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Lack of chromosome 15q11–q13 region involvement in a family with Cowden disease/Bannayan-Zonana syndrome

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We read with interest the case report entitled, “Cowden’s disease with a defined genetic alteration-chromosomal duplication at 15q11-q13” by Suzuki et al.,¹ which appeared recently in the Journal. Cowden disease is a dominantly inherited multiple hamartoma syndrome characterized by hamartomas of ectodermal, endodermal, or mesodermal origin, and a high incidence of malignant tumors.² Cowden disease and the Bannayan-Zonana syndrome (BZS) share multiple phenotypic features and were recently found to be allelic.² Suzuki et al.¹ report a case of Cowden disease in which the chromosomal analysis suggested a small duplication in chromosome region 15q11-q13, a region commonly deleted in Prader-Willi and Angelman syndrome subjects. It is also considered a “hot spot” for chromosomal duplication.

We have also studied a family consisting of two boys and their parents. The father was aged 30 years, with macrocephaly, extensive multiple anterior abdominal wall and brain arteriovenous malformations, and penile freckling. Both sons (aged 7 months and 6 years) were macrocephalic with hemangiomas and mild developmental delay. The 7-month-old child was hypotonic and had neck and scrotal hemangiomas. The older brother had an extra-articular hemangioma of the left knee and penile freckling as well. The mother was asymptomatic but had had eight first-trimester abortions. Her pregnancies with both sons had been complicated by severe pre-eclampsia. The findings in boys and their father were consistent with the clinical diagnosis of Bannayan-Zonana syndrome.

We have undertaken molecular genetic and cytogenetic analysis with chromosome 15q11-q13 markers in this family. Routine G-banded cytogenetic analysis was performed on peripheral blood lymphocytes from the affected father and his unaffected and unrelated spouse. Chromosomal study results were normal. Molecular cytogenetic analysis with fluorescence-in-situ hybridization (FISH), using the SNRPN probe from the 15q11-q13 region (Oncor, Gaithersburg, MD, USA) was undertaken on the boys and their father, following the manufacturer’s recommendations. No duplication/deletion was seen (data not shown). This probe is localized to the middle segment of the Prader-Willi syndrome chromosome region, which is approximately four mega bases in size. Suzuki et al.,¹ also did not find a duplication in their patient, using the same probe and also the more distal D15S10 probe within 15q11-q13 region.

Polymerase chain reaction (PCR) analysis was undertaken with seven DNA microsatellite markers within the 15q11-q13 region (Table 1). The markers D15S541 and D15S1035 map at the proximal end of the region; markers GABRB3, D15S822, D15S217, and D15S165 span

the distal 1/3 of this region; and markers D15S1021 and SNRPN map to the middle segment of this region.³ No evidence of duplication or deletion was found with any of the markers. In addition, analysis of the microsatellites GABRB3, D15S822, D15S217, and D15S165 showed that both paternal alleles were transmitted to both affected sons, excluding close linkage between the Cowden disease/Bannayan syndrome gene and these microsatellites.

So far, few patients with Bannayan-Zonana syndrome/Cowden disease have been reported with constitutional chromosomal abnormalities. In an 11-year-old boy with features of BZS, Israel et al.⁴ found a 19; Y translocation [46,X,t(Y;19)(q11;q13)]. Arch et al.² described an 18-month-old patient with BZS who had an interstitial deletion of 10q23.2-q24.1, while Tsuchiya et al.⁵ found a similar deletion (10q23.2-q23.33) in a patient with gastrointestinal juvenile polyposis and other features of a Cowden-like syndrome. Marsh et al.^{6,7} and Liaw et al.⁸ demonstrated germline mutations in the *PTEN* (*Phosphatase, Tensin homolog*) gene in patients with Bannayan-Zonana syndrome and Cowden disease. Thus, Cowden disease and Bannayan syndrome are allelic disorders. The findings in our family, coupled with the evidence discussed above, suggest to us that the chromosomal abnormalities reported by Israel et al.⁴ and Suzuki et al.¹ are probably coincidental to the phenotype of Cowden disease/Bannayan-Zonana syndrome.

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Microsatellite data from our family with Cowden disease/Bannayan-Zonana syndrome genotyped at the 15q11–13 region

Table 1.

Subject	D15S541	D15S1035	D15S1021	GABRB3	D15S822	D15S217	D15S165
Father ^a	1,2	2,4	1,3	1,3	2,3	2,3	1,2
Mother	1,2	1,3	1,2	2,3	1,1	1,3	2,2
Son (B) ^a	2,2	1,4	1,1	2,3	1,3	2,3	2,2
Son (J) ^a	1,2	3,4	1,2	1,3	1,2	1,3	1,2

Microsatellites in bold print show biallelic paternal inheritance

^aIndicates affected family members