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Paternal Isodisomy for Chromosome 7 Is Compatible with Normal Growth and Development in a Patient with Congenital Chloride Diarrhea

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Summary

Uniparental disomy for maternal chromosome 7 has been described in three patients with recessive disorders. Short stature in each of these patients has been explained by the effect of imprinting of growth-related genes on maternal chromosome 7. Alternatively, although less likely, all these patients may be homozygous for a rare recessive mutation. Here we report both paternal isodisomy for chromosome 7 and normal growth in a patient with a recessive disorder, congenital chloride diarrhea. She had inherited only paternal alleles at 10 loci and was homozygous for another 10 chromosome 7 loci studied. Her physical status and laboratory tests were normal except for a mild high-frequency sensorineural hearing loss. As the patient has normal stature, it is likely that the paternal chromosome 7 lacks the suggested maternal imprinting effect on growth. Paternal isodisomy for human chromosome 7 may have no phenotypic effect on growth.

Introduction

In uniparental disomy both homologues of a certain chromosome in a diploid offspring are derived from one parent only. The phenomenon was first proposed by Engel in 1980 and subsequently has been demonstrated by molecular genetic methods in an increasing number of patients, occasionally ascertained because of concomitant autosomal recessive disorders. In some cases, additional signs, such as growth alteration, mental retardation, or minor anomalies, are present. At least some phenotypic effects in uniparental disomy may be mediated by the differential imprinting of parental alleles. This epigenetic modification regulates the activity of certain genes, depending on their parental origin, possibly by the differential methylation of DNA in oogenesis and spermatogenesis (Driscoll et al. 1992).

Distinct phenotypes of uniparental disomy of different parental origin have been clues in the identification of the imprinting phenomenon. The chromosomal region 15q11-q13, when only maternally inherited, was noted to result in the Prader-Willi syndrome (Nicholls et al. 1989) but, in the case of paternal disomy, caused the Angelman syndrome (Malcolm et al. 1991). However, normal phenotypes with uniparental disomy for certain chromosomes have been documented (Frézal and Schinzel 1991; Schinzel et al. 1994). Thus, it is evident that only part of the human genome is involved in differential imprinting. This has been well demonstrated also in mice (Cattanach and Kirk 1985; Cattanach and Beechey 1990; Surani et al. 1990). Homologous regions in human and mouse genomes provide a setting for the identification of genomic regions imprinted in humans. In addition to the imprinting effect, uniparental disomy may manifest recessive diseases by reducing genotypes to homozygous. These disorders and other effects of uniparental disomy have been reviewed by Engel (1993).

Maternal uniparental disomy for chromosome 7 has been identified in three patients with recessive diseases; two patients have cystic fibrosis (CF) (Spence et al. 1988; Voss et al. 1989), and one has osteogenesis imperfecta (Spotila et al. 1991). Both patients with CF have uniparental isodisomy for the complete chromosome, whereas the third patient displays heterozygosity at the IGBP-1 locus encoding insulin-like growth factor–binding protein. Heterozygosity is probably due to a meiotic double crossover and thus is consistent with uniparental heterodisomy. In theory, somatic recombination might also have resulted in biparental inheritance and, thus, heterozygosity at that locus. Severe growth retardation diagnosed in all these patients (−4.2 SD, −5.6 SD, and −5.8 SD, respectively) suggests that there may be imprinted growth-related genes on the maternal chromosome 7. Alternatively, although less likely, short stature could be due to homozygosity for a recessive mutation that occurs at sufficient frequency to be seen in all three patients found to date.

No cases of paternally derived disomy for chromosome 7 had been known previously. Here we report a patient with paternal isodisomy for chromosome 7. The patient was originally ascertained because she had a recessive dis-

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order, congenital chloride diarrhea (CLD; MIM 214700 [McKusick 1991]), whose gene has recently been mapped to chromosome 7 (Kere et al. 1993).

In order to define whether uniparental isodisomy for chromosome 7 leads to unusual features in the clinical picture of CLD or is associated with additional signs of imprinted genes caused by paternal disomy, we performed a thorough clinical evaluation of our patient, with a view to genes localized in chromosome 7 (Frézal and Schinzel 1991; Grzeschik et al. 1994).

