PATIENTS WITH PWS DISPLAY DIFFERENTIALLY METHYLATED REGIONS INVOLVED IN NEURODEVELOPMENTAL AND NUTRITIONAL TRAJECTORY.

Juliette Salles1,2,3, Sanaa Edddy3, Emmanuelle Lacassagne3, Virginie Laurier4, Catherine Molinas5, Éric Bieth6, Nicolas Franchitto7, Jean-Pierre Salles5, Malika Tauber3,8,9


INTRODUCTION

Prader-Willi syndrome is a rare genetic neurodevelopmental disorder caused by a paternally deficient of maternally imprinted gene expression located in the chromosome 15q11-q13 region. Previous studies have demonstrated that several classes of neurodevelopmental disorders can be attributed to either under- or over-expression of specific genes that may lead to impairments in neurodevelopment, differentiation, maturation and growth. Moreover, epigenetic changes that modify gene expression have been highlighted in these disorders.

One recent study focused on epigenetic analysis and compared patients with PWS with patients with other imprinting disorders(1). No study, however, has yet focused on epigenetics in patients with PWS specifically by comparing the mutations associated with this syndrome.

AIM

This study investigated the epigenetic modifications in patients with PWS and patients with PWS-related disorders caused by inactivation of two genes of the PWS chromosomal region, SNORD116 and MAGEL2. Our approach also aimed to compare the genetic modifications in PWS and PWS-related disorders.

METHOD

We compared genome-wide methylation analysis (GWAS) in seven blood samples from patients with PWS phenotype (5 with deletions of the PWS locus, one with a microdeletion of SNORD116, one with a frameshift mutation of MAGEL2 presenting with Schaal-Yang syndrome), as well as two control patients.

We used a reduced representation bisulfite sequencing (RRBS) approach to determine differentially methylated regions (DMRs) between patient with PWS and control patients.

The reads were aligned on the genome of reference (2).

RESULTS

The analysis identified 29,234 differentially methylated cytosines, corresponding to 5,308 differentially methylated regions (DMRs), which matched with 2,280 genes.

The functional pathways associated with the DMRs in PWS included biological processes and pathways related to nervous system development, generation of neurons and neurogenesis, anatomical structure development, synapses, aldosterone synthesis, Cushing syndrome, cortisol synthesis, cholinergic synapse, oxytocin signaling and endocrine resistance (see Table 1). In addition, some genes involved in neurodevelopment overlapped with other systems related to the PWS phenotype (endocrine resistance and oxytocin pathway). Figure 1

Regarding the eating disorders and the specific nutritional trajectory observed in PWS, we explored the connection between PWS DMRs and the genes related to addiction and obesity. The results revealed that 18 of the DMR genes were associated with addiction and obesity (ADCS, ADCY9, ATPH1, CD5K1, CHRNA2, GAPBD1, GABRB3, GABRI, GN3Q, GRK3, HDAC4, HDAC9, MAP2K1, PDE11A, PDE2A, PDE3A, PPP1CA, SLCE6A).

Figure 1: Venn diagram for the PWS DMRs of the oxytocin pathway (OXT), nervous system development (Neuro), the endocrine pathway (Endo), and the Prader-Willi differentially methylated regions (PWS DMGs)

The separate analysis for the SNORD116 and MAGEL2 deletions revealed that the DMRs associated with the SNORD116 microdeletion were found in genes implicated in metabolic pathways and nervous system development, whereas MAGEL2 mutations mostly concerned genes involved in macrocycle biosynthesis. (see Table 2).

CONCLUSIONS

These data suggest that genetic defects of the imprinted chromosomal region 15q11-q13 that lead to PWS are associated with epigenetic methylation signatures. Those epigenetic signatures are associated with pathways involved in brain development, endocrine function and metabolism. The SNORD116 MD and MAGEL2 mutation are also associated with specific DMRs in DMRs that may explain at least partially the complex PWS phenotype. A question of utmost importance arises from these results concerning whether it would be possible to modify the methylation status caused by a lack of expression of SNORD116, MAGEL2 and perhaps other genes in the PWS region with, for example, oxytocin treatment or other drugs and/or social disability rehabilitation.

REFERENCES


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CONTACT INFORMATION

Juliette Salles
Nouveau bâtiment de Psychiatrie, Hôpital Purpan, Centre-hospitalo-universitaire de Toulouse, 330, avenue de Grande-Bretagne, T3A 70024, 31059 Toulouse cedex 9, France
juliette.salles@hotmail.fr

All results are available in the article of Salles et al.2021(3).