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

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ESPE 2021
The 59th Annual Meeting Online
22-26 September 2021

INTRODUCTION

Prader-Willi syndrome is a rare genetic neurodevelopmental disorder caused by a paternal deficiency 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 over- or under-expression of specific genes that may lead to impairments in neuronal generation, 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 epigenetic 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 Schaaf-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 (ADCY3; ADCY9; ATF4; CDK5R1; CHRNB2; GABRD; GABRG3; GNB1; GNB3; GRK5; HDAC4; HDAC9; MAP2K1; PDE11A; PDE2A; PDE3A; PPP1CA; SLC6A3).*

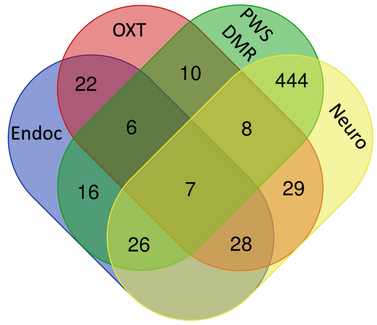

Figure 1:
Venn diagram for the PWS DMRs of the oxytocin pathway (OXT), nervous system development (Neuro), the endocrine pathway (Endoc), and the Prader-Willi differentially methylated regions (PWS DMRs).

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 macromolecule biosynthesis. (see Table 2).*

Biological process/KEGG pathway	GO/KEGG ID	adjusted_p_value
Nervous system development	GO:0007399	1.23E-14
Generation of neurons	GO:0048699	1,30E-13
Neurogenesis	GO:0022008	1,71E-13
Anatomical structure development	GO:0048856	1,16E-12
Synapse	GO:0045202	1,51E-11
Aldosterone synthesis and secretion	KEGG:04925	2,54E-03
Cushing syndrome	KEGG:04934	5,01E-03
Cortisol synthesis and secretion	KEGG:04927	9,20E-03
Cholinergic synapse	KEGG:04725	1,00E-02
Oxytocin signaling pathway	KEGG:04921	1,39E-02
Endocrine resistance	KEGG:01522	1,54E-02

Table 1:
Top biological processes and KEEG pathway connected to the PWS DMRs.

MAGEL2	Cellular macromolecule biosynthetic process	GO:0034645	2,83E-07
	Macromolecule biosynthetic process	GO:0009059	7,87E-07
	Organic substance biosynthetic process	GO:1901576	3,08E-06
	Biosynthetic process	GO:0009058	4,21E-06
	Cellular biosynthetic process	GO:0044249	9,83E-06
	Regulation of RNA metabolic process	GO:0051252	5,03E-05
	Nucleobase-containing compound metabolic process	GO:0006139	6,72E-05
	Nucleic acid metabolic process	GO:0090304	8,69E-05
SNORD116	Cellular metabolic process	GO:0044237	8,54E-09
	Nervous system development	GO:0007399	9,56E-09
	Metabolic process	GO:0008152	6,57E-08
	Primary metabolic process	GO:0044238	3,31E-07
	Nitrogen compound metabolic process	GO:0006807	5,41E-07
	Nucleic acid metabolic process	GO:0090304	9,97E-07
	Organic substance metabolic process	GO:0071704	1,15E-06
	Central nervous system development	GO:0007417	1,34E-06
	Hippo signaling pathway	KEGG:04390	6,29E-03
	Chronic myeloid leukemia	KEGG:05220	1,25E-02
	Neurotrophin signaling pathway	KEGG:04722	4,77E-02

Table 2:
Top biological processes and KEEG pathways connected to the MAGEL2 mutation and SNORD116 deletion

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

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 specificities in DMRs that may explain at least partly 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.

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ACKNOWLEDGEMENTS

This work was supported by a grant from the French Association for Prader-Willi Syndrome (grant R15062BB).

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