

FUT2 polymorphism (rs492602) associates with vitamin B12 deficiency, but may be independent with proton pump inhibitor or metformin usages, diabetes mellitus, and thyroid diseases

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RATIONALE

GWAS have suggested plasma vitamin B12 concentration is associated with SNP rs492602-C in fucosyltransferase 2 (FUT2) (Nat Genet 2008;40:1160). Medical conditions (e.g., diabetes mellitus [DM], thyroid diseases, and use of proton pump inhibitors [PPI], and metformin) are also found to associate with B12 deficiency. However, it has not been established if this SNP associates with B12 deficiency as a disease state, nor is it known if the effect on B12 is a result of interactions between medications or other diseases, rather than representing an independent effect. Thus, we performed an association analysis between rs492602 and B12 deficiency, and also tested interactions between the SNP and related medical conditions.

CONCLUSION

We found rs492602-T associates with clinically significant B12 deficiency, and replicated known associations between B12 deficiency and 2 diseases and 1 medication. We did not find any evidence of rs492602 either confounding or potentiating the association between B12 deficiency and DM, thyroid diseases, PPI use, or metformin use. Thus, we suggest FUT2 polymorphism is an independent factor of vitamin B12 deficiency.

METHODS

We used rs492602 data from 29,929 European-ancestry individuals genotyped on the Illumina Exome array v1 with traits defined by VUMC electronic health records. We ascertained B12 deficiency cases and matched them with controls (as described in Lam 2013, JAMA, 310:2435). We also collected their related comorbid status (DM, thyroid diseases) and medication usages (PPIs, metformin). Associations between B12 deficiency and the SNP or medical conditions were computed using logistic regression, and each interