# The lack of association between catechol-O-methyl-transferase Val108/158Met polymorphism and smoking in schizophrenia and alcohol dependence

**Nikolac, Matea; Šagud, Marina; Nedić, Gordana; Nenadić Šviglin, Korona; Mihaljević Peleš, Alma; Uzun, Suzana; Vuksan Ćusa, Bjanka; Kozumplik, Oliver; Živković, Maja; Mustapić, Maja; ...**

*Source / Izvornik:* **Psychiatry Research, 2013, 205, 179 - 180**

**Journal article, Accepted version**
**Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)**

https://doi.org/10.1016/j.psychres.2012.08.001

*Permanent link / Trajna poveznica:* https://urn.nsk.hr/urn:nbn:hr:105:529366

**Letter to the editor**

# The lack of association between catechol-*O*-methyl-transferase Val108/158Met polymorphism and smoking in schizophrenia and alcohol dependence

Matea Nikolac[a], Marina Sagud[b], Gordana Nedic[a], Korona Nenadic Sviglin[c], Alma Mihaljevic Peles[b], Suzana Uzun[d], Bjanka Vuskan Cusa[e], Oliver Kozumplik[d], Maja Zivkovic[f], Maja Mustapic[a], Miro Jakovljevic[b], Mladen Pavlovic[g], Dorotea Muck-Seler[a], Fran Borovecki[h], Nela Pivac[a*]

[a]Division of Molecular Medicine, Rudjer Boskovic Institute, Zagreb, Croatia

[b]University of Zagreb School of Medicine; University Hospital Center Zagreb, Zagreb, Croatia

[c]Center for Alcoholism and Other Addictions, Clinics for Psychiatry Vrapce, Zagreb, Croatia

[d]Department of General Psychiatry, Clinics for Psychiatry Vrapce, Zagreb, Croatia

[e]University Hospital Center Zagreb, Department of Psychiatry, Zagreb, Croatia

[f]Neuropychiatric Hospital "Dr Ivan Barbot" Popovaca, Division for Acute Psychiatry, Popovaca, Croatia

[g]Institute for Medical Research and Occupational Health, Zagreb, Croatia

[h]Department of Neurology, University Hospital Center Zagreb; Department for Functional Genomics, Center for Translational and Clinical Research, University of Zagreb School of Medicine, Zagreb, Croatia

*Corresponding author: Nela Pivac, Division of Molecular Medicine, Rudjer Boskovic Institute, Bijenicka 54, 10000 Zagreb, Croatia; Tel: ++385 1 4571207; Fax: ++385 1 4561010. E-mail: npivac@irb.hr

Patients with schizophrenia and alcohol dependence are often smokers. There are inconsistencies across the literature data on the relationship between the functional catechol-*O*-methyl-transferase (COMT) Val108/158Met polymorphism and smoking and/or nicotine dependence (Redden et al., 2005; Tammimaki and Mannisto, 2010).

The study elucidated the association between the COMT Val108/158Met polymorphism and smoking in 828 ethnically homogenous non-related Caucasian patients with schizophrenia (40.3±12.6 years old), 616 patients with alcohol dependence (49.7±10.2 years old), diagnosed using a Structured Clinical Interview based on DSM-IV criteria, and in 1058 healthy control subjects (40.5±15.3 years old). The COMT Val108/158Met polymorphism was genotyped using a Taqman-based allele-specific polymerase chain reaction assay (Applied Biosystems, Foster City, CA, USA).

COMT genotypes in the studied groups were in the Hardy-Weinberg equilibrium. The present smoking status differed significantly ($\chi^2$=327.71; $P$<0.001) between the studied groups, since male schizophrenic patients smoked more frequently, while healthy control women smoked less frequently than other subjects. The stepwise logistic regression (*OR*=1.56, 95% *CI*=1.10-2.23, $P$=0.014) and the $\chi^2$ test (Table 1) revealed that COMT Val/Val genotype was significantly associated with smoking in healthy male subjects, since carriers of one ($\chi^2$=5.686; $P$=0.017) or two ($\chi^2$=9.783; $P$=0.008) Val alleles were more frequently current smokers.

