Tilghman & Schoenherr respond: Bernhard Horsthemke and his colleagues have provided new data that shed light on our proposal that the imprinting control region (IC) mutations in the Prader Willi (PWS) and Angelmann (AS) syndrome region can be explained by enhancer competition. They show that the minimally deleted region in AS patients is fully methylated on both chromosomes, which makes it unlikely that the AS-IC is equivalent to the primary gametic imprint at the *H19* or *Igf2r* genes, as we suggested. If the AS-IC is not the gametic imprint, what is it? Our motivation in writing the article

was to look for common features among imprinted regions. Unfortunately, we know of no element in the *H19* or *Igf2r* regions whose deletion leads to undermethylation of the paternal or maternal chromosomes, respectively, except the gametic mark itself!

The genetic aspects referred to by Schumacher *et al.* do not undermine our proposal that the IC is involved in setting and maintaining, not switching, parental marks. We would argue that the finding that PWS and AS display strict grandparental inheritance patterns is the consequence of an ascertainment bias that is

imposed by the nature of the disease. For example, you can't inherit PWS from your grandfather because your father would have had the disease. So, the only cases where the grandparental chromosomes have an equal chance of transmitting the disease are the *de novo* deletions, of which there are too few to form the basis for a statistical argument for switching.

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