Environmental Interaction Influences on the Monoamine Oxidase A (*MAOA*) Gene, Methylation in relation to Alcohol abuse, Depression and Aggression

Kent W. Nilsson [1,2] Megha Bendre [1,2], David Checknita [1,2], Erika Comasco [1], Sheilagh Hodgins [3].
1 Department of Neuroscience, Uppsala University, Uppsala
2 Centre for Clinical Research, Uppsala University, Region of Västmanland
3 Institut Universitaire en Santé Mentale de Montréal, Département de Psychiatrie, Université de Montréal

Objective

To examined how environmental adversity, *MAOA*-genotype, and MAOA-ROI methylation interface to modify risk for alcohol misuse, depression, and antisocial behaviour.

Material and methods

Male rats and a clinical sample of young men and women.

Results

To date, four key findings have emerged. One, in male rats, CpG-specific MAOA-methylation was associated with early life stress, alcohol consumption, and MAOA-expression in reward-related brain regions. Two, maltreated men carrying MAOA-L who displayed low exonic- and intronic methylation reported high levels of alcohol-related problems. Three, sexually abused women exhibited hypermethylation of the MAOA first exon, and these methylation levels mediated associations between sexual abuse and adult depression. Four, in our clinical sample, the highest levels of aggressive behaviour were shown by maltreated men carrying MAOA-L with high levels of exonic methylation, and by maltreated women carrying MAOA-H with low levels of exonic methylation.

Conclusion

Our findings highlight the roles of genetic and epigenetic factors as important moderators of associations between environmental adversity and the development of alcohol misuse and antisocial behaviours.

Background

Environmentally-driven influences of the monoamine-oxidase-A (*MAOA*) gene has shown robust associations with antisocial behaviour, by the interaction of the functional variable-number-tandem-repeat (*uVNTR*) polymorphism in the MAOA promoter and adversity in childhood. Among males it is the low-expressing variant (MAOA-L) and among females the high-expressing variant (MAOA-H) that confer vulnerability for externalizing problems in the presence of adversity. Altered methylation levels in a region-of-interest (ROI) spanning the first exonic and partial intronic region of MAOA has also been implicated in alcohol misuse and antisocial behaviour.

Component Methylation Level	*MAOA* Genotype	Unstandardized Simple Slope (beta coefficient)	95% Confidence Interval	P
Men Component 1 Methylation CpGs 13-16				
1 SD below mean[a]	L	0.2858	-1.12 – 1.69	.687
	S	**1.7828**	**0.44 – 3.12**	**.009***
Mean [b]	L	0.4427	-0.41 -1.29	.302
	S	0.5737	-0.35 – 1.50	.219
1 SD above mean [a]	L	0.5997	-0.43 – 1.63	.249
	S	-0.6355	-2.02 – 0.75	.364
Men Component 3 Methylation CpGs 7-12				
1 SD below mean [b]	L	-0.7102	-2.11 – 0.69	.313
	S	0.1501	-0.90 – 1.20	.755
Mean [c]	L	0.3157	-0.49 – 1.12	.437
	S	1.3484	0.31 – 2.39	.012
1 SD above mean [b]	L	1.3415	0.16 – 2.52	.027
	S	**2.5468**	**0.94 – 4.15**	**.002***
Women Component 1 Methylation CpGs 2-12				
1 SD below mean [c]	SS	1.0223	-0.52 – 2.57	.193
	SL/LL	**0.9005**	**0.41 – 1.39**	**<.001***
Mean [c]	SS	0.5466	-0.37 – 1.46	.238
	SL/LL	0.5837	0.22 – 0.95	.002
1 SD above mean [c]	SS	0.0709	-0.88 – 1.02	.883
	SL/LL	0.2668	-0.27 – 0.80	.324

Table 1. Results of analyses of methylation levels and *MAOA* risk genotype, on the association of maltreatment and total number of aggressive behaviours in young adults.

Figure 1. Group-wise correlations between *Maoa* expression and methylation in the *Maoa* promoter in NAc or DS of water or alcohol drinking MS rats.

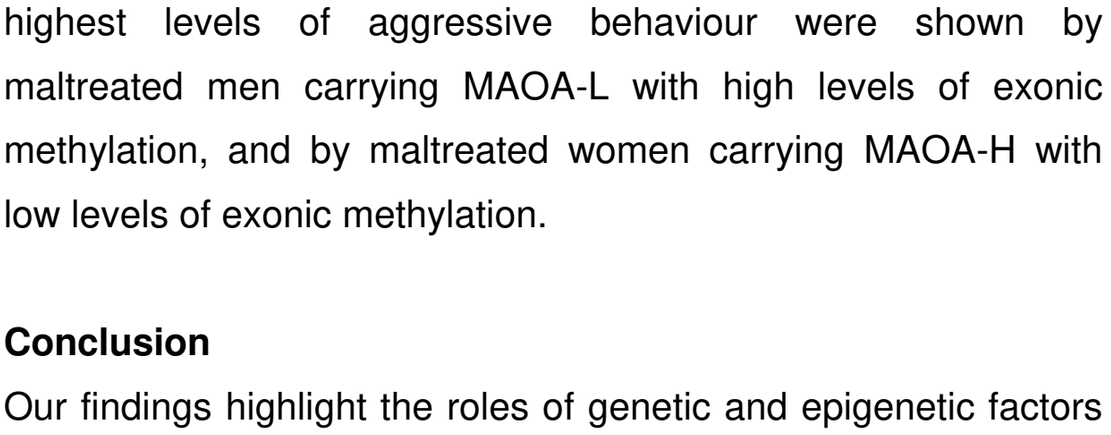

Figure 2. Interaction effect between MAOA-uVNTR genotype and maltreatment on follow-up AUDIT scores at different levels of MAOA methylation.