The significant association between smoking, age and gender, with no interaction between smoking and COMT Val108/158Met variants in patients with schizophrenia and alcohol dependence might be explained by the different effects of nicotine on social and interpersonal factors in mental versus healthy subjects, or by the different interactions between dopamine activity and nicotine in the regions involved in the regulation of the reward pathways in healthy opposed to subjects with schizophrenia and alcohol dependence. Although the hypothesis of the study was that COMT Val108/158Met genotypes will be significantly associated with smoking in schizophrenia and alcohol dependence, our study, with sufficiently large sample size (N=2502) and power (higher than 0.800), matched for ethnicity and gender, showed for the first time the lack of significant association between smoking and COMT Val108/158Met polymorphism in schizophrenia, and confirmed no association between smoking and COMT Val108/158Met in alcoholism (Foroud et al., 2007). In line with previous results obtained in smaller groups (Nedic et al., 2010), COMT Val108/158Met polymorphism was significantly

associated with smoking in healthy male subjects, due to the over-representation of the Val/Val genotype in healthy male current smokers.

References

Foroud, T., Wetherill, L.F., Dick, D.M., Hesselbrock, V., Nurnberger, J.I., Jr., Kramer, J., Tischfield, J., Schuckit, M., Bierut, L.J., Xuei, X., Edenberg, H.J., 2007. Lack of association of alcohol dependence and habitual smoking with catechol-O-methyltransferase. Alcoholism: Clinical and Experimental Research 31, 1773-1779.

Nedic, G., Nikolac, M., Borovecki, F., Hajnsek, S., Muck-Seler, D., Pivac, N., 2010. Association study of a functional catechol-o-methyltransferase polymorphism and smoking in healthy Caucasian subjects. Neuroscience Letters 473, 216-219.

Redden, D.T., Shields, P.G., Epstein, L., Wileyto, E.P., Zakharkin, S.O., Allison, D.B., Lerman, C., 2005. Catechol-O-methyl-transferase functional polymorphism and nicotine dependence: an evaluation of nonreplicated results. Cancer Epidemiology, Biomarkers & Prevention 14, 1384-1389.

Tammimaki, A.E., Mannisto, P.T., 2010. Are genetic variants of COMT associated with addiction? Pharmacogenetics and Genomics 20, 717-741.

**Table 1.** COMT Val108/158Met genotype counts and frequencies in male and female control subjects, patients with schizophrenia or alcohol dependence, further subdivided according to the smoking status into smokers and non-smokers.

| | **COMT Val$^{108/158}$Met genotype** | | | | | |
|---|---|---|---|---|---|---|
| | Male subjects | | | Female subjects | | |
| | *Met/Met* | *Val/Met* | *Val/Val* | *Met/Met* | *Val/Met* | *Val/Val* |
| | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| Healthy control smokers | 56 | 93 | 69[a] | 15 | 39 | 15 |
| | (25.7) | (42.7) | (31.6) | (22.4) | (55.2) | (22.4) |
| Healthy control non-smokers | 108 | 267 | 111 | 78 | 134 | 73 |
| | (22.2) | (54.9) | (22.9) | (28.6) | (45.0) | (26.4) |
| Smokers with schizophrenia | 104 | 185 | 93 | 29 | 58 | 36 |
| | (27.2) | (48.4) | (24.4) | (23.6) | (47.1) | (29.3) |
| Non-smokers with schizophrenia | 47 | 87 | 42 | 31 | 68 | 48 |
| | (26.7) | (49.4) | (23.9) | (21.1) | (46.3) | (32.6) |
| Smokers with alcoholism | 75 | 154 | 72 | 23 | 30 | 15 |
| | (24.9) | (51.2) | (23.9) | (33.8) | (44.1) | (22.1) |
| Non-smokers with alcoholism | 52 | 103 | 37 | 14 | 27 | 14 |
| | (27.1) | (53.6) | (19.3) | (25.4) | (49.2) | (25.4) |

[a] $P = 0.008$ vs. healthy male non-smokers ($\chi^2$ test).

COMT: catechol-O-methyl transferase; Met: methonine; Val: valine; N: genotype count.