

# The Effect of CPAP Treatment in Patients with Obstructive Sleep Apnea on the Global Gene Expression Profile in the Whole Blood

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**Background:** The mechanisms and molecular diagnostics of obstructive sleep apnea (OSA) remain poorly investigated. Recently few groups analyzed the blood cells transcriptome in OSA patients, volunteers exposed to intermittent hypoxia and also the effect of continuous positive airway pressure (CPAP) treatment. However, these studies produced rather inconsistent sets of differentially expressed genes (DEGs) involved in a multitude of different pathways, such as systemic and vascular inflammation, neoplastic processes, induction of apoptosis, and cell adhesion and communication.

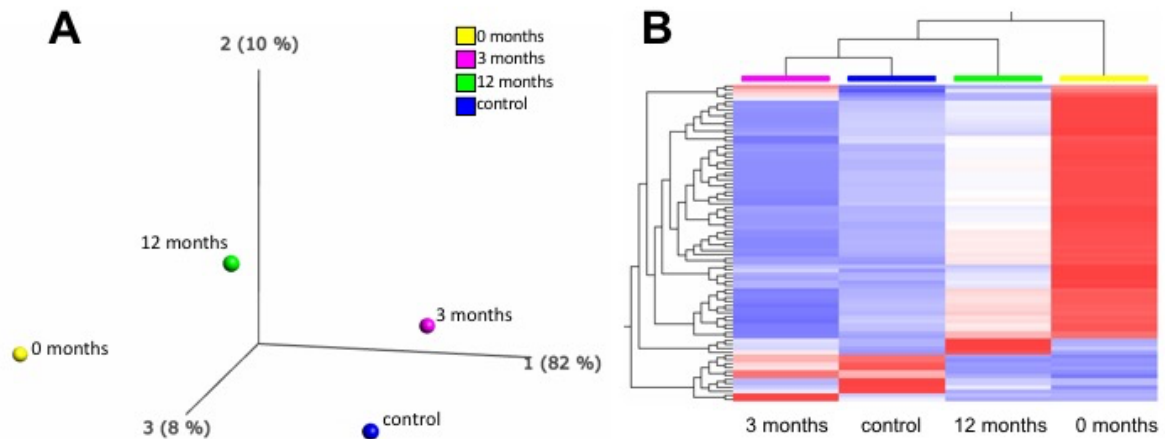
**General Aim:** To identify the whole blood gene expression signature in patients with at least moderate OSA and to what extent three and twelve months with nightly CPAP treatment effects the gene expression

**Materials and Methods:** The study was approved by the Regional Ethics Committee on Human Research at the Karolinska Institutet, Stockholm, Sweden. Oral and written consent was obtained from all study subject. Thirty patients with untreated moderate/severe OSA (apnea-hypopnea index (AHI) >15) were enrolled together with 20 matched controls. The whole blood transcriptome was analyzed by RNA sequencing (RNA-seq).

**Results:** Seven (7) OSA patients that demonstrated substantial improvement after CPAP treatment together with 6 matched controls were selected for the transcriptome analysis. Patient median AHI was 70.5 (57.3), 1.4 (3.0) and 2.5 (4.0), at 0, 3 and 12 months respectively and their median CPAP usage, hrs/night were 6.6 (3.4) and 7.5 (1.8) and % of possible nights were 100 (20.8) and 99.6 (3.5) at 3 and 12 months respectively. The mean BMI was 31.4 (4.5), mean age was 45.6 (12.9) years and 57% were males. Matched controls had a median AHI of 2.3 (4.4), mean BMI of 27.2 (2.2), mean age of 49.5 (15.5) years and 50% were males.

Principal component analysis (Fig. 1A) and hierarchical clustering of DEGs (Fig. 1B) revealed explicit separation of the control group from the untreated OSA patients (0 months). Analysis of 60 DEGs in the latter group (fold change cut-off  $\geq 2$ , adjusted  $p \leq 0.05$ ) shows remarkable prevalence of various immunoglobulins among the downregulated genes including also IL3RA, interleukin 3 receptor. Clustering of the control group with the three months CPAP treatment group speaks in favor of partial recovery of OSA patients (Fig. 1B), consistent with normalization of AHI. This is also reflected by the reduction of the number of DEGs from 60 to 13. Surprisingly, despite still substantially lower (as compared to the control) number of DEGs after 12 months of CPAP treatment, the overall gene expression profile remains rather different from the control (Fig. 1A, B). The changes in the expression of DEGs as revealed by RNA-seq were validated by qPCR.

Figure 1



Differentially expressed genes in the whole blood of 7 OSA patients with high AHI index at 0 months (adjusted  $p \leq 0.05$ )

**Conclusions:** Untreated OSA leads to the substantial modification of the whole blood transcriptome, which is partially recovered after three months of CPAP treatment. Gene expression recovery correlates with the positive AHI dynamics. Functional analysis of the DEGs in untreated OSA patients indicates decline in the immune-related functions as reflected by the lower immunoglobulins' and IL3RA expression.