# Monoamine Oxidase A DNA Hypomethylation Predicts Impaired Treatment Response in Depression

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## Background

The monoamine oxidase A (MAO-A) involved in the degradation of epinephrine, norepinephrine and serotonin has been suggested as one of the prime candidates in the pathogenesis and treatment of depression. On a genetic level, the more active alleles of a VNTR polymorphism in the promoter of the *MAO-A* gene (Xp11.4-p11.3) have been found to be associated with major depression and impaired antidepressant treatment response particularly in female patients (e.g., Domschke et al., 2008). Recently, *MAO-A* DNA hypomethylation, presumably leading to increased MAO-A expression, was reported to be associated with depression in female patients (Melas et al., 2013).

## Aims

On this background, we for the first time aimed at investigating the influence of *MAO-A* DNA methylation patterns on antidepressant treatment response applying a pharmacoepigenetic approach.

## Results

- Given the X-chromosomal location of the *MAO-A* gene, all analyses were carried out separately for female and male patients.
- Male patients showed no or only very minor methylation across all CpG sites, which was not associated with antidepressant treatment response.
- In female patients, lower methylation at three CpG sites in the *MAO-A* promoter region (positions 43.514.063, 43.514.574, 43.514.684; UCSC Human Genome Browser; Feb 2009; GRCh37/hg19) was associated with a significantly worse response under antidepressant treatment after weeks 4, 5 and 6 ($p \leq 0.04$-$0.001$).
- After applying Bonferroni correction for multiple testing yielding a corrected p-value of ≤0.001, the result for CpG 5 in amplicon B (43.514.684) remained significant for response at week 5 (see figure 3).
- *MAO-A* VNTR genotype, age or smoking status did not influence *MAO-A* methylation status.

## Discussion

The present pilot data suggest that *MAO-A* gene hypomethylation - possibly leading to increased *MAO-A* expression and consecutively decreased serotonin and/or norepinephrine availability - negatively influences antidepressant treatment response in female patients. These findings are in line with *MAO-A* hypomethylation being associated with depression (Melas et al., 2013) and the more active *MAO-A* VNTR alleles conferring impaired antidepressant treatment response (e.g., Domschke et al., 2008). Future studies are warranted to replicate the present results in larger samples and to functionally evaluate *MAO-A* hypomethylation.

A pharmacoepigenetic approach as applied in the present study might eventually contribute to the development of a more individualized treatment concept of major depression based on epigenetic information, e.g. by suggesting a potentially beneficial use of MAO-A inhibitors as an adjunct treatment in patients displaying *MAO-A* DNA hypomethylation.

## References

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## Methods

94 patients with a Major Depressive Episode (f=61, m=33; DSM-IV) of Caucasian descent were analyzed for DNA methylation status at 43 *MAO-A* CpG sites in the promoter region as well as exon 1 and parts of intron 1 (see figure 1; Philibert et al., 2008). Methylation analysis was done by means of direct sequencing of sodium bisulfite converted DNA extracted from whole blood, analysis of electropherograms by means of Epigenetic Sequencing Methylation analysis software (ESME) (see figure 2; cf. Domschke et al., 2012; Lewin et al., 2004). Patients were additionally genotyped for the functional *MAO-A* VNTR (Deckert et al., 1999). The clinical response to antidepressant pharmacological treatment with escitalopram (plus mirtazapine N=33; 35.1%) was assessed by weekly changes of HAM-D-21 scores relative to HAM-D at week 1 over the six weeks study period adjusted for age, smoking status, lifetime duration of depression, lifetime hospitalisations, lifetime number of MDD episodes and co-medication with neuroleptics and mood stabilizers.

**Figure 1: Localization of amplicons A, B, and C comprising CpG dinucleotides in the *MAO-A* promoter/exon1/intron1 region**

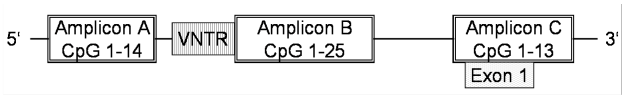
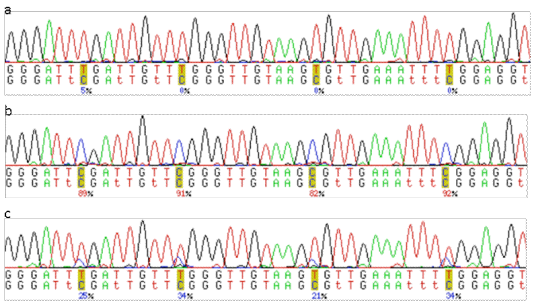
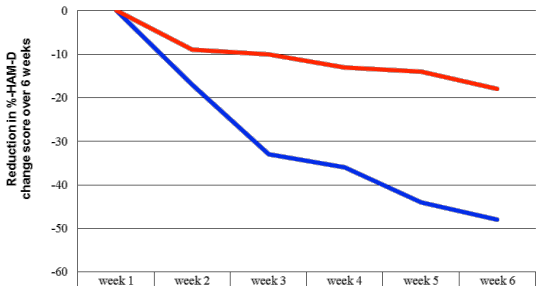



**Figure 2: Representative examples of DNA sequencing results of *MAO-A* amplicon B after bisulfite treatment**




Electropherograms of DNA sequencing of a) non-methylated control DNA, b) highly methylated control DNA and c) individual patient's DNA after analysis using ESME software (Lewin et al., 2004). Methylation rates (%) are displayed beneath each CpG site.

**Figure 3: Relative change of HAM-D score over six weeks of antidepressant treatment among N=61 female patients with MDD dependent on *MAO-A* DNA methylation at CpG5 in amplicon B**




| | week 1 | week 2 | week 3 | week 4 | week 5 | week 6 |
|---|---|---|---|---|---|---|
| Methylation high | 0 | -17 | -33 | -36 | -44 | -48 |
| Methylation low | 0 | -9 | -10 | -13 | -14 | -18 |

Methylation status "high" includes values above and "low" includes values below median split of MAO-A DNA methylation values at CpG 5 in amplicon B (43.514.684; UCSC Human Genome Browser; Feb 2009; GRCh37/hg19).

## Contact

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No potential conflict of interest