Shwachman syndrome associated with de novo reciprocal translocation t(6;12)(q16.2;q21.2)

M Masuno, K Imaizumi, G Nishimura, M Nakamura, I Saito, K Akagi, Y Kuroki

Abstract
We describe a de novo apparently balanced reciprocal translocation t(6;12)(q16.2; q21.2) in an 18 month old girl with Shwachman syndrome, characterised by exocrine pancreatic insufficiency and bone marrow dysfunction. The cause of this syndrome is unknown, although autosomal recessive inheritance has been proposed. The translocation breakpoints in the present patient may be candidate regions for a gene responsible for Shwachman syndrome.

(J Med Genet 1995;32:894-895)

Shwachman syndrome (MIM *260400) is a rare genetic disorder characterised by exocrine pancreatic insufficiency, growth retardation, bone marrow dysfunction resulting in neutropenia, and metaphysical chondrodysplasia. In some instances, psychomotor development is impaired. At the present time, the cause of this syndrome is unknown, although autosomal recessive inheritance has been suggested.

A similar constellation of the digestive abnormalities, haematological changes, and metaphysical chondrodysplasia is seen in cartilage-hair hypoplasia (MIM *250250), which has been shown to be linked to 9p21–p13. A gene for Fanconi anaemia (MIM *227650) characterised by skeletal abnormalities and progressive bone marrow failure has been cloned, with no significant homology to any of the database sequences. It has been localised to 9q22.3.

Here we report a patient with Shwachman syndrome associated with a de novo reciprocal t(6;12)(q16.2;q21.2). The possibility that one of the chromosome breakpoints includes the critical region for Shwachman syndrome is discussed.

Case report
The female proband was born at 38 weeks of gestation after an uneventful pregnancy, labour, and delivery. The 26 year old primigravid mother was unrelated to her 30 year old husband. The birth weight of the proband was 2940 g, length 47.0 cm, and occipitofrontal circumference (OFC) 30.0 cm. Right incomplete cleft of the upper lip and hypertelorism were noted at birth. The early neonatal period was complicated by pneumonia. She has had chronic diarrhoea with recurrent steatorrhoea since 2 months of age.

She was first evaluated by us at the age of 3 months because of failure to thrive and liver dysfunction was found at that time. She lifted her head at the age of 4 months. At 7 months, hepatosplenomegaly was noted. She was able to sit up unaided at 9 months. At 10 months, she was admitted to our hospital for clinical investigation. Her weight was 5882 g (−2.9 SD), length 65.0 cm (−2.5 SD), and OFC 45 cm (−2.6 SD). Her muscle tone was normal. She was found to have a haemoglobin (Hb) level of 11.4 g/dl, a platelet count of 28.7 × 10^4/μl, and a range of white cell count of 4800–11400/mm^3 (neutrophils 184–2052/mm^3), indicating cyclic neutropenia. Hb electrophoresis showed a mild increase in the proportion of Hb F (4%). A bone marrow examination showed a slightly hypocellular marrow without maturation arrest. The range of liver transaminases was increased (AST 75–228 IU/l; ALT 78–232 IU/l). A systemic skeletal survey showed a mildly hypoplastic thoracic cage, slight expansion of the anterior ends of the ribs, and metaphysical dysplasia of the proximal femur. CT scan of the abdomen showed a pancreas that was totally replaced by fatty tissue (HU –91.4). Both liver and spleen were moderately enlarged with a normal density. In addition magnetic resonance imaging of the abdomen was performed. The pancreas was absent. Other biochemical findings are listed in Table 1. At 7 months, diabetes mellitus was suspected.


discussion
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Although the translocation in this patient appears to be balanced, the possibility that subtle chromosome material is deleted from one or both the chromosomes involved is not excluded. The present patient is a sporadic case with typical Shwachman syndrome except for incomplete cleft lip. Cleft lip and palate was described in a patient with interstitial deletion of 12q13.3-q21.1. Cutaneous syndactyly and hypertelorism are rarely found in Shwachman syndrome, but are observed in patients with an interstitial deletion or apparently balanced translocations involving the breakpoints of 12q15-q21.2. Therefore, the present patient may have a submicroscopic deletion at 12q21.2 and the locus of the gene responsible for Shwachman syndrome seems to be at 12q21.2 rather than 6q16.2, if the translocation results in a gene mutation leading to this syndrome.

Careful cytogenetic studies in other patients with Shwachman syndrome will be of great interest to establish whether the present association is fortuitous or whether it is an indication for the localisation of this autosomal recessive syndrome at 6q16.2 or 12q21.2.

We are grateful to A Omiya and I Namba for their technical assistance in the cytogenetic study. This study was supported in part by a Research Grant (5A-5) for Nervous and Mental Disorders and a grant for research on mental retardation from the Ministry of Health and Welfare, Japan.


Discussion

This report concerns an 18 month old Japanese girl with typical Shwachman syndrome and a de novo apparently balanced reciprocal translocation t(6;12)(q16.2;q21.2). The cause and gene locus responsible for this syndrome are unknown but autosomal recessive inheritance has been suggested. Physical gene disruption with consequent loss of function at the breakpoints of a chromosomal translocation may lead to functional homozygosity of a recessive gene located at one of the sites of the respective translocation chromosomes. Thus, the translocation breakpoints 6q16.2 or 12q21.2 in the present patient may indicate a candidate region for Shwachman syndrome.

Aggett et al. hypothesised that the basic defect in Shwachman syndrome is attributable to abnormal cellular secretion owing to malfunction of the microtubules and microfilaments. Interestingly, an alpha tubulin gene (TUBAL1) has been assigned to chromosome 12, which is one of the chromosomes involved in the translocation breakpoints in our patient. Confirmation of the precise chromosome localisation of this gene may provide insight into the molecular defects of Shwachman syndrome.

CYTOGENETIC FINDINGS

Chromosome analysis was made from peripheral lymphocyte culture for 72 hours with PHA stimulation. The proband's karyotype by high resolution GTG banding was 46,XX,t(6;12)(q16.2;q21.2) (figure). Although it is less likely, an alternative possibility of 46,XX,t(6;12)(q15q15) is not excluded. This finding was confirmed by bone marrow analysis. The chromosomes of both parents were normal. At the age of 11 months, spontaneous chromosomal breakage was not observed in 100 Giemsa stained metaphases of the proband in agreement with the findings of Koifmann et al., but in contrast to the report of Tada et al. EBV transformed lymphoblastoid cell lines from the present patient (KCMC-530) and her parents (KCMC-614 and KCMC-632) are available from Dr M Masuno.

Partial G banded karyotype of the proband. Arrows show the breakpoints of 6q16.2 and 12q21.2.