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Are Specific Short Arm Variants or Heteromorphisms Over-Represented in the Chromosome 15 Deletion in Angelman or Prader-Willi Syndrome Patients?

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To the Editor

The cytogenetic and molecular genetic research by Dr. Zackowski and colleagues [1993] on Angelman syndrome, reporting differences in the relative sizes of the heterochromatic region of the short arm of chromosome 15, suggested that chromosomes with large heterochromatic regions may be more prone to de novo deletions. Of their 22 individuals with Angelman syndrome and the 15q11q13 deletion, 15 patients had chromosome 15 homologs which could be distinguished from one another by a relative size differential of the short arm (p) heterochromatic region. In 12 of their 15 subjects the chromosome 15 with the deletion possessed the larger heterochromatic region. Their preliminary observation suggested that the event that produces the deletion of proximal 15q (i.e., female gametogenesis in Angelman syndrome [deletion is maternal in origin] or, similarly, male gametogenesis in Prader-Willi syndrome [deletion is paternal in origin], an entirely different clinical syndrome, both representing the first examples in humans of genetic imprinting) may have created the large short arm variant or heteromorphism. Herein, I report our experience with p arm variants and heterochromatic staining in both Prader-Willi and Angelman syndrome patients with the 15q11q13 deletion.

Thirty-four subjects with the Prader-Willi syndrome and four patients with Angelman syndrome, but with the 15q11q13 deletion, were studied. The deletion was confirmed with quantitative Southern hybridization of proximal 15q DNA probes (e.g., 3–21, 34, 189-1, 39, 43R, and/or IR-10) using H2–26 or H2–42 as internal control probes following established protocols [Tantravahi et al., 1989; Nicholls et al., 1989a,b; Mascari et al., 1992; Butler et al., 1993]. The relative sizes of the short arm and stalk length were recorded for each patient after the analysis of several GTG banded chromosome spreads during the course of high resolution cytogenetic analysis. In addition, the relative sizes and intensity of staining of the heterochromatin on the p arm and pericentromeric area of each of the chromosome 15s were also recorded. Twenty-one (18 Prader-Willi and three Angelman syndrome) of the 38 patients had relatively larger or more intensely stained heterochromatin of the deleted chromosome 15 in the majority of cells analyzed, compared with the normal homolog,

supporting an over-representation of larger heterochromatic regions of the short arm or pericentromeric area of the deleted chromosome 15 compared with the normal homolog. Thirteen patients (12 Prader-Willi and one Angelman syndrome) were uninformative (i.e., no difference in relative size or intensity of staining of heterochromatin or no clear majority seen in the cells examined for larger size or intensity of heterochromatin in either chromosome 15 [deleted or normal]), and four (three Prader-Willi and one Angelman syndrome) patients showed larger or more intensely stained heterochromatin in the normal chromosome 15 in the majority of cells. Specifically, 45% of the Prader-Willi syndrome patients were either uninformative or showed that the normal chromosome 15 homolog had a relatively larger heterochromatic region, and similarly in one of the four Angelman syndrome patients. There was no correlation with the size of the satellite stalk or short arm length identified with GTG banding and the deleted chromosome 15 (i.e., the chromosome 15 with the shorter or longer p arm or satellite stalk length did not consistently show the 15q11q13 deletion).

We reported previously [Butler and Palmer, 1983; Butler et al., 1986] in 13 Prader-Willi syndrome families that parental chromosomes were normal but interestingly the deletion was paternal in origin. In addition, there were no differences in the size of the short arm of the chromosome 15 that had undergone the deletion and received from the father. Thus, the short arms were inherited intact, and the alteration occurred in the long arm only of chromosome 15. Table I shows the chromosome 15 satellite stalk and short arm length and heterochromatic data from the 38 Prader-Willi and Angelman syndrome patients with 15q11q13 deletions in the current study. In addition, we reported (Butler and Greenstein, 1991] that previously undetectable translocations involving the pericentromeric region of chromosome 15 are rare as a cause of 15q deletions in Prader-Willi or Angelman syndrome patients as shown by in situ hybridization of D15Z1, a satellite non-isotopic probe (available from Oncor, Gaithersburg, Maryland) localized to the pericentromeric area, but more precisely the short arm region of chromosome 15. The in situ hybridization studies with the D15Z1 probe did show a difference in size of the fluorescent area detected by this probe in nine of 14 Prader-Willi or Angelman syndrome patients. However, the size of the fluorescent area did not correlate with the deletion status of the chromosome 15 (i.e., the smaller fluorescent area did not consistently correlate with the deleted or normal chromosome 15). A size difference was also observed in a parent. Thus, the in situ hybridization studies using D15Z1 probe for chromosome 15 did not identify a consistent size difference in the deleted chromosome 15, but did support the use of this probe as a polymorphic marker for parental origin studies.

