Am. J. Hum. Genet. 60:160–165, 1997

Uniparental Disomy of the Entire X Chromosome in a Female with Duchenne Muscular Dystrophy

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Summary

Duchenne muscular dystrophy (DMD) is a severe, progressive, X-linked muscle-wasting disorder with an incidence of ~1/3,500 male births. Females are also affected, in rare instances. The manifestation of mild to severe symptoms in female carriers of dystrophin mutations is often the result of the preferential inactivation of the X chromosome carrying the normal dystrophin gene. The severity of the symptoms is dependent on the proportion of cells that have inactivated the normal X chromosome. A skewed pattern of X inactivation is also responsible for the clinical manifestation of DMD in females carrying X;autosome translocations, which disrupt the dystrophin gene. DMD may also be observed in females with Turner syndrome (45,X), if the remaining X chromosome carries a DMD mutation. We report here the case of a karyotypically normal female affected with DMD as a result of homozygosity for a deletion of exon 50 of the dystrophin gene. PCR analysis of microsatellite markers spanning the length of the X chromosome demonstrated that homozygosity for the dystrophin gene mutation was caused by maternal isodisomy for the entire X chromosome. This finding demonstrates that uniparental isodisomy of the X chromosome is an additional mechanism for the expression of X-linked recessive disorders. The proband's clinical presentation is consistent with the absence of imprinted genes (i.e., genes that are selectively expressed based on the parent of origin) on the X chromosome.

Introduction

Duchenne muscular dystrophy (DMD) is a severe, progressive, X-linked muscle-wasting disorder with an incidence of ~1/3,500 male births. Affected males are nonambulatory by the age of 9 or 10 years, and death from respiratory failure often occurs by the age of 20 years. DMD and its milder variant, Becker muscular dystrophy (BMD), are caused by mutations in the gene coding for dystrophin, a high-molecular-weight cytoskeletal protein. The mutational spectrum includes both deletions and duplications involving one or more exons of the dystrophin gene. Deletions are most frequent, being found in ~60% of affected males. Duplications account for another 5% of cases. The remaining cases are caused by point mutations or other subtle changes in the dystrophin gene (reviewed in Worton and Brooke 1995).

While DMD and BMD predominately affect males, females heterozygous for dystrophin mutations are also severely affected, in rare instances. In many cases, these females are carriers of balanced X;autosome translocations that disrupt the dystrophin gene. The manifestation of DMD in these females is due to the preferential inactivation of the normal X chromosome (Boyd et al. 1986), most likely as a consequence of random X chromosome inactivation followed by selection against cells in which autosomal genes have been inactivated as a result of their proximity to inactivated X chromosome sequences. A skewed pattern of X chromosome inactivation is also seen in severely affected females with a normal appearing karyotype (Pegoraro et al. 1994). Since X chromosome inactivation occurs early in embryogenesis, this skewed pattern of X inactivation is most likely a consequence of the stochastic variation observed for a random process. It is interesting that a number of MZ female twin pairs heterozygous for dystrophin gene mutations and discordant for the DMD phenotype have also been reported (Richards et al. 1990; Lupski et al. 1991; Zneimer et al. 1993). In these cases, a skewed pattern of X chromosome inactivation is observed in the affected twin, while a random or oppositely skewed pattern of X chromosome inactivation is seen in the unaffected twin. Since no cases of MZ female twin pairs concordant for the DMD phenotype have been observed, the skewed pattern of X inactivation has been proposed to be the result of random X chromosome inactivation followed by asymmetric splitting of the in-

Received April 24, 1996; accepted for publication October 22, 1996.

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0002-9297/97/6001-0022$02.00

ner cell mass as part of the twinning process (Nance 1990; Lupski et al. 1991). Finally, females with Turner syndrome (45,X) are affected with DMD if they carry a dystrophin mutation on the remaining X chromosome (Chelly et al. 1986).