Patient, Material, and Methods

Patient

Patient LGL4588 was a 23-year-old female attending a business school at the time of examination. She is the youngest of five children. Her mother was 39 years old, her father 44, at the time of her birth. Pregnancy was complicated by hydramnios, and she was born after 34 wk gestation. Birthweight was 1,900 g and length was 45 cm, both appropriate for the gestational age. The placenta weighed 550 g and was large relative to her birthweight (29%). Distended abdomen, watery diarrhea, and marked hyperbilirubinemia treated by an exchange transfusion were noted. CLD was diagnosed at the age of 8 d (fecal chloride content 148 mmol/liter), and substitution therapy with sodium and potassium chloride solution was instituted. She was discharged in good clinical condition at 6 mo of age.

Subsequently, her clinical course has been uneventful, and her electrolyte balance has been stable with salt substitution. Her development has been normal. She suffered no major illnesses besides recurrent urinary-tract infections during her first 6 years.

At age 6 years a mild, high-frequency sensorineural hearing loss extending to the speech range was diagnosed. A hearing aid was prescribed, but she stopped using it, feeling it to be unnecessary for communication in everyday life. Her family history is negative for both CLD and hearing defects.

Analysis of Genomic DNA

High-molecular-weight genomic DNA was extracted from blood by standard methods (Sambrook et al. 1989). Analysis of microsatellite markers by PCR and denaturing PAGE were performed as described elsewhere (Kere et al. 1993). Oligonucleotide primers used have been published by Weissenbach et al. (1992), and loci are summarized in table 1.

All the family members were initially included in an extended linkage study to refine the localization of the CLD locus. When three CLD-linked polymorphic microsatellite markers in the patient's DNA displayed only one paternal allele and lacked maternal ones, this family was excluded from the search for linkage. Instead, the molecular analysis was expanded to include the genotyping of the proband, her parents, and one healthy sibling, at 20 loci spanning chromosome 7 from pter to qter (193 cM; Weissenbach et al. 1992). The widest gap between two fully informative markers was 38 cM. Parentage was confirmed by studying

Table 1

DNA Markers and Results of Analysis

Marker Locus[a]	Alleles			Heterozygosity[b]
	Father	Mother	LGL4588	
Chromosome 7:				
D7S531	1,1	1,1	1,1	.77
D7S517	1,1	1,4	1,1	.83
D7S493[c]	1,3	3,10	1,1	.88
D7S519[c]	1,6	3,3	6,6	.80
D7S502	1,4	1,4	4,4	.84
D7S527	1,5	2,5	5,5	.74
D7S479[c]	1,3	4,6	3,3	.82
D7S518[c]	2,7	1,3	7,7	.87
D7S515	8,9	1,9	9,9	.81
D7S501[c]	2,4	1,2	4,4	.80
D7S496[c]	3,6	1,2	6,6	.74
D7S523[c]	2,3	1,5	2,2	.79
D7S490	1,4	1,4	1,1	.77
D7S487	1,4	1,3	1,1	.73
D7S504[c]	1,6	5,5	6,6	.78
D7S530[c]	1,5	2,2	5,5	.78
D7S509[c]	1,2	1,1	2,2	.72
D7S495	1,6	3,6	6,6	.81
D7S483	1,1	1,1	1,1	.81
D7S550	2,2	1,2	2,2	.78
Other chromosomes:				
D1S191	4,4	1,1	1,4	.74
D2S131	1,2	2,3	1,3	.85
D3S1294	3,3	1,1	1,3	.73
D4S414	1,5	1,2	1,2	.88
D5S428	1,5	3,6	3,5	.76
D6S290	1,3	3,3	1,3	.70
D8S265	1,3	6,7	1,7	.77
D9S158	3,4	1,1	1,3	.69
D10S192	2,7	1,2	2,7	.77
D11S917	4,4	1,2	1,4	.80
D12S94	2,2	1,2	1,2	.78
D13S157	4,4	1,5	4,5	.72
D14S63	1,4	2,3	3,4	.76
D15S120	1,6	1,1	1,6	.73
D16S413	2,4	1,4	2,4	.83
D17S791	1,8	2,7	2,8	.87
D18S59	1,7	1,3	3,7	.66
D19S210	4,6	1,6	1,4	.73
D20S100	1,3	2,3	2,3	.75
D21S267	1,10	3,11	1,11	.88
D22S284	2,4	1,1	1,2	.76
DXS986	1	4,6	1,4	.75

