MOSAIC SUPERNUMERARY r(1)(p13.2q23.3) IN A 10-YEAR-OLD GIRL WITH EPILEPSY, FACIAL ASYMMETRY, PSYCHOMOTOR RETARDATION, KYPHOSCOLIOSIS, DERMATOFIBROSARCOMA AND MULTIPLE EXOSTOSES

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Summary: *Mosaic supernumerary r(1)(p13.2q23.3) in a 10-year-old girl with epilepsy, facial asymmetry, psychomotor retardation, kyphoscoliosis, dermatofibrosarcoma and multiple exostoses:* We report molecular cytogenetic characterization of mosaic supernumerary r(1)(p13.2q23.3) in a 10-year-old girl with epilepsy, facial asymmetry, psychomotor retardation, kyphoscoliosis, dermatofibrosarcoma and multiple exostoses. The supernumerary r(1) is associated with gene dosage increase of *CHRNB2*, *ADAR* and *KCNJ10* in the pericentromeric area of 1q, and a breakpoint within *CTTNBP2NL* at 1p13.2. We speculate that the gene dosage increase of *CHRNB2*, *ADAR* and *KCNJ10* is most likely responsible for epilepsy, and the breakpoint at 1p13.2 in the supernumerary r(1) is most likely responsible for the development of multiple exostoses and osteochondroma in this patient.

Key-words: 1p13.2 - *ADAR* - *CHRNB2* – Chromosome 1 duplication – *CTTNBP2NL* – Epilepsy – *KCNJ10* – Multiple exostoses – Osteochondroma – Supernumerary ring chromosome 1.

INTRODUCTION

Small supernumerary marker chromosomes (sSMCs) are small supernumerary chromosomes that have a size smaller than a chromosome 20 and difficulties in identification and characterized by conventional cytogenetic techniques (11, 13, 15). sSMCs can occur in 0.044% of newborn infants and in 0.075% of prenatal cases, and 70% of sSMCs arise *de novo* (12, 14). Here, we present our experience of molecular cytogenetic characterization of an sSMC derived from chromosome 1.

CLINICAL REPORT

The 10-year-old girl was the first child born to healthy and non-consanguineous parents. When she was born, the father was 44 years old and the mother was 40 years old. The family history was unremarkable. She was delivered uneventfully at term. When examined at 6 years of age, she manifested developmental delay, speech delay, unstable gaits, kyphoscoliosis, hyporeflexia, facial asymmetry, a round face, a depressed nasal bridge, epicanthic folds, dysplastic low-set ears, hypertelorism, a prominent forehead, and a 5×5 cm subcutaneous mass over the occipital scalp (Fig. 1). Her body weight was 20 Kg (50 centile), and body length was 120 cm (85 centile). Cytogenetic analysis of the blood lymphocytes showed mosaicism for an SMC (Fig. 2). Of 50 cultured blood lymphocytes, 18 cells had an SMC, while the rest 32 cells were normal. The maternal karyotype was normal. Spectral karyotyping (SKY) showed that the SMC was derived from ring chromosome 1,

Figure 1: Craniofacial appearance of the proband at age 10 years.

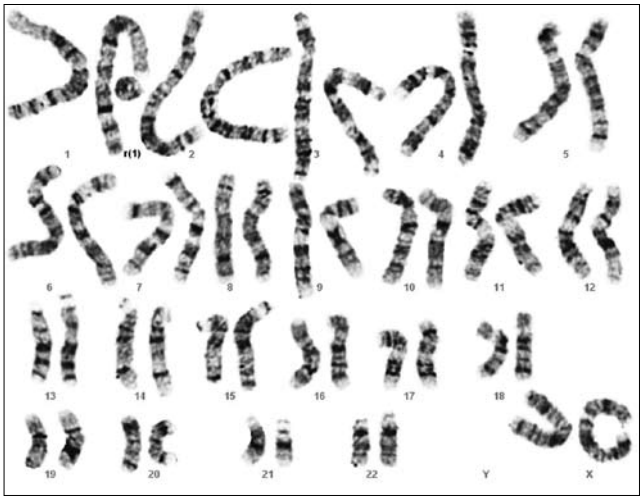

Figure 2: A karyotype of 47,XX,+r(1)(p13.2q23.3).