We report here the case of a karyotypically normal female affected with DMD as a result of homozygosity for a deletion of the dystrophin gene. Homozygosity for the dystrophin gene deletion was the result of maternal isodisomy of the entire X chromosome. This finding demonstrates that uniparental isodisomy of the X chromosome is an additional mechanism for the expression of X-linked recessive disorders in females. The proband's clinical presentation is consistent with the absence of imprinted genes (i.e., genes that are selectively expressed based on the parent of origin) on the X chromosome.

Subjects and Methods

Case Report

The proband was a 6-year-old female who presented with persistent right calf pain following a period of increased activity. She had difficulty keeping up with her peers, preferred sedentary activities, and had a tendency to toe walk. Her neurological exam was significant for mild hypotonia, weakness of neck flexion, weakness of the proximal musculature of the upper and lower extremities, and foot dorsiflexion. Deep tendon reflexes were depressed. Calves were not enlarged. A modified Gowers maneuver was present, and her stance was mildly lordotic. Further evaluation revealed a markedly elevated serum creatine kinase (CK) level of 45,210 IU/ml. A subsequent determination revealed a serum CK level of 22,700 IU/ml. A muscle biopsy of the right vastus lateralis showed muscle fiber necrosis and marked variation of fiber size with both hypertrophic and atrophic fibers present. Occasional regenerating fibers were also observed. Immunohistochemistry revealed a virtual absence of dystrophin. The parents were nonconsanguineous with a negative family history of an underlying neuromuscular disorder.

Dystrophin Deletion/Duplication Analysis

Deletions and duplications in the dystrophin gene were tested for by quantitative Southern blot analysis. DNA was prepared from peripheral blood lymphocytes according to standard procedures. DNA (2 μg) was digested with *Hin*dIII, electrophoresed through 1.0% agarose gels, and transferred to Biodyne B membranes. Dystrophin cDNA probes were labeled with α^{32}P-dCTP by random priming. Hybridizations were performed in 7% SDS, 0.5 M sodium phosphate dibasic, 1 mM EDTA, and 1% BSA at 65°C. Membranes were washed in 1% SDS, 40 mM sodium phosphate dibasic, and 1 mM EDTA at 65°C.

Deletion analysis was also performed using two multiplex-PCR assays. These multiplex reactions each test for nine exons located in deletion-prone regions of the dystrophin gene and together, will detect >98% of all DMD/BMD deletions (Chamberlain et al. 1988; Beggs et al. 1990).

Analysis of X Chromosome Microsatellite Markers

The X-linked microsatellite markers used for genotyping are shown in table 1. Primers for the amplification of these markers, with the exception of those located within the dystrophin gene, were obtained from Research Genetics, Inc. The dystrophin microsatellites STR44 (DXS1238), STR45 (DXS1237), STR49 (DXS1236), and STR50 (DXS1235) were amplified as diplexes as described by Clemens et al. (1991). PCR

Table 1

X Chromosome Genotypes

Locus	Location	Father	Mother	Proband
DXS1060	Xp22.33	2	1,2	1,1
DXS1226	Xp22.13	1	2,3	2,2
DXS989	Xp22.12	3	1,2	1,1
DXS1235 (STR50)	Xp21 (DMD intron 50)	1	1,1	–/–
DXS1236 (STR49)	Xp21 (DMD intron 49)	1	2,2	–/–
DXS1237 (STR45)	Xp21 (DMD intron 45)	2	1,1	1,1
DXS1238 (STR44)	Xp21 (DMD intron 44)	1	2,3	3,3
DXS1213	Xq11.2	1	2,3	3,3
DXS339	Xq12	2	1,3	3,3
DXS986	Xq21.1	3	1,2	1,1
DXS1002	Xq21.31	1	1,2	1,1
DXS1001	Xq23	1	1,2	2,2
DXS102	Xq26.3	2	1,3	1,1
FRAXE	Xq28	2	1,3	3,3

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products were resolved by denaturing PAGE, transferred to Biodyne B membranes, and visualized by autoradiography after hybridization to ^{32}P-labeled oligonucleotides as described by Quan et al. (1995).

