



IMPRINTING DEFECTS IN PRADER WILLI SYNDROME

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Whereas the majority of patients with PWS have a common large deletion of the chromosomal region 15q11-q13 (70%) or uniparental maternal disomy (29%), a few patients (~1%) with Prader-Willi syndrome (PWS) have apparently normal chromosomes 15 of biparental inheritance, but the paternal chromosome carries a maternal imprint. This leads to a complete loss of the paternally expressed genes in 15q11-q13. Thus, the functional consequence of the incorrect imprint is identical to that of maternal uniparental disomy.

In approximately 15% of patients with PWS and an imprinting defect, the incorrect imprint is the result of a microdeletion affecting the imprinting center (IC). The IC overlaps with the SNURF-SNRPN gene and regulates in cis DNA methylation, gene expression and chromatin structure of the whole imprinted domain. Most of the IC deletions are familial mutations. A deletion of the PWS-SRO can be transmitted silently through the female germ line, but leads to an incorrect, maternal imprint on the paternal chromosome when inherited from a male. Familial IC deletions are associated with a 50% recurrence risk. In the case of a de novo deletion, the recurrence risk is not increased when it occurred after fertilization, but it can be up to 50% when the father has a germ line mosaic.

The majority of patients with PWS and an imprinting defect (85%) have no IC deletion or point mutation of the PWS-SRO. This indicates that the imprinting defect occurred spontaneously in the absence of a DNA sequence change. Interestingly, in all informative cases the chromosome carrying the incorrect imprint was inherited from the paternal grandmother. These data suggest that the imprinting defect results from a failure to erase the maternal imprint in the father's germ line. In contrast to patients with an IC deletion, some of these patients share the same paternal chromosome with a healthy sibling. This indicates that the recurrence risk for another child with the disease is very low.