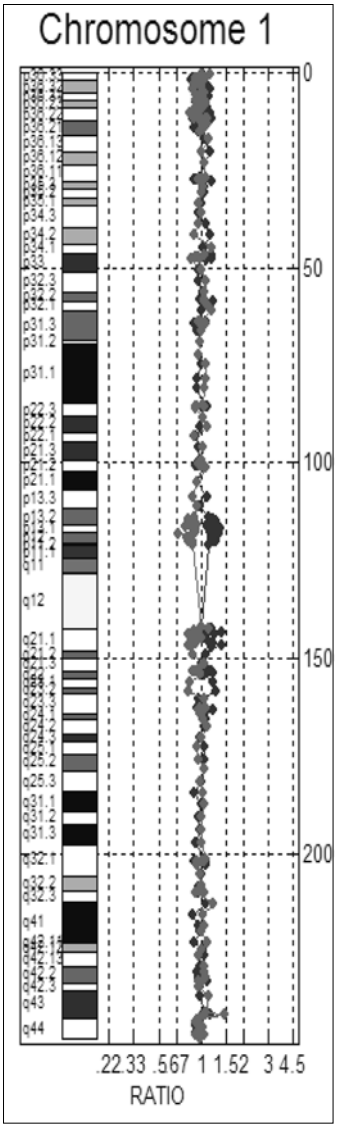

Figure 3: Bacterial artificial chromosome-based array comparative genomic hybridization (aCGH) shows a gain in the gene dosage on the pericentric euchromatic region of chromosome 1.

r(1). Array comparative genomic hybridization (aCGH) of blood using bacterial artificial chromosome (BAC)-based aCGH (CMDX BAC aCGH CA3000 Chips) (CMDX, Irvine, CA, USA) and oligonucleotide-based aCGH (Oligo HD Scan) (CMDX, Irvine, CA, USA) demonstrated genomic imbalance with a gain in the gene dosage on the pericentric euchromatic region of chromosome 1 (Figs 3 and 4). There was a 45.85-Mb duplicated segment encompassing 1p13.2→q23.3 (112,750,000-158,600,000 bp) (NCBI Build 36, March 2006). Polymorphic DNA marker analysis excluded chromosome 1 uniparental disomy (UPD). The SMC was r(1)(p13.2q23.3). The karyotype thus was 47,XX,+r(1)(p13.2q23.3)[18]/46,XX[32]. At the age of 7 years, she underwent a surgical excision of the scalp mass. The mass was found to be dermatofibrosarcoma protuberans by pathological examination (Fig. 5). At the age of 8 years, she developed intermittent seizures. Electroencephalography showed chaotic short waves arising from right temporal area. Computed tomography scans did not show any abnormalities. At the age of 10 years, she developed multiple exostoses over the left thigh. The X-ray findings of the exostoses over left distal femur and left proximal fibula were consistent with the diagnosis of osteochondroma (Fig. 6).

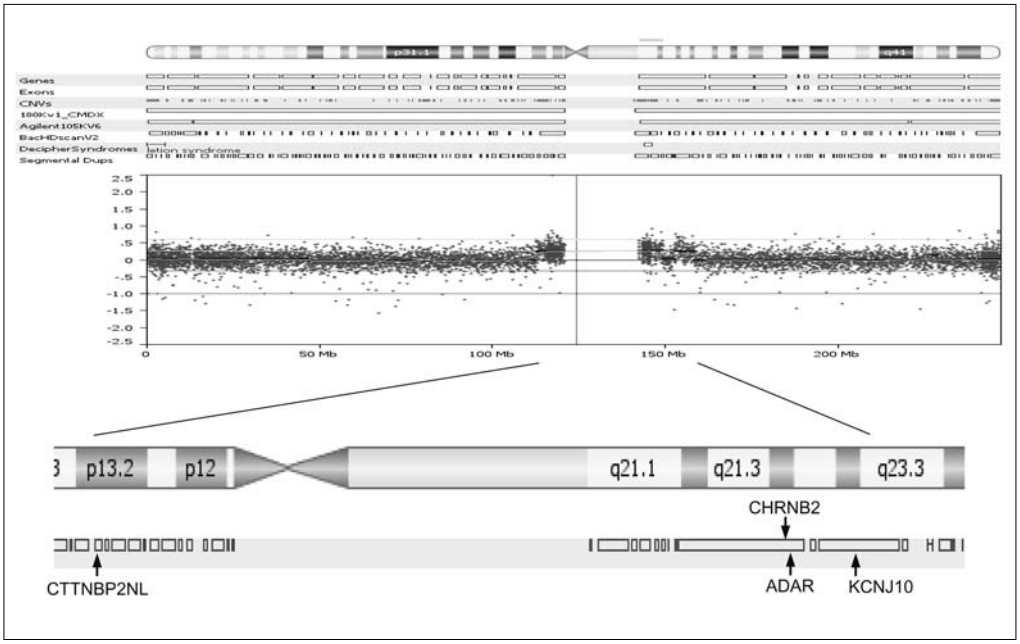

Figure 4: Oligonucleotide-based aCGH shows a 45.85-Mb duplicated segment encompassing 1p13.2→q23.3 (112,750,000-158,600,000 bp).

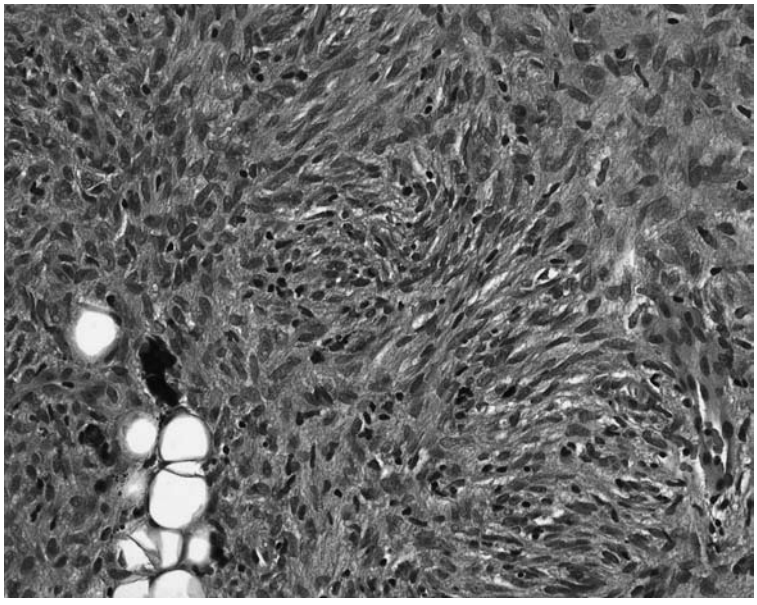

Figure 5: Typical histology of dermatofibrosarcoma protuberans with spindle cells in an irregularly whorled and storiform pattern (Hematoxylin-eosin stain; original magnification ×200).

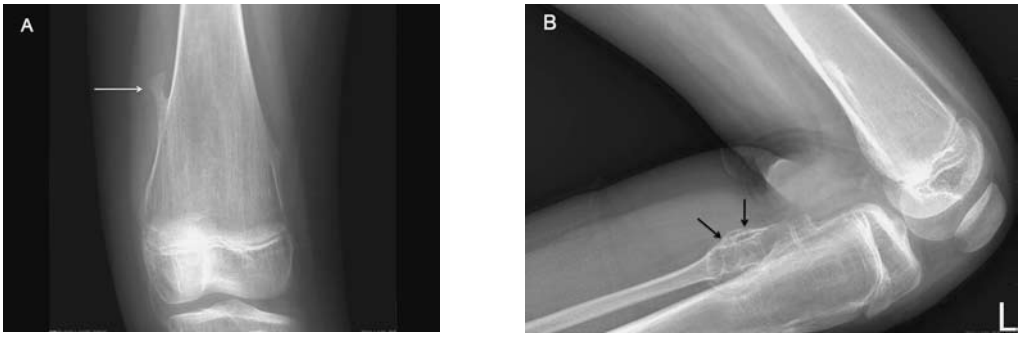

Figure 6: (A) An osteochondroma arising from medial aspect of left distal femur (arrow) and (B) an osteochondroma arising from the left proximal fibula (arrows).

DISCUSSION

The present case provides evidence for the correlation of a duplication of the pericentromeric area of chromosome 1q and epilepsy. Chen *et al*. (5) reported seizures in a 15-year-old boy with 14% of mosaicism for supernumerary r(1)(p13q23), multiple anomalies and involuntary movement. Leask and Clayton-Smith (9) reported severe seizures in a 9-year-old girl with 6% of mosaicism for supernumerary r(1). Liehr *et al*. (13) reported generalized epilepsy in a 44-year-old female with 38% of mosaicism for supernumerary r(1)(p12q12). Muhle *et al*. (17) reported a duplication in 1q21.3 in the father and son in a family with early onset and childhood absence epilepsy, and suggested that *CHRNB2* and *ADAR* are candidate genes for seizure disorders. The present case had a duplicated chromosome 1 segment encompassing the genes of *CHRNB2*, *ADAR* and *KCNJ10* (Fig. 4). *CHRNB2* (OMIM 118507) encodes β2 neuronal nicotinic acetylcholine receptor in which mutations may result in autosomal dominant nocturnal frontal lobe epilepsy type 3 (ENFL3) (OMIM 605375) (6, 18). Manfredi *et al*. (16) hypothesized that mutant nicotinic receptors lead to epilepsy by abnormal formation of neural circuits and/or long-lasting alteration of network assembly in the developing brain. *ADAR* (OMIM 146920) encodes RNA-specific adenosine deaminase. *ADAR1* and *ADAR2* are involved in rapid electrical and chemical neurotransmission (8). Muhle *et al*. (17) suggested that *ADAR* might play a role in human epilepsy. *KCNJ10* (OMIM 602208) encodes an inwardly rectifying potassium channel that is expressed in glials in the central nervous system. Mutations in *KCNJ10* cause a complex autosomal recessive disorder of SeSAME syndrome (OMIM 612780) comprising seizures, sensorineural deafness, ataxia, mental retardation and electrolyte imbalance (3, 20).

So far, at least 34 cases of mosaic supernumerary r(1) have been repor-

ted, but there is lack of a consistent phenotype due to different degrees of mosaicism and involvement in the chromosome 1 (22). The present case manifested kyphoscoliosis, facial asymmetry, and soft tissue and bone tumors in addition to seizures and psychomotor retardation. Levy *et al*. (10) reported a 15-year-old boy with 50% of mosaicism for supernumerary r(1)(p13q12) and scoliosis. Callen *et al*. (4) reported a 5-year-old boy with 30% of mosaicism for supernumerary r(1) and kyphosis, and a 2½-year-old boy with 70% of mosaic supernumerary r(1) and kyphoscoliosis. Finelli *et al*. (7) reported a 15-year-old girl with 35% of mosaicism for supernumerary r(1)(::cen→q22::q22→sq21::), chest asymmetry and severe kyphoscoliosis. Barbi *et al*. (1) reported a 5½-year-old girl with > 95% of mosaicism for supernumerary r(1)(q10q21.3) and asymmetry of face and skull. Bernardini *et al*. (2) reported a 14-year-old boy with 15% of mosaicism for supernumerary r(1)(::p11.2→q12::) and body asymmetry. The present case additionally shows that facial asymmetry and kyphoscoliosis can be features of mosaic supernumerary r(1).

Soft tissue and bone tumors as presented in this case have not previously been described in patients with mosaic supernumerary r(1). In this case, the occurrence of dermatofibrosarcoma which is associated with t(17;22)(q22;q13) (*COL1A1*/*PDGFB*) (21) can be casual. However, the association of bone tumors in this case is in accordance with the observation of Sawyer *et al*. (19) who reported a clustering of breakpoints in the region of 1p13-p22 including the inversion, insertion and translocation of primary and secondary chromosome aberrations in osteochondroma. Sawyer *et al*. (19) suggested that aberrations of chromosome 1p in a region spanning 1p13-p22 may non-randomly involve in the cytogenetic progression of osteochondroma. We found that the breakpoint at 1p13.2 in this case was within *CTTNBP2NL* and near the tumor suppressor gene of *ST7L* and the oncogenes of *MOV10* (OMIM 610742) and *RHOC* (OMIM 165380). Of interest is that the genetic alteration of *CTTNBP2NL* has previously been reported to be associated with oral squamous cell carcinoma tumorigenesis and progression.

In summary, we present molecular cytogenetic characterization of mosaic supernumerary r(1)(p13.2q23.3) in a girl with epilepsy, facial asymmetry, psychomotor retardation, kyphoscoliosis, dermatofibrosarcoma and multiple exostoses. The supernumerary r(1) is associated with gene dosage increase of *CHRNB2*, *ADAR* and *KCNJ10* in the pericentromeric area of 1q, and a breakpoint within *CTTNBP2NL* at 1p13.2. We speculate that the gene dosage increase of *CHRNB2*, *ADAR* and *KCNJ10* is most likely responsible for epilepsy, and the breakpoint at 1p13.2 in the supernumerary r(1) is most likely responsible for the development of multiple exostoses and osteochondroma in this patient.

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