

Triple-X Syndrome in a Trisomic Down Syndrome Child: Both Aneuploidies Originated from the Mother

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ABSTRACT Here we report a case of double aneuploidy showing trisomy 21 and triple-X chromosome in a case of Down syndrome born to young non-consanguineous parents. The child presented with strabismus, periorbital swelling, scanty eyebrows and microganthia in addition to Down features. Molecular characterization has shown the maternal origin of double aneuploidy with trisomy 21 at meiosis-II and triple-X at meiosis-I.

INTRODUCTION

Aneuploidy is the second most important category of chromosome mutations relating to abnormal chromosome number. Trisomy 21 and numerical sex chromosome anomalies are common chromosomal disorders, with a birth incidence of 1:700 to 1:2,500 respectively (Kovaleva and Mutton 2005). The chances of two chromosomal anomalies occurring in a single conceptus are a rare event and the reported incidence varies from 0.21% to 2.8% in spontaneous miscarriages subjected to cytogenetic study (Guzel et al. 2009). Nonetheless, the incidences might be more than the expected occurrence if multiplied by the individual frequencies of each aneuploidy (Hook 1992). However, the underlying mechanism involved in the formation of double aneuploidy (DA) is not well understood. Parental origin is studied only in a small number of cases and both non disjunctions occurring in a single parent is an extremely rare event. Because of the rarity and for an addition to the existing literature, we present a case of double aneuploidy in a clinically suspected case of Down syndrome.

CASE REPORT

A 10-days old female child with clinical features of Down syndrome was taken up for cyto-

genetic investigation. She was born to a young, healthy mother from a non-consanguineous marriage. The age of the father was 29 years and the mother was 26 years at the time of the child's birth. This was their second pregnancy and their first pregnancy ended at 2 months in a miscarriage. Though the second pregnancy was uncomplicated, the proband was born preterm (8 months) with a birth weight of 2.5 kg. The child had features of Trisomy 21 with upslanting palpebral fissures, flat nasal bridge, thin lips, macroglossia, low set ears, neonatal hypotonia, high arched and narrow palate, short neck and bilateral single transverse palmer crease (Figs. 1). In addition, strabismus, periorbital swelling, scanty eyebrows and microganthia were also observed. However, the child did not present any striking features of triple-X syndrome. Additionally, no cardiac anomalies were detected at birth.



Fig. 1. Clinical features of the proband

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Cytogenetic analysis was carried out using the standard procedure, and revealed a karyotype 48,XXX,+21 in the patient with Down syndrome (Fig.2). The trisomy 21 and triple-X was acquired de novo, as parental chromosome analysis revealed normal chromosomal pattern. Over 200 metaphase cells were analyzed and no mosaicism was detected.

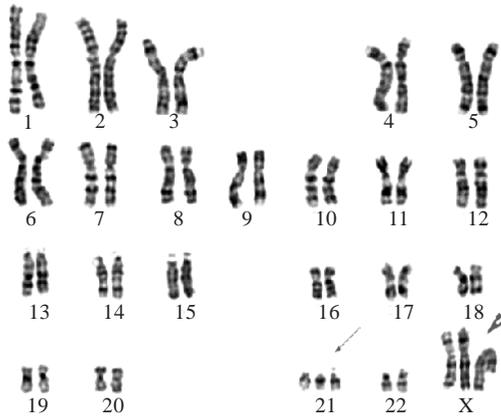


Fig. 2. Karyotype showing both triple-x [depicted by bold arrow] and trisomy 21[shown by arrow]

Genomic DNA was purified from peripheral blood lymphocytes from the proband and her parents by standard SDS-proteinase K extraction method (Old and Ludlam 1991). DNA polymorphisms were studied using various STR locus for chromosome 21 (D21S1432, D21S1435, D21S1446) and for chromosome X (DXS6807, DXS1068, DXS6799, DXS1047). This has shown that chromosome 21 is derived due to non-disjunction occurring at meiosis-II and chromosome X due to meiosis-I. It has also been interpreted that both non-disjunction events have occurred in the mother (Table 1).

Table 1: Genotype of DNA polymorphism of proband's family

	Father	Mother	Child
D21S1432	2,4	1,3	1,1,4
D21S1435	1,3	2,2	1,2,2
D21S1446	1,2	1,1	1,1,2

Chr21: supernumerary allele is of maternal origin and both maternal are same, suggesting an error at SECOND division

DXS6807 1,0 1,2 1,1,2
 DXS1068 2,0 1,2 1,2,2
 DXS6799 1,0 1,2 1,2,2
 DXS1047 1,0 2,3 1,2,3

ChrX: supernumerary allele is also of maternal origin, but both maternal alleles are not same (except for marker DXS6799 due to recombination following a crossing over), suggesting an error at FIRST division

Additional study for common polymorphism in MTHFR gene (677CT or TT) was also carried out in the parents which was found to be normal, whereas vitamin B-12 was low in father and normal in mother. Folate and homocysteine were normal in both the parents.