Results

Dystrophin Gene Deletion/Duplication Analysis

The proband was a 6-year-old female with a clinical presentation that was consistent with DMD. Her grossly elevated serum CK levels and the lack of immunohistochemical staining for dystrophin in muscle sections were both suggestive of an abnormality of the dystrophin gene. High-resolution chromosome banding revealed a normal appearing 46, XX karyotype. This demonstrated that the proband's symptoms were not the result of a balanced X;autosome translocation disrupting the dystrophin gene or monosomy for an X chromosome carrying a dystrophin gene mutation.

In order to determine whether the proband carried a deletion or duplication of one or more exons of the dystrophin gene, the organization of the gene was examined by quantitative Southern blotting. This analysis was performed with the restriction enzyme *Hin*dIII and nine cDNAs spanning the length of the dystrophin transcript. As shown in figure 1, an abnormality of the dystrophin gene was detected in the proband with the probe 44.1, a cDNA specific for exons 47 to 52 (Koenig et al. 1987). The 3.7-kb and 3.1-kb *Hin*dIII fragments, carrying exons 50 and 51, respectively, were absent and were apparently replaced by an aberrant 8.0-kb *Hin*dIII fragment. This suggested that the proband was homozygous for a dystrophin gene deletion that included either exon 50 or 51 but not both. Alternatively, the proband may have been homozygous for a deletion that removed only a portion of the intron between exons 50 and 51, leaving both exons intact. All other exons in the proband were qualitatively and quantitatively normal. No abnormality of the dystrophin gene was seen in either the father or the mother of the proband.

To further investigate the possibility of a dystrophin gene deletion, PCR analysis of exons 50 and 51 was carried out. Exons 50 and 51 were amplified as part of two multiplex-PCR assays, each specific for nine different exons located in deletion-prone regions of the dystrophin gene (Chamberlain et al. 1988; Beggs et al. 1990). All of the tested exons, with the exception of exon 50, were detected in the proband (fig. 2). The absence of the exon 50 amplification product confirmed that the proband was homozygous for a deletion of the dystrophin gene. Since no abnormality of exon 49 was detected by quantitative Southern blotting (fig. 1), this deletion spanned only the region of exon 50. The identification of a deletion affecting both of the proband's dystrophin genes confirmed that her clinical symptoms were the result of a dystrophinopathy.

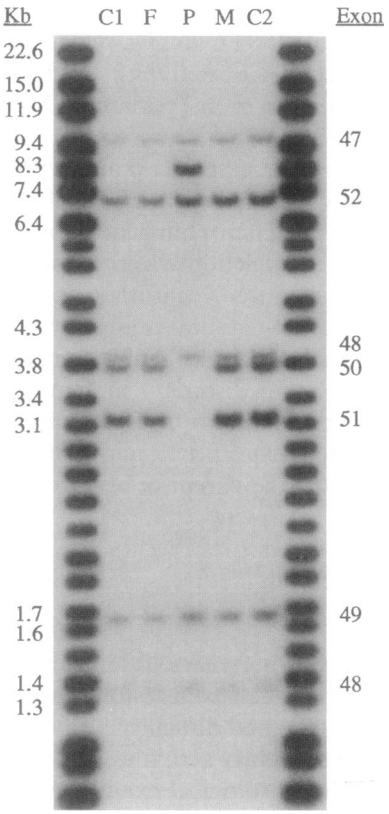

Figure 1 DMD deletion/duplication analysis by quantitative Southern blotting. Genomic DNA was prepared from peripheral blood lymphocytes, digested with *Hin*dIII, and hybridized with the dystrophin cDNA 44.1. Restriction fragments carrying exons 50 and 51 were replaced by an 8.0-kb junction fragment in the proband. Lanes M and F, mother and father of the proband, respectively. Lane P, proband. Lane C1, normal male control. Lane C2, normal female control. Molecular sizes were determined by use of the BRL Analytical Marker.

