We report on an 8-year-old girl with congenital scoliosis (segmented hemivertebra between the second and third lumbar vertebrae) and psychomotor developmental delay. She has a de novo reciprocal translocation, t(13;17)(q34;p11.2). Congenital scoliosis is one type of structural spine deformation and hemivertebra is the most common anomaly causing congenital scoliosis. The cause and the mode of inheritance of hemivertebrae are unknown. Our patient has a de novo balanced chromosome aberration and retains two copies of the LLGL gene, which is usually lacking in patients with Smith-Magenis syndrome (SMS). Since some SMS patients who showed a deletion at 17p11.2 had congenital scoliosis, it is likely that one (17p11.2) of the breakpoints in our patient is a candidate region for a hemivertebra locus. Am. J. Med. Genet. 73:244–246, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: hemivertebra; balanced translocation; 17p11.2; Smith-Magenis syndrome

INTRODUCTION

Scoliosis is one of the most common deformities of the spine and may be defined as lateral deviation and rotation of a series of vertebrae from the midline anatomic position of the normal spine axis. Scoliosis is classified into structural and nonstructural types by the Scoliosis Research Society, and congenital scoliosis is one type of structural scoliosis. Hemivertebra results from a failure of complete unilateral spine formation and is the most common disorder causing congenital scoliosis [Goldstein and Waugh, 1973]. Although idiopathic scoliosis shows a familial incidence and is believed to be inherited as an autosomal-dominant trait, congenital scoliosis usually occurs sporadically and its cause is largely unknown.

We report here on a female patient with hemivertebra and a de novo balanced reciprocal translocation, t(13;17)(q34;p11.2), suggesting that a putative locus for spine formation is assigned to either of these breakpoints.

CLINICAL REPORT

The patient, an 8-year-old Japanese girl, was the only child of healthy nonconsanguineous parents. The mother was 36 and the father 38 years old at her birth. Family history was unremarkable, especially for scoliosis. The girl was born by vaginal delivery after an uncomplicated 40-week gestation. Her birth weight was 2,885 g, length 48.5 cm, head circumference 33.5 cm, and chest circumference 31.0 cm. Her weight gain was poor because of poor sucking and hypotonia. "Dysplastic" hip joints were noted at age 8 months. She was referred to our hospital at age 21 months because of congenital scoliosis and psychomotor developmental delay. Roentgenographic examination showed a fully separated, segmented hemivertebra between the second and third lumbar vertebrae, and the spine curve was estimated at 18°. Scoliosis progressed each year and she was treated with a corset since age 4 years. When seen again at age 8 years, the curve was 38° (Fig. 1). Somatic growth was within normal limits, and no other anomalies except for scoliosis were noted. Results of examinations of blood and urine were all normal. Psychomotor development was mildly retarded as follows: she controlled her head at 4 months, sat alone at 8 months, walked without support at 2½ years, and spoke meaningful words at 3 years. Computerized tomographic scanning of the brain showed mild "cortical atrophy."
CYTOGENETIC ANALYSIS

Metaphase and prometaphase chromosomes were prepared from cultured peripheral blood lymphocytes of the patient and her parents, and GTG-banding was performed according to standard methods. Chromosome analysis of the patient revealed a balanced reciprocal translocation between chromosomes 13 and 17 (Fig. 2). Her parents had normal chromosomes. Thus, the patient’s karyotype was 46,XX,t(13;17)(q34;p11.2) de novo. Fluorescence in situ hybridization on the patient’s metaphase chromosomes was performed as described elsewhere [Takahashi et al., 1989]. A biotin-labeled cosmid that covers the human LLGL gene was used as a probe. Of 50 metaphase chromosomes examined, 48 showed clear, discrete signals on 17p11.2 of both normal and derivative chromosomes. There were no signals seen on the derivative chromosome 13 (data not shown).

DISCUSSION

Failures of unilateral spine formation can be classified into segmented, semisegmented, and nonsegmented hemivertebra forms. The hemivertebra in our patient was the unilateral, segmented type involving the lumbar vertebrae. The cause of most hemivertebrae is unknown, because they occur sporadically, whereas familial cases of idiopathic scoliosis have occasionally been reported, suggesting autosomal-dominant inheritance [Cowell et al., 1972]. Since the spinal curve usually progresses more slowly in hemivertebrae than in idiopathic scoliosis, some familial members with mild scoliosis may be overlooked. Such familial occurrence may be diagnosed by radiographic examination.

Our patient had a de novo balanced reciprocal translocation with breakpoints of 13q34 and 17p11.2. This finding suggests that a putative gene or genes important for spine development may have been disrupted at either of the breakpoints in this patient. Several chromosome deletions associated with hemivertebrae have previously been reported. They include del(1q4) [Johnson et al., 1985], del(3p2) [Fineman et al., 1978], monosomy 4p [Stengel-Rutkowski et al., 1984], interstitial 5q-deletion [Kobayashi et al., 1991], r(15) [Butler et al., 1988], and interstitial deletion of 17p [Smith et al., 1986]. Some patients with Smith-Magenis syndrome (SMS) who showed a deletion involving a chromosomal region, 17p11.2, also had congenital scoliosis [Smith et al., 1986]. Therefore, it seems that 17p11.2 rather than 13q34 is one candidate chromosomal region responsible for hemivertebrae. Linkage analysis was performed in 24 pedigrees of familial idiopathic scoliosis using 17p11.2 markers, but a high lod score has not been obtained for any of the markers examined [Inoue et al., unpublished data].

LLGL is the human homolog of the mouse Lihg gene, which was originally isolated as a homolog of the Drosophila tumor suppressor gene, l(2)gl (lethal (2) giant larvae) [Jacob et al., 1987]. Lihg was recently isolated as a target for Hox-c8 [Tomotsune et al., 1993], a
homeobox gene which may control pattern formation during embryogenesis [Le Mouellic et al., 1988]. The human LLGL was located on chromosome 17p11.2 by fluorescence in situ hybridization (FISH) [Koyama et al., 1996], and some SMS patients lacked one copy of the gene [Koyama et al., 1996]. Although LLGL was not largely deleted in our patient by FISH analysis, the possibility of partial destruction or deletion of the gene remains.

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