[a] Twenty polymorphic loci were used to prove paternal isodisomy for chromosome 7, and 22 additional loci on other chromosomes were used to confirm parentage in the proband.

[b] These values were used to estimate the likelihood that the proband is homozygous for 10 chromosome 7 markers by chance alone. This probability was 3.0×10^{-7}.

[c] Marker demonstrates uniparental disomy.

an additional 22 loci on chromosomes other than chromosome 7 (table 1).

Laboratory Tests

In order to search for subtle effects of possibly imprinted or recessively acting genes on chromosome 7, the following metabolic, hematologic, and biochemical parameters were studied: blood hemoglobin, erythrocytes, leukocytes, thrombocytes, reticulocytes, fetal hemoglobin, thromboplastin time, and activated partial thromboplastin time; serum bilirubin, conjugated bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, creatine kinase, lactate, pyruvate, iron, transferrin, ferritin, immunoglobulin A, immunoglobulin G, immunoglobulin M, complements 3 and 4, calcium, ionized calcium, and phosphorus; proteins and amino acids in plasma and urine; and oligosaccharides and glycosaminoglycans in urine. Additional parameters studied because of the CLD were electrolytes (K, Na, and Cl) in serum and urine, acid-base balance, serum urea-nitrogen, creatinine, and uric acid.

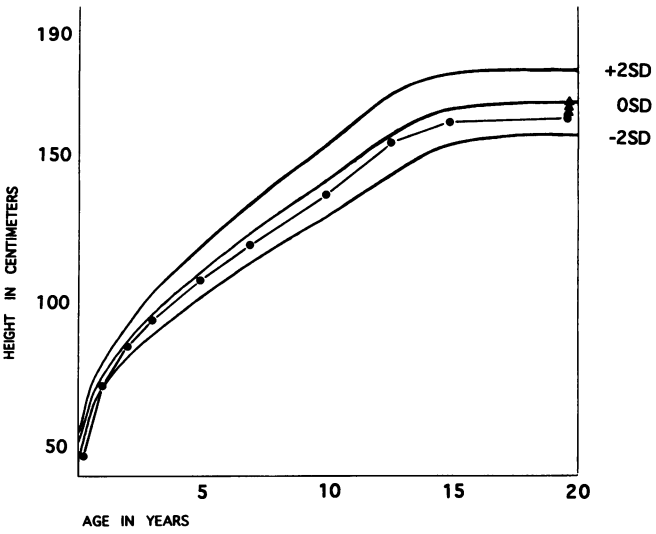

Figure 2 Growth of the patient LGL4588, and adult heights of her three sisters (*triangles*), along with limits for normal growth (±2 SD) for Finnish women. There is no difference in growth between the three sisters.

Results

Paternal Isodisomy for Chromosome 7

Ten informative microsatellite markers on chromosome 7 showed that the proband did not have any maternal contribution to her genotype, for that chromosome (fig. 1*A*). Maternal and paternal alleles could not be distinguished for the other 10 markers tested for chromosome 7, but the proband was always homozygous (fig. 1*B*). These results suggested paternal isodisomy. Other chromosomes had allele contributions from both parents, as demonstrated by the assessment of at least one informative marker per chromosome (table 1). Cytogenetic analysis displayed a normal female karyotype, 46,XX.