Parental Origin of the Proband's X Chromosomes

The possibility that homozygosity for the dystrophin gene mutation was the consequence of uniparental disomy (UPD) of the X chromosome was evaluated by determining the parental origin of the proband's X chromosomes. This was done by PCR amplification of microsatellite markers spanning the length of the entire X chromosome. The results are summarized in table 1. DXS1236 (STR49) and DXS1235 (STR50), located in introns 49 and 50 of the dystrophin gene, respectively, were not detected in the proband and were therefore included in her deletion. At DXS1002, parental origin could not be determined, since the allele inherited by the proband was present in both her mother and father. All of the other loci tested were informative for parental origin. In no instance was a paternal allele inherited by the proband. The proband was homozygous for a maternal allele at all of the loci tested, including those at which her mother was heterozygous. These results

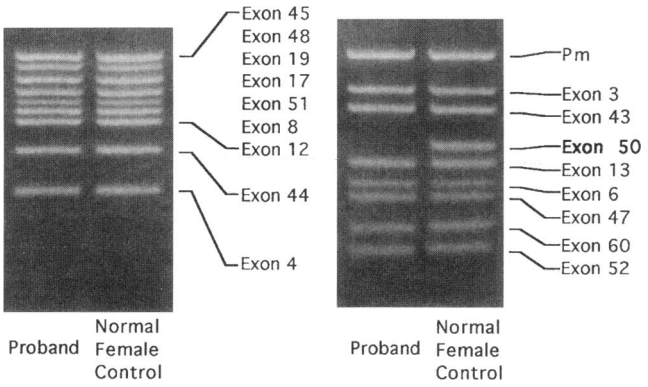

Figure 2 Multiplex-PCR deletion analysis. The multiplex-PCR assays described by Chamberlain et al. (1988) and Beggs et al. (1990) are shown in the *left* and *right* panels, respectively. Exon 50 was not detected in the proband.

indicated that both of the proband's X chromosomes were identical and maternal in origin. The possibility that the microsatellite results were the result of a consanguineous mating was eliminated by use of polymorphic VNTR markers. The probability of the stated paternity was >99.9% (data not shown). These results were therefore consistent with maternal isodisomy of the entire X chromosome in the proband.

Discussion

The proband was a 6-year-old female with the clinical manifestations of DMD but a normal appearing 46, XX karyotype. Deletion analysis of the dystrophin gene, performed by quantitative Southern blotting and PCR, demonstrated that the proband carried a deletion of only exon 50 and flanking DNA. Surprisingly, this deletion was found in both of her dystrophin genes, indicating that homozygosity for a dystrophin mutation, and not skewed lyonization, was the cause of her clinical symptoms. Genotyping of the proband's X chromosomes, using microsatellite markers spanning the length of the X chromosome, revealed that homozygosity for the dystrophin mutation was a consequence of maternal isodisomy of the entire X chromosome.

Several mechanisms for the occurrence of UPD have been described. These include meiosis I or meiosis II errors followed by gametic complementation, monosomy duplication, or trisomy rescue (Spence et al. 1988; Engel 1993). The observation that the proband was homozygous at all of the X chromosome markers examined (table 1) suggested that UPD of the X chromosome was not the result of a maternal meiosis I error. In addition, the data do not support the occurrence of a maternal meiosis II error. If a meiosis II error had occurred, the proband would be expected to be heterozygous at some of the markers examined as a result of crossover events occurring during meiosis I. Chromosomal segregation during maternal meiosis was therefore most likely normal. However, a maternal meiotic error cannot be completely ruled out, since homozygosity for all X chromosome markers in the proband could also have resulted from the absence of recombination during meiosis I followed by a meisois II error.

The most-likely sequence of events leading to UPD of the X chromosome, and the subsequent manifestation of DMD in the proband, is diagrammed in figure 3. Since the dystrophin gene deletion was not detected in maternal peripheral lymphocytes, the deletion probably was a de novo event that occurred during oogenesis. Alternatively, the proband's mother may have been mosaic for the deletion in her germ line. Chromosome segregation during maternal meiosis was most likely normal