DISCUSSION

Double trisomies are rarely seen among live births as most of the cases are inevitably lethal (Guzel et al. 2009). Trisomy- 21 and triple- X in the same individual has been reported earlier (Balwan et al. 2008; Devlin and Morrison 2004; Guzel et al. 2009; Kovaleva and Mutton 2005) and phenotypic features of classical Down syndrome were only seen. However, strabismus, periorbital swelling, scanty eyebrows and micrognathia observed in the present case have not been observed in earlier reports. Molecular research though carried out in a small number has shown that they are either derived from a single parent or have different parental origin (Guzel et al. 2009). In the present study, molecular characterization has shown maternal origin of double aneuploidy with origin of trisomy 21 at meiosis-II and triple X at meiosis-I. Though the origin of meiotic error is not known precisely, several factors like age (Diego-Alvarez et al. 2006; Li et al. 2005; Baird and Sadovnick 1988), nutritional (B12/Folate deficiency with hyperhomocystenemia) and/or polymorphism in the gene regulating B12/Folate pathways have shown to be associated with an increased risk of meiotic error (James et al. 1999; Sheth and Sheth 2003). However, in the present case, the age factor is ruled out as maternal age was 26 years at the time of the child's birth. Further study for the common polymorphism in MTHFR gene (677CT or TT) was also normal with low vitamin B-12 in father and normal B-12 status in the mother. Since both non-dysjunction occurred in mother, low vitamin B12 in the father is unlikely to have any role in the present case. This again shows that the cause of meiotic error was either due to abnormal function, due to mutation or regulatory anomaly of unknown genes involved in the meiotic error or genetic predisposition in some families for the double aneuploidy (Diego-Alvarez et al. 2006). Prognosis for patients with trisomic miscarriage is favorable. However, the risk of trisomic pregnancies with advanced maternal age is higher (Warburton et al. 1987). Also, patients with an euploid miscarriage have

a poor prognosis. This suggests that an alternative cause of miscarriage may exist, such as variants in proteins affecting DNA methylation or meiotic segregation (Robinson et al. 2001), gonadal mosaicism for a chromosome abnormality or balanced translocations (Sugiura-Ogasawara et al. 2004; Lorda-Sanchez et al. 2005). In the present case, pregnancy loss in first trimester was difficult to ascertain as no information about the fetal loss was available, and recurrence risk would be difficult to ascertain to the family in presence of normal chromosomal status in both parents. It is likely that some other mechanism of independent non-disjunction might be playing a role in such cases and further studies are needed to elucidate the molecular events for double aneuploidy. Nonetheless, it would be appropriate to advise the family for prenatal diagnosis in subsequent pregnancies.

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REFERENCES

- Baird PA, Sadovnick AD 1988. Maternal age-specific rates for Down syndrome: Changes over time. *Am J Med Genet*, 29(4): 917-927.
- Balwan WK, Kumar P, Raina TR, Gupta S 2008. Double trisomy with 48, XXX+21 karyotype in a Down's syndrome child from Jammu and Kashmir. *Ind J Genet*, 87(3): 257-259.
- Diego-Alvarez D, Ramos-Corrales C, Garcia-Hoyos M, Bustamante-Aragones et al. 2006. Double trisomy in spontaneous miscarriages: Cytogenetic and molecular approach. *Human Reproduction*, 21(4): 958-966
- Devlin L Morrison PJ 2004. Accuracy of the clinical diagnosis of Down's syndrome. *Ulster Med J*, 73(1): 4-12.
- Guzel AI, Demirhan O, Pazarbasi A, Ozgunen FT et al. 2009. Detection of parental origin and cell stage errors of a double non-disjunction in a fetus by QF-PCR. *Genet Test Mol Biomarkers*, 13(1): 73-77.
- Hook EB 1992. Chromosome abnormalities: Prevalence risk and recurrence. In: DJH Brock, CH Rodeck, MA Ferguson-Smith (Eds.): *Prenatal Diagnosis and Screening*. Edinburgh: Churchill-Livingston, pp. 351-39.
- James SJ, Pogribna M, Pogribny IP, Melynk S et al. 1999. Abnormal folate metabolism and mutation in the MTHFR gene may be maternal risk factors for Down syndrome. *Am J Clin Nutr*, 70: 495-550.
- Kovaleva NV, Mutton DE 2005. Epidemiology of double aneuploidies involving chromosome 21 and the sex chromosomes. *Am J Med Genet A*, 134A(1): 24-32.
- Li QY, Tsukishiro S, Nakagawa C, Tanemura M et al. 2005. Parental origin and cell stage of non-disjunction of double trisomy in spontaneous abortion. *Congenit Anom (Kyoto)*, 45: 21-25.
- Lorda-Sanchez I, Diego-Alvarez D, Ayuso C, de Alba MR et al. 2005. Trisomy 2 due to a 3:1 segregation in an abortion studied by QF-PCR and CGH. *Prenat Diagn*, 25: 934-938.
- Old JM, Ludlam CA 1991. Antenatal diagnosis. *Baillieres Clin Hematology*, 4: 391-428.
- Robinson WP, McFadden DE, Stephenson MD 2001. The origin of abnormalities in recurrent aneuploidy/polyploidy. *Am J Hum Genet*, 69: 1245-1254.
- Sheth JJ, Sheth FJ 2003. Gene polymorphism and folate metabolism: A maternal risk factor for Down syndrome. *Ind Pediatr*, 40(2): 115-123.
- Sugiura-Ogasawara M, Ozaki Y, Sato T, Suzumori N et al. 2004. Poor prognosis of recurrent aborters with either maternal or paternal reciprocal translocations. *Fertil Steril*, 81: 367-373
- Warburton D, Kline J, Stein Z, Hutzler M et al. 1987. Does the karyotype of a spontaneous abortion predict the karyotype of a subsequent abortion? Evidence from 273 women with two karyotyped spontaneous abortions. *Am J Hum Genet*, 41: 465-483.