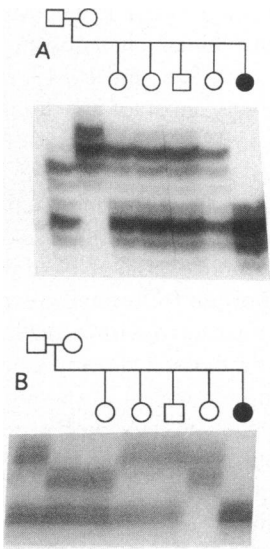

Figure 1 Analysis of the polymorphic loci D7S496 (*A*) and D7S495 (*B*) in patient LGL4588 and her family. *A*, No maternal and only one paternal allele present in the patient, suggesting paternal isodisomy. *B*, Example of an uninformative marker for which the patient is homozygous.

Growth

At 22 years of age our patient's height was 159 cm (−1.1 SD for Finnish women; Sorva et al. 1990), her weight 60.1 kg (+13% with respect to average weight at given height [Durant and Linder 1981], body-mass index 24). Maternal height was 166.5 cm (+0.2 SD), paternal height 172 cm (−1.1 SD). The heights of the three adult sisters of the proband were 160 (−1.0 SD), 162 (−0.6 SD), and 165 cm (−0.1 SD), and her adult brother measured 183 cm (+0.7 SD). The height of our patient matched her expected height, which is 162 ± 4.5 cm, according to European standards. Her growth curve was normal (fig. 2), and she had menarche at 12 years of age. Skeletal maturation had been normal at 4, 6, and 9 years of age.

Clinical Investigations and Laboratory Tests

Her clinical status was normal, with no dysmorphic features, skeletal abnormalities, or muscular atrophies. Skull and thorax radiographs were normal, as were her sense of smell and ophthalmologic examinations, including color vision (Farnsworth) and visual fields (Goldmann). Audiological investigation revealed a mild, high-frequency sensorineural hearing loss of 15 dB at 0.5 kHz and 80 dB at 8 kHz. The pure-tone average thresholds of 0.5, 1, and 2 kHz were 38 dB in the right ear and 42 dB in the left ear. All laboratory values were within the normal range.

Discussion

The phenotype of CLD in patient LGL4588 was apparently due to homozygosity for a recessive mutation, caused by paternal isodisomy for chromosome 7, as suggested by homozygosity for all 20 markers studied spanning 193 cM of the chromosome (Weissenbach et al. 1992). This is the first instance of paternal disomy described for chromosome 7. For other chromosomes, paternal disomy is at least 10 times rarer than maternal disomy (Mascari et al. 1992; Nicholls 1993). The higher frequency of aneuploidy occurring in oocytes (Brandriff et al. 1985; Pellestor 1991), especially in the case of advanced maternal age, may explain the majority of the extra chromosomes in maternal uniparental disomy for, e.g., chromosome 15 originating from nondisjunction in meiosis I, whereas most paternal uniparental disomies appear to have a postzygotic origin (Robinson et al. 1993).

Uniparental disomy may arise by several mechanisms, and it can result in either isodisomy or heterodisomy (Engel 1980, 1993; Nicholls et al. 1989). Isodisomy may arise de novo during gametogenesis. Without crossing-over, nondisjunction in the second meiotic division results in a sperm with two identical copies of one chromosome. A maternal copy may be eliminated in a trisomic conceptus, to preserve euploidy. Depending on the time of the correction of the trisomy, confined placental or partial true chromosome mosaicism may result. More likely, the primary event in paternal isodisomy is maternal meiotic nondisjunction resulting in a nullisomic oocyte. This fits the advanced maternal age (39 years) at the time of the birth of the proband. In a monosomic conception, euploidy is achieved through a duplication of the single available paternal chromosome, resulting in a complete isodisomy regardless of crossovers.

Many patients with CLD show some growth retardation during their first year of life, before optimal electrolyte substitution is reached. Our patient was born prematurely and reached normal growth in her first year (fig. 2). Additional findings, such as hydramnios and hyperbilirubinemia, are typical features of CLD (Norio et al. 1971; Holmberg et al. 1977; Holmberg 1986). The origin of the hearing loss in our patient remains speculative. Of Finnish children attending ordinary schools, 1.7% have been demonstrated to have a significant (20–75 dB) hearing loss in the speech range or in the frequency area of 3–4 kHz (Haapaniemi 1992). As audiometric examinations of school children are performed at the ages of 7, 10, and 14 years, with a screening level 15–20 dB, a hearing loss such as that in the proband is not commonly overlooked. Thus, we suggest that the detection of her hearing defect did not result from biased ascertainment but reflects a relatively rarely occurring impairment. The defect could be of genetic origin, because of a recessive mutation in chromosome 7 or an imprinting effect. Alternatively, it is an entirely independent defect. A mutation in, e.g., the COL1A2 gene is unlikely, because the impairment of hearing had no conductive component.

