LETTER TO THE EDTIOR

A 20.5-MB GERMLINE DELETION OF 13q13.1→q14.3 AND SOMATIC MUTATIONS OF THE RB1 GENE IN AN 8-YEAR-OLD GIRL WITH UNILATERAL RETINOBLASTOMA, DEVELOPMENTAL DELAY AND MENTAL RETARDATION

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The 8-year-old female patient was the first child of a healthy and unrelated couple. Both the mother and father were 28 years old at her birth. There was no family history of congenital malformations. She was born uneventfully at 38 weeks of gestation with a birth weight of 2,430 g (< 3rd centile). She was first seen at the pediatric department at the age of 2 years because of speech delay, developmental delay and mental retardation. Electroencephalography revealed diffuse cortical dysfunction, and brain magnetic resonance imaging (MRI) revealed a pineal cyst. The growth parameters at that time were body weight 10.4 Kg (15-50th centile), body length 79 cm (< 3rd centile) and head circumference 48 cm (50-85th centile). The facial dysmorphism was not prominent. At the age of 3 years, leukocoria was present in her left eye. At that time, the growth parameters were body weight 13.5 Kg (15-50th centile) and body length 85 cm (< 3rd centile). Computed tomography scans revealed a 17×12×7 mm left intraocular tumor consistent with the diagnosis of retinoblastoma. Echocardiographic findings were unremarkable. She underwent primary enucleation of the left eyeball. Pathological examination of the tumor confirmed retinoblastoma. Mutational analysis of the *RB1* gene using the tumor tissue of retinoblastoma revealed mutations of c.515_516 del TA in exon 5 and c.2391_2392 ins A in exon 23 (Fig. 1). However, DNA testing on the blood sample did not reveal any *RB1* mutation (Fig. 1). Peripheral blood chromosomal analysis of the patient had shown a deletion encompassing the region of 13q13-q14. Array comparative genomic hybridization (aCGH) was performed to delineate the size of deletion. Oligonucleotide-based aCGH using Oligo HD Scan™ (CMDX, Irvine,

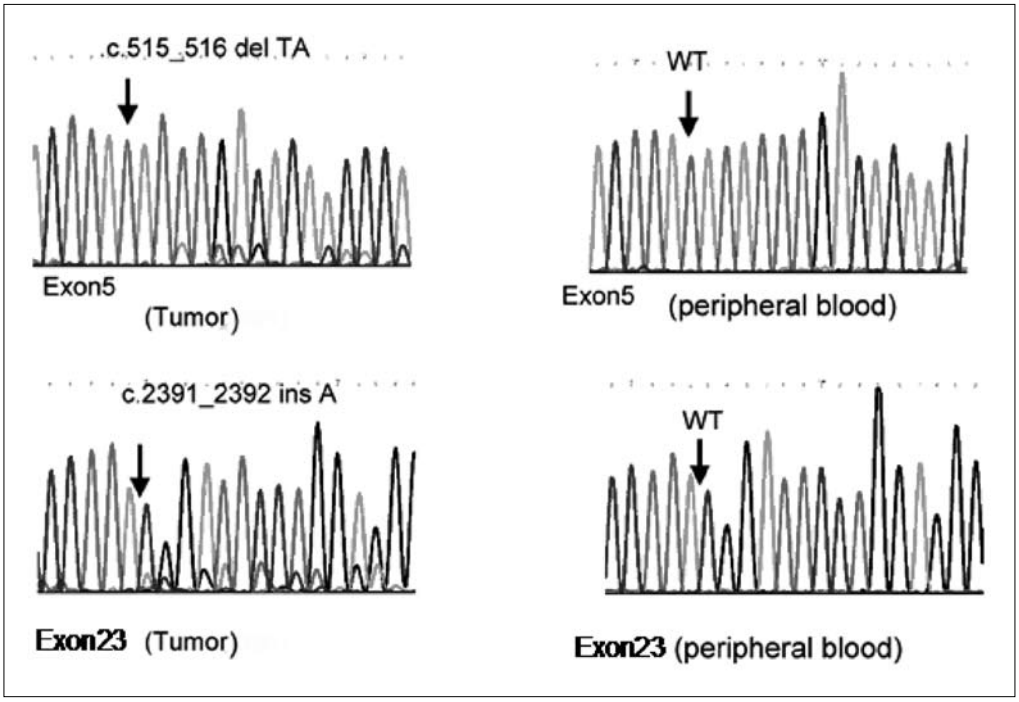

Figure 1: Mutational analysis of the *RB1* gene mutations of c.515_516 del TA in exon 5 and c.2391_2392 ins A in exon 23 in the retinoblastoma tumor tissue but not in the peripheral blood. WT: wild type.

CA, USA) revealed a 20.5-Mb deletion of 13q [arr cgh 13q13.1q14.3 (31,273,669-51,725,747)×1] (NCBI build 36, March 2006) in the peripheral blood (Fig. 2). The karyotype of the patient was 46,XX,del (13)(q13.1q14.3). At the age of 8 years, her right eye remained free of disease.

