagged-site markers distributed throughout the critical region were used to search for submicroscopic deletions, and none were identified (data not shown). Furthermore, the protein-encoding exons from the gene now known to be responsible for X-linked heterotaxy (*ZIC3;* Gebbia et al. 1997) was sequenced from the patient, and no mutation was identified. In addition, the differential display technique (Liang and Pardee 1992) was used to compare transcripts present in lymphoblasts from this patient, a patient with maternal isodisomy of chromosome 7 (Spence et al. 1988), and from control cell lines. This analysis failed to identify any differentially expressed transcripts among these cell lines (except for immunoglobulin light-chain transcripts), possibly because of the cell type used as the source of RNA.

Several possible mechanisms for UPD have been proposed, including gamete complementation, postzygotic monosomy duplication, reduction to disomy of a trisomic conception, and somatic crossing over (Spence et al. 1988). The two more likely explanations in this case would be (1) monosomy duplication associated with a nullisomic maternal gamete or (2) a paternal meoisis II nondisjunction resulting in a trisomic conceptus, with subsequent reduction to disomy through loss of the maternal chromosome 7 (trisomic rescue). UPD is increasingly recognized as a mechanism for the non-Mendelian transmission of a recessive disorder (reviewed by Ledbetter and Engel 1995). In addition to CF, examples include methylmalonic aciduria (MIM 251000; Abramowicz et al. 1994), rod monochromacy (MIM 216900; Pentao et al. 1992), Bloom syndrome (MIM 210900; Woodage et al. 1994), lipoprotein lipase deficiency (MIM 238600; Benlian et al. 1996), Duchenne muscular dystrophy in a female (MIM 310200; Quan et al. 1997), Herlitz junctional epidermolysis bullosa (MIM 226700; Pulkkinen et al. 1997), and congenital chloride diarrhea (CLD; MIM 214700; Hoglund et al. 1994). As with several cases of maternal disomy of chromosome 7, the patient was initially identified because of CF. Maternal isodisomy for chromosome 7 or 7p is consistently associated with short stature (Spence et al. 1988; Voss et al. 1989; Spotila et al. 1992; Eggarding et al. 1994; Langlois et al. 1995), and in one patient this has been attributed to growth-hormone deficiency (Hubbard et al. 1980). Similarly, both hetero- and isodisomy of chromosome 7 has been reported in association with dwarfism, either unspecified dwarfism or with clinical features of Russell-Silver syndrome (MIM 180860; Kotzot et al. 1995; Preece et al. 1997). The finding of maternal heterodisomy implies that genomic imprinting may be the underlying cause of the dwarfism. Since it is known that the region of conserved synteny in the mouse undergoes imprinting (Cattanach and Kirk 1985), it is reasonable to predict that there is one or more loci on chromosome 7 involved in the growth-hormone axis that undergoes imprinting during development. Potential genes located on chromosome 7 include, among others, insulin-like growth-factor binding protein 1 (IGF-BP1), insulin-like growth-factor binding protein 3 (IGF-BP3), or the growth hormone–releasing hormone receptor (GHRHR). In contrast, paternal isodisomy for the entire chromosome has been reported in only a single patient, who came to medical attention because of CLD, a disorder previously mapped to chromosome 7 (Hoglund et al. 1994). The patient was reported to have normal stature and, apart from CLD, has no clinically detectable abnormalities except for mild high-frequency hearing loss.

A parsimonious interpretation of this case would suggest that the child inherited two recessive disorders from his father: CF, and immotile cilia associated with complete situs inversus. It is, of course, possible that the two disorders are unrelated in this patient; for example, he may coincidentally have autosomal dominant or recessive heterotaxy, especially in light of the unavailability of the father for a detailed clinical evaluation. X-linked heterotaxy is less likely given the failure to identify any sequence alterations in the causative gene or any small deletions in the adjoining regions.

Immotile-cilia syndrome (MIM 242650) is likely a genetically heterogeneous disorder that typically comes to medical attention because of sinopulmonary infections (rhinosinusitus, bronchitis, and bronchiectasis) and male infertility. In the face of situs inversus, it is referred

to eponymically as "Kartagener syndrome" (MIM 244400), with an estimated prevalence of 1/20,000–1/60,000 individuals (Afzelius and Mossberg 1995). Although, by use of electron microscopy, abnormalities of ciliary structures are a frequent finding, there are a number of cases of Kartagener syndrome with structurally normal cilia that are dysmotile or immotile (Herzon and Murphy 1980; Pedersen 1983), and a recent report indicates that subtle structural deficiencies may be much more common than has been previously recognized (Teknos et al. 1997). In examining ciliary function, care must be taken to process the sample properly, and acute or chronic inflammation from a variety of sources may lead to false-positive results, especially in the case of a CF patient. In light of the fact that only half of the patients with immotile-cilia syndrome have situs inversus, electron microscopic evaluation of ciliary structure in those CF patients with unusually severe respiratory disease may be warranted. Interestingly, one other well-established case of CF in association with situs inversus that was interpreted to be Kartagener syndrome has been reported (Burnell and Robertson 1974). In contrast, Liechti-Gallati and Kraemer (1995) failed to detect any CF mutations in a cohort of patients with immotile-cilia syndrome.

It is noteworthy that laterality defects have been associated with complex chromosome rearrangements involving chromosome 7. One patient has been described (Koiffman et al. 1993) with an insertion of chromosome 8 material into 7q22 (46,XY,ins[7;8][q22;q12q24]), whereas the offspring of a mother with ectrodactyly and an apparently balanced reciprocal translocation, t(2;7)(q21.1;q22.1), was found to have situs ambiguus and complex heart disease (analysis of a karyotype from the infant was not performed) (Genuardi et al. 1993). Although genes such as *nodal* and *Vg1* have been implicated in the lateralization of vertebrate embryos (Collignon et al. 1996; Hyatt et al. 1996), a variety of other genes may be involved in laterality and ciliary defects, including other extracellular signalling molecules, transcription factors, and cytoskeletal components. In this regard, the gene for actin-binding protein 2 (FLN2), previously localized to chromosome 7, may represent a candidate gene. It is proposed that chromosome 7 should be examined in a large collection of families with Kartagener syndrome.

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Familial Skewed X Inactivation and X-Linked Mutations: Unbalanced X Inactivation is a Powerful Means to Ascertain X-Linked Genes That Affect Cell Proliferation

To the Editor:

We read with great interest the article by Pegoraro et al. (1997) in which they report familial skewed X inactivation associated with a submicroscopic deletion at Xq28. This deletion, which spans ~800 kb near the F8C locus, is transmitted in the expected X-linked fashion through females, but no males have the deletion. Although we agree that the skewed X-inactivation pattern in this family is attributable to the region around or included in the deletion, we disagree with their inter-