

Abstract

The two main causes of Prader-Willi syndrome (PWS) are a paternally derived deletion in the maternally imprinted 15q11-q13 region or UPD(15)mat. Both mechanisms result in a loss of the active paternal contribution to the region. The affective psychosis associated with PWS has been found to be mainly confined to the propositi with UPD(15)mat rather than to those with a deletion. This suggests that the psychosis may be related to the presence of two copies rather than a single copy of a gene or genes located in the distal half of the region which is paternally imprinted, but maternally active, and whose loss results in Angelman syndrome (AS). A large population-based study of PWS allowed the identification of 12 people with a 15q11-q13 deletion who had suffered psychotic episodes and four adults with UPD(15)mat who so far had not. When these people were investigated using microsatellite markers, the 12 with a deletion were found to have two maternally derived copies of a narrow region between D15S975 and D15S661 making them effectively disomic for these loci. Thus all of the people with psychosis had two active copies of any imprinted genes in the region while all non-psychotic people (including controls) had only one. Quantitative RT-PCR studies suggest that a lack of expression of FLJ33332, either as a result of or resulting in gene dysregulation, may be associated with psychosis in PWS.