Some of the genes responsible for growth have developed to function differently, depending on the parental origin (Haig and Graham 1991). For example, the expression of paternally derived alleles favors increased size and macrosomia of the offspring in the case of uniparental disomy for chromosome 11 (Henry et al. 1991), while the expression of maternal alleles leads to growth retardation, as suggested in uniparental disomy for chromosomes 7 and 16. However, in the case of chromosome 16, it is not clear whether this is an imprinting effect or is due to confined placental trisomy, since, as with low-level placental trisomy, no intrauterine growth retardation was noted (Kalousek et al. 1993). Triploidy in human fetuses has been demonstrated to lead to two distinct phenotypes, depending on the parental origin of the extra haploid set: androgynic fetuses have relatively normal growth with a large placenta, whereas digynic fetuses display intrauterine growth retardation and a small placenta. The placental phenotype may reflect imprinting, but evaluation of the fetal phenotype is impossible, because of the secondary effect of placental malfunction (McFadden and Kalousek 1991).

Imprinting in mammals, especially in mice, has been well studied (Cattanach and Kirk 1985; Cattanach and Beechey 1990; Surani et al. 1990). In human, most data are available from model diseases such as Prader-Willi, Angelman, and Beckwith-Wiedemann syndromes (Henry et al. 1991; Malcolm et al. 1991; Nicholls 1993; Weksberg et al. 1993). A comparison of corresponding regions in the mouse and human gene maps may help to predict imprinted areas in human chromosomes, even if imprinting is not strictly conserved (Kalscheuer et al. 1993). Mouse genomic regions syntenic with human chromosome 7 are distributed over chromosomes 2, 5, 6, and 10–13, of which chromosomes 5 and 6 carry most of the homologous material (Grzeschik et al. 1994). Four of these regions display imprinting in mouse; if derived from one parent only, they are lethal or cause other developmental disturbances. Interestingly, the proximal part of mouse chromosome 11 is differentially imprinted (Cattanach and Beechey 1990) and appears to be important for normal growth: maternal contribution only is associated with a smaller size of progeny, whereas paternally derived disomy causes general overgrowth. This genomic region in the mouse chromosome 11 carries three genes syntenic with genes in human chromosome 7, encoding erythroblastosis oncogene B identical to epidermal growth factor receptor (EGFR), a homologous zinc-finger protein, and glucokinase (Copeland et al. 1993).

In human chromosome 7, EGFR is localized in 7p13-p12. Interestingly, there are two genes encoding insulin-like growth factor–binding proteins (IGBP1 and IGBP3) in the same genetic region (Ehrenborg et al. 1992). These

binding proteins modulate the actions of insulin-like growth factors (IGFI and IGFII) on target cells. We can speculate that, as insulin-like growth factors mediate cellular proliferation and differentiation as well as growth-promoting action of growth hormone, the IGBP loci might be differentially imprinted and thus play a role in growth retardation. In addition, several other genes encoding growth factors have been localized within chromosome 7 (for a review, see Spotila et al. 1992).

Severe growth delay in all patients with uniparental disomy for maternal chromosome 7 is most likely due to the imprinting effect of a growth-related gene(s). However, an independent autosomal recessive mutation cannot be excluded as an alternative explanation, since these patients may represent biased ascertainment, because of an associated recessive disorder. The slightly but definitely large placenta seen in our patient is typical neither in CLD nor in confined placental mosaicism for chromosome 7 (Fryburg et al. 1993), and thus it might suggest an effect on growth in the extraembryonic tissues. Our patient demonstrates that paternal isodisomy for chromosome 7 is compatible with normal growth and development.

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