We report on clinical and molecular findings in an 8-year-old girl with unilateral retinoblastoma, developmental delay, mental retardation, a germline *RB1* deletion and somatic mutations of the *RB1* gene. The present case demonstrates concomitant germline large cytogenetic 13q deletion and somatic mutations in the *RB1* gene in unilateral retinoblastoma. The frequency of cytogenetic 13q deletion in retinoblastoma patients has been reported as 3.3-11.3% (4). In a study of frequency of 13q abnormalities among patients with retinoblastoma, Bunin *et al*. (2) found 13q14 deletion in about 4.9% (6/123) of patients with unilateral retinoblastoma. In retinoblastoma patients with cytogenetic 13q deletion, an excess of patients with unilateral retinoblastoma has been observed (1-3). It has been postulated that among patients with a germline cytogenetic 13q deletion, fewer tumors may arise in those

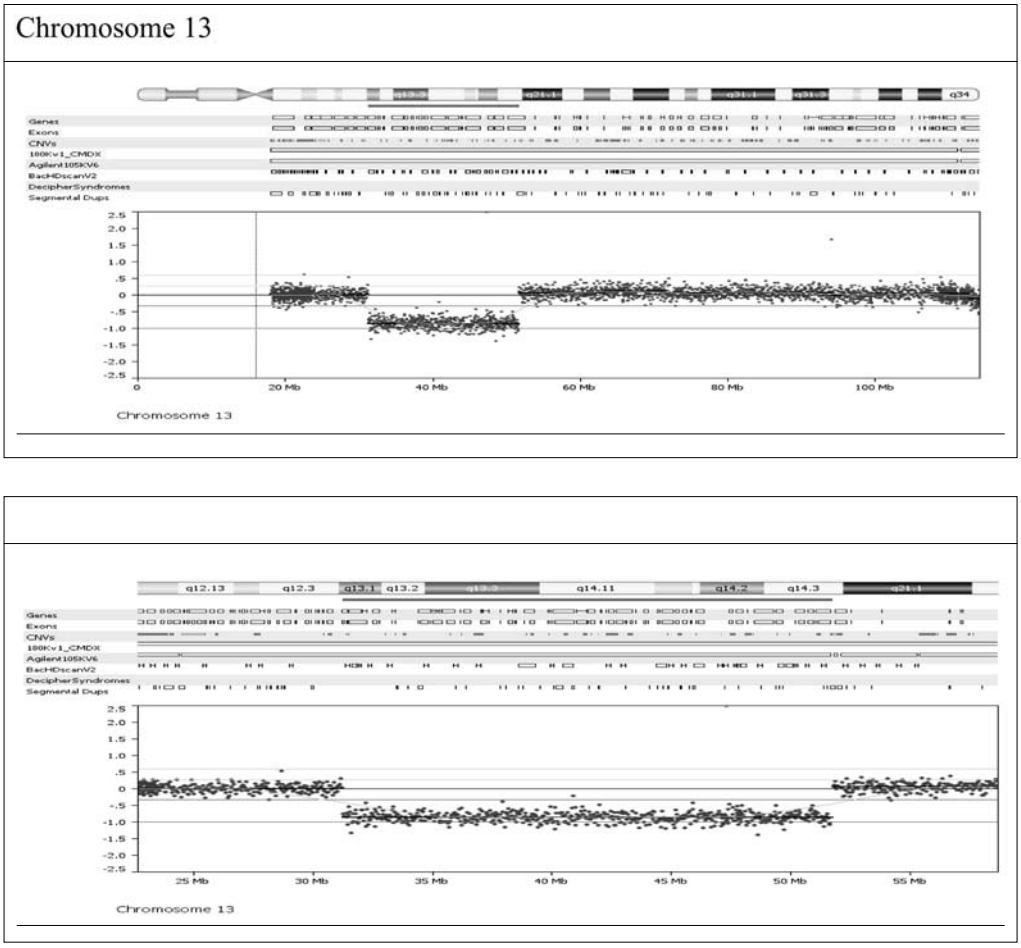

Figure 2: Oligonucleotide-based comparative genomic hybridization reveals a 20.5-Mb deletion of 13q [arr cgh 13q13.1q14.3 (31,273,669-51,725,747)×1] (NCBI build 36, March 2006) in the peripheral blood.

patients, giving more patients with a unilateral tumor (1, 2). Albrecht *et al*. (1) suggested that carriers of cytogenetic and submicroscopic whole *RB1* gene deletions often have unilateral retinoblastoma only. Bunin *et al*. (2) hypothesized that if the first hit is loss of a significant portion of chromosome 13q involving 13q14, the second hit must be a local mutation at the *RB1* gene. It is likely that the mitotic non-disjunction event with loss of the normal chromosome 13 will result in homologous large cytogenetic 13q deletions causing lethality of the cells. Our presentation provides evidence that somatic *RB1* gene mutations can play the role of the second hit in patients with a germline large cytogenetic 13q deletion and unilateral retinoblastoma.

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