In summary, our high resolution cytogenetic data from a relatively large number of Prader-Willi and Angelman syndrome patients with 15q11q13 deletions did support an over-representation of the larger relative size or intensity of staining of the heterochromatic region of the short arm and possibly the pericentromeric area of the deleted chromosome 15 in these patients, but not for the size of the satellite stalk or short arm length. This over-representation may be explained by the presence of the G-positive 15q12 band, which may be placed in close proximity to the centromere by the deletion of the G-negative 15q11 band. This misplaced G-positive band (15q12) may give the impression of a larger G-positive

heterochromatic area at or near the centromere. Additional studies will be needed to further explain this observation.

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Chromosome 15 Satellite Stalk and Short Arm Polymorphism and Heterochromatic Data Detected by GTG Banding from Prader-Willi and Angelman Syndrome Patients With the Chromosome 15 Deletion

TABLE I

Subject	Age (yr)	Sex	Short (p) arm and satellite stalk length ^a		Larger or more intensely stained heterochromatic region on del(15q) chromosome
			del(15q)	Normal	
PWS 1	0.5	F	sp	lp	No
PWS 2	0.5	F	lp+	mp	Yes
PWS 3	1.5	M	mp	mp	— ^b
PWS 4	3.0	F	sp+	mp	Yes
PWS 5	3.5	M	lp+	mp	Yes
PWS 6	4.0	M	sp	—p	Yes
PWS 7	5.0	F	sp	mp	—
PWS 8	5.0	F	mp	lp	Yes
PWS 9	5.0	M	mp	mp	—
PWS 10	6.0	F	mp	lp	Yes
PWS 11	8.5	M	lp	sp	Yes
PWS 12	12.5	F	sp	mp	Yes
PWS 13	13.0	M	sp	lp	Yes
PWS 14	14.0	M	mp	mp	—
PWS 15	15.0	M	mp	mp	—
PWS 16	15.0	M	sp—	mp	—
PWS 17	16.0	F	lp+	mp	No
PWS 18	17.0	F	lp	mp	Yes
PWS 19	17.0	M	lp—	mp	Yes
PWS 20	17.5	F	mp	sp	Yes
PWS 21	18.0	M	mp	—p	—
PWS 22	18.0	M	mp	mp+	No
PWS 23	18.0	M	mp	mp	—
PWS 24	19.0	M	lp	mp	Yes
PWS 25	20.0	M	sp+	lp	Yes

Subject	Age (yr)	Sex	Short (p) arm and satellite stalk length ^a		Larger or more intensely stained heterochromatic region on del(15q) chromosome
			del(15q)	Normal	
PWS 26	20.0	F	lp	lp	—
PWS 27	20.5	F	lp	mp	Yes
PWS 28	21.0	F	mp	mp	—
PWS 29	22.0	F	sp	lp	Yes
PWS 30	23.0	F	mp	mp	—
PWS 31	23.5	M	mp	lp	Yes
PWS 32	23.5	M	mp	lp	No
PWS 33	34.5	F	mp	mp	—
PWS 34	38.5	M	p+	sp	Yes
AS 1	2.0	M	mp	sp	Yes
AS 2	3.0	F	mp	lp	Yes
AS 3	4.0	F	lp	mp+	—
AS 4	10.0	M	sp	mp	Yes

^a GTG stained chromosomes were scored for satellite stalk and short arm length (l = long, m = medium, s = short, — = absent stalk, p+ = long, p = average, p- = absent p arm.
^b — = uninformative.