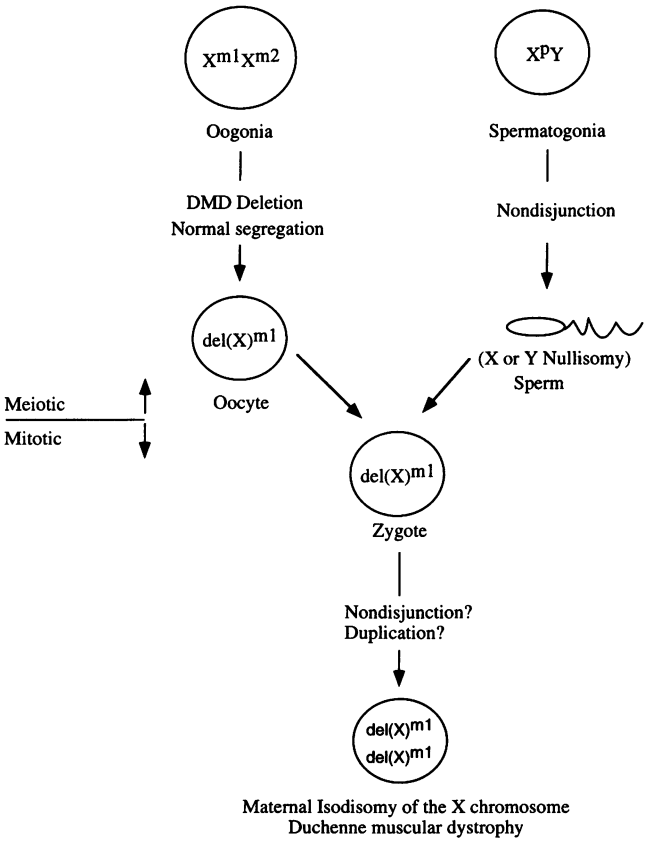

Figure 3 Proposed sequence of events leading to maternal isodisomy and homozygosity for a dystrophin deletion in the proband. Developmental stages are as indicated. Only the X chromosomes are indicated. The dystrophin deletion may have arisen as a de novo event during oogenesis or may have already been present as a result of maternal gonadal mosaicism. Following normal meiotic segregation, an oocyte carrying an X chromosome with a dystrophin deletion was fertilized by a sperm nullisomic for the X or Y chromosome, resulting in a 45, X conceptus. Maternal isodisomy of the X chromosome resulted from either duplication of the single X chromosome or a nondisjunction event.

and resulted in a haploid oocyte carrying an X chromosome with a dystrophin gene deletion. The proband's lack of a paternal sex chromosome contribution indicates that the oocyte was fertilized by a sperm that was nullisomic for an X or Y chromosome, as the result of a nondisjunction event that occurred during spermatogenesis. The occurrence of a second nondisjunction event in the zygote, or a duplication of the single maternal X chromosome, resulted in maternal isodisomy and homozygosity for all loci on the X chromosome and the dystrophin gene deletion.

UPD, resulting in homozygosity for a mutant allele, has previously been observed in patients who have inherited autosomal recessive diseases from a single carrier parent. For example, maternal isodisomy of chromosome 7 has been observed in patients with cystic fibrosis and very short stature (Spence et al. 1988; Voss et al. 1989). Maternal isodisomy of chromosome 14 has been reported in a patient with autosomal recessive rod monochromacy, short stature, and premature puberty (Pentao et al. 1992). In the case of X-linked recessive disorders, the manifestation of symptoms in females heterozygous for a mutant allele has been observed as a result of uneven lyonization (Richards et al. 1990; Lupski et al. 1991; Zneimer et al. 1993; Pegoraro et al. 1994). The present study demonstrates that homozygosity caused by UPD is an additional mechanism for the manifestation of X-linked recessive disorders in females.

UPD may also lead to phenotypic effects as a result of genomic imprinting. Specific phenotypes have been associated with UPD of maternal chromosome 7, paternal chromosome 11, maternal chromosome 14, paternal chromosome 15, and maternal chromosome 15 (Ledbetter and Engel 1995). Studies of X inactivation have revealed that imprinting of the X chromosome also occurs. For example, in marsupials, the paternally derived X chromosome is preferentially inactivated in somatic tissues (Cooper et al. 1971; Sharman 1971). In addition, in the extraembryonic tissues of female mice, the paternally derived X chromosome is also preferentially inactivated (Takagi and Sasaki 1975). This may also be the case in the extraembryonic tissues of human females (Harrison and Warburton 1986; Harrison 1989). However, it is unknown whether genomic imprinting (i.e., the differential expression of alleles based on the parent of origin) occurs on the X chromosome. Two observations suggest that genomic imprinting of X-linked genes does not occur. The first is that the phenotype in Turner syndrome is not affected by the parental origin of the remaining X chromosome (Jacobs et al. 1990). The second is that the random nature of X chromosome inactivation results in the random expression of maternal and paternal alleles of genes that are subject to inactivation. However, the possibilty of imprinting cannot be completely ruled out, since there are a number of genes that escape inactivation and that are expressed from both the active and inactive X chromosomes (for review, see Willard 1995). Within this group of genes, imprinting may occur.

