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The two-domain hypothesis in Beckwith-Wiedemann syndrome

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Letter to the Editor

The authors reply A.P. Feinberg raises two questions: (a) the origin of the two-domain model, and (b) the organization of enhancers and insulators within chromosome 11p15.5. Our concept that two imprinting control centers exist within chromosome 11p15.5 was developed independently. In a series of reports, we established, first, that loss of imprinting of IGF2 in Beckwith-Wiedemann syndrome (BWS) may be associated with H19 hypermethylation and silencing, consistent with loss of function in a distal imprinting center (1); second, that a BWS-associated maternally inherited inversion with a breakpoint within KCNQ1 was associated with an H19-independent loss of imprinting in IGF2 (2); and, finally, that such H19-independent loss of IGF2 imprinting is frequently found in sporadic cases of BWS that lack chromosomal rearrangements (3). The finding that epigenetic alterations at KvDMR1 and H19 appeared to be mutually exclusive provided us with confirmation of our concept (4). With regard to the organization of imprinting elements within 11p15.5, we agree that it is possible that the CDKN1C (p57KIP2) enhancer could be on the centromeric side, but we favor a telomeric location for several reasons. First, if the enhancer were centromeric, CDKN1C would need its own imprinting mechanism. This is less likely because (a) there is no differential methylation in the human (5); (b) a maternal germline imprint is required for activity of cdkn1c (6); […]

tion of their independent thinking that led to the two-domain model in their *JCI* review. I emphasize my point that either location for a shared enhancer is possible with current data, but I did not suggest that *KvDMR1* is itself the insulator. Indeed, I think that unlikely, as we find that the sequence is not conserved in the mouse.

1. Maher, E.R., and Reik, W. 2000. Beckwith-Wiedemann syndrome: imprinting in clusters revisited. *J. Clin. Invest.* **105**:247–252.
2. Lee, M.P., et al. 1999. Loss of imprinting of a paternally expressed transcript, with antisense orientation to KVLQT1, occurs frequently in Beckwith-Wiedemann syndrome and is independent of insulin-like growth factor II imprinting. *Proc. Natl. Acad. Sci. USA.* **96**:5203–5208.
3. Feinberg, A.P. 2000. Genomic imprinting and cancer. In *The metabolic and molecular bases of inherited disease.* 8th edition. C. Scriver et al., editors. McGraw-Hill. New York, New York, USA.
4. Mitsuya, K., et al. 1999. LIT1, an imprinted antisense RNA in the human KvLQT1 locus identified by screening for differentially expressed transcripts using monochromosomal hybrids. *Hum. Mol. Genet.* **8**:1209–1217.
5. Rainier, S., et al. 1993. Relaxation of imprinted genes in human cancer. *Nature.* **362**:747–749.
6. Lee, M.P., et al. 1998. Somatic mutation of TSSC5, a novel imprinted gene from human chromosome 11p15.5. *Cancer Res.* **58**:4155–4159.
7. Lam, W.W., et al. 1999. Analysis of germline CDKN1C (p57KIP2) mutations in familial and sporadic Beckwith-Wiedemann syndrome (BWS) provides a novel genotype-phenotype correlation. *J. Med. Genet.* 36:518–523.

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With regard to the organization of imprinting elements within 11p15.5, we agree that it is possible that the *CDKN1C* ($p57^{KIP2}$) enhancer could be on the centromeric side, but we favor a telomeric location for several reasons. First, if the enhancer were centromeric, *CDKN1C* would need its own imprinting mechanism. This is less likely because (a) there is no differential methylation in the human (5); (b) a maternal germline imprint is required for activity of *cdkn1c* (6); (c) *cdkn1c* transgenes do not become imprinted (7); and (d) in Dnmt1-deficient mice, *cdkn1c* is biallelically expressed, but inspection of the gels shows that this could be a low-level expression from both alleles (8), corresponding to the low-level paternal expression in humans. Finally, and importantly, the organization suggested by A.P. Feinberg would require a closed boundary on the maternal chromosome and an open one on the paternal chromosome, but *KvDMR1* methylation is maternal (presumably indicating that the boundary is open, as with the *H19* upstream region).

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1. Reik, W., et al. 1995. Imprinting mutations in the Beckwith-Wiedemann syndrome suggested by an altered imprinting pattern in the IGF2-H19 domain. *Hum. Mol. Genet.* **4**:2379–2385.
2. Brown, K.W., et al. 1996. Imprinting mutation in the Beckwith-Wiedemann syndrome leads to biallelic IGF2 expression through an H19 independent pathway. *Hum. Mol. Genet.* **6**:2027–2032.
3. Joyce, J.A., et al. 1997. Imprinting of IGF2 and H19: lack of reciprocity in sporadic Beckwith-Wiedemann syndrome. *Hum. Mol. Genet.* **6**:1543–1548.
4. Smilinich, N.J., et al. 1999. A maternally methylated CpG island in KCNQ1 is associated with an antisense paternal transcript and loss of imprinting in Beckwith-Wiedemann syndrome. *Proc. Natl. Acad. Sci. USA.* **96**:8064–8069.
5. Chung, W.Y., Yuan, L., Feng, L., Hensle, T., and Tycko, B. 1996. Chromosome 11p15.5 regional imprinting: comparative analysis of KIP2 and H19 in human tissues and Wilms' tumors. *Hum. Mol. Genet.* **5**:1101–1108.
6. Obata, Y., et al. 1998. Disruption of primary imprinting during oocyte growth leads to the modified expression of imprinted genes during embryogenesis. *Development.* **125**:1553–1560.
7. John, R.M., Hodges, M., Little, P., Barton, S.C., and Surani, M.A. 1999. A human p57(KIP2) transgene is not activated by passage through the maternal mouse germline. *Hum. Mol. Genet.* **8**:2211–2219.
8. Caspary, T., Cleary, M.A., Baker, C.C., Guan, X.-J., and Tilghman, S.M. 1998. Multiple mechanisms regulate imprinting of the mouse distal chromosome 7 gene cluster. *Mol. Cell. Biol.* **18**:3466–3474.