

Analysis Of Candidate Imprinted Genes In PWS Subjects With Atypical Genetics: A Possible Inactivating Mutation In The SNURF/SNRPN Minimal Promoter.

Abstract:

Prader-Willi syndrome (PWS) is a neurodevelopmental disorder associated with abnormalities of chromosome 15q11q13. The majority of cases result either from a deletion approximately 4 Mb in size, affecting chromosome 15 of paternal origin or from UPD(15)mat; these account for approximately 70 and approximately 20-25% of PWS cases, respectively. In the remaining 3-5% of PWS cases where neither the deletion nor UPD is detectable, PWS is thought to be caused either by a defect in the imprinting centre resulting in a failure to reset the paternally inherited chromosome 15 derived from the paternal grandmother or, very occasionally, from a balanced translocation involving a breakpoint in 15q11q13. Nine probands with a firm clinical diagnosis of PWS but who had neither a typical deletion in the PWS region nor UPD(15)mat were investigated for inactivating mutations in 11 genes located in the PWS region, including SNURF and SNRPN, which are associated with the imprinting centre. Other genes studied for mutations included MKRN3, NDN, IPW, HBII-85, HBII-13, HBII-436, HBII-438a, PAR1 and PAR5. A possibly inactivating mutation in the SNRPN minimal promoter region was identified. No other inactivating mutations were found in the remainder of our panel of PWS subjects with atypical genetics. Expression levels of several of the candidate genes for PWS were also investigated in this series of probands. The results indicate that PWS may result from a stochastic partial inactivation of important genes.