Definitive imprinting studies of the X chromosome have been difficult, since only a few patients with UPD of the X chromosome have been identified, to date. In addition, these patients have been mosaic for cell lines with abnormal karyotypes. For example, Schinzel et al. (1993) described a mosaic 45, X/46, XX female with paternal isodisomy of the X chromosome in her normal cells. The mild manifestations of Turner syndrome and short stature observed in this patient may have been the result of her low-level mosaicism for a 45, X cell line. Migeon et al. (1996) reported the case of a female with a mosaic 45, X/46, X del(X)(q21.3-qter)/46, X r(X) karyotype. All of the X chromosomes carried by this patient were derived from the same maternal X chromosome, and all, as a result of the failure of X inactivation, were transcriptionally active in each cell. The severe mental retardation and multiple congenital abnormalities observed in this patient were thought to be due to her functional maternal X isodisomy and not due to a maternal imprinting effect (Migeon et al. 1996). In the case of the patient described in our study, her clinical presentation is consistent with her homozygosity for a dystrophin mutation. The deletion of exon 50 from the dystrophin transcript is predicted to cause a shift of the translational reading frame (Roberts et al. 1993). As has previously been observed in male DMD patients (reviewed in Worton and Brooke 1995), the presence of a frameshifting deletion is consistent with the proband's lack of immunohistochemical staining for dystrophin and her severe phenotype. The fact that the proband lacks obvious clinical stigmata that are unrelated to her DMD is consistent with a lack of imprinting effects for maternal UPD of the X chromosome.

In conclusion, the present study demonstrates that UPD of the X chromosome is unlikely to produce imprinting effects but may still be responsible for the expression of X-linked disorders in females. UPD of the X-chromosome must therefore be considered as a possible cause in females with unexplained severe manifestations of X-linked conditions.

References

Beggs AH, Koenig M, Boyce FM, Kunkel LM (1990) Detection of 98% of DMD/BMD gene deletions by polymerase chain reaction. Hum Genet 86:45–48

Boyd Y, Buckle V, Holt S, Munro E, Hunter D, Craig I (1986) Muscular dystrophy in girls with X;autosome translocations. J Med Genet 23, 484–490

Chamberlain JS, Gibbs RA, Ranier JE, Nguyen PN, Caskey CT (1988) Deletion screening of the Duchenne muscular dystrophy locus via multiplex DNA amplification. Nucleic Acids Res 16:11141–11156

Chelly J, Marlhens F, Le Marec B, Jeanpierre M, Lambert M, Hamard G, Dutrillaux B, et al (1986) De novo DNA microdeletion in a girl with Turner syndrome and Duchenne muscular dystrophy. Hum Genet 74:193–196

Clemens PR, Fenwick RG, Chamberlain JS, Gibbs RA, de Andrade M, Chakraborty R, Caskey CT (1991) Carrier detection and prenatal diagnosis in Duchenne and Becker muscular dystrophy families, using dinucleotide repeat polymorphisms. Am J Hum Genet 49:951–960

Cooper DW, VandeBerg JL, Sharman GB, Poole WE (1971) Phosphoglycerate kinase polymorphism in kangaroos provides further evidence for paternal X inactivation. Nat New Biol 230:155–157

Engel E (1993) Uniparental disomy revisited: the first twelve years. Am J Med Genet 46:670–674

Harrison KB (1989) X-chromosome inactivation in the human cytotrophoblast. Cytogenet Cell Genet 52:37–41

Harrison KB, Warburton D (1986) Preferential X-chromosome activity in human female placental tissues. Cytogenet Cell Genet 41:163–168

Jacobs PA, Betts PR, Cockwell AE, Crolla JA, Mackenzie MJ, Robinson DO, Youings SA (1990) A cytogenetic and molecular reappraisal of a series of patients with Turner's syndrome. Ann Hum Genet 54:209–223

Koenig M, Hoffman EP, Bertelson CJ, Monaco AP, Feener C, Kunkel LM (1987) Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. Cell 50:509–517

Ledbetter DH, Engel E (1995) Uniparental disomy in humans: development of an imprinting map and its implications for prenatal diagnosis. Hum Mol Genet 4:1757–1764

Lupski JR, Garcia CA, Zoghbi HY, Hoffman EP, Fenwick RG (1991) Discordance of muscular dystrophy in monozygotic female twins: evidence supporting asymmetric splitting of the inner cell mass in a manifesting carrier of Duchenne dystrophy. Am J Med Genet 40:354–364

Migeon BR, Jeppesen P, Torchia BS, Fu S, Dunn MA, Axelman J, Schmeckpeper BJ, et al (1996) Lack of X inactivation associated with maternal X isodisomy: evidence for a counting mechanism prior to X inactivation during human embryogenesis. Am J Hum Genet 58:161–170

Nance WE (1990) Do twin lyons have larger spots? Am J Hum Genet 46:646–648

Pegoraro E, Schimke RN, Arahata K, Hayashi Y, Stern H, Marks H, Glasberg MR, et al (1994) Detection of new paternal dystrophin gene mutations in isolated cases of dystrophinopathy in females. Am J Hum Genet 54:989–1003

Pentao L, Lewis RA, Ledbetter DH, Patel PI, Lupski JR (1992) Maternal uniparental isodisomy of chromosome 14: association with autosomal recessive rod monochromacy. Am J Hum Genet 50:690–699

Quan F, Zonana J, Gunter K, Peterson KL, Magenis RE, Popovich BW (1995) An atypical case of fragile X syndrome caused by a deletion that includes the FMR1 gene. Am J Hum Genet 56:1042–1051

Richards CS, Watkins SC, Hoffman EP, Schneider NR, Milsark IW, Katz KS, Cook JD, et al (1990) Skewed X inactivation in a female MZ twin results in Duchenne muscular dystrophy. Am J Hum Genet 46:672–681

Roberts RG, Coffey AJ, Borrow M, Bentley DR (1993) Exon structure of the human dystrophin gene. Genomics 16:536–538

Schinzel AA, Robinson WP, Binkert F, Torresani T, Werder EA (1993) Exclusively paternal X chromosomes in a girl with short stature. Hum Genet 92:175–178

Sharman GB (1971) Late DNA replication in paternally derived X chromosome of female kangaroos. Nature 230:231–232

Spence JE, Perciaccante RG, Greig GM, Willard HF, Ledbetter DH, Hejtmancik JF, Pollack MS, et al (1988) Uniparental disomy as a mechanism for human genetic disease. Am J Hum Genet 42:217–226

Takagi N, Sasaki M (1975) Preferential inactivation of the paternally derived X chromosome in the extraembryonic membrane of the mouse. Nature 256:640–641

Voss R, Ben-Simon E, Avital A, Godfrey S, Zlotogora J, Dagan J, Tikochinski Y, et al (1989) Isodisomy of chromosome 7 in a patient with cystic fibrosis: could uniparental disomy be common in humans? Am J Hum Genet 45:373–380

Willard HF (1995) The sex chromosomes and X chromosome inactivation. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic and molecular bases of inherited disease, 7th ed. McGraw-Hill, New York, pp 719–737

Worton RG, Brooke MH (1995) The X-linked muscular dystrophies. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic and molecular bases of inherited disease, 7th ed. McGraw-Hill, New York, pp 4195–4226

Zneimer SM, Schneider NR, Richards CS (1993) In situ hybridization shows direct evidence of skewed X inactivation in one of monozygotic twin females manifesting Duchenne muscular dystrophy. Am J Med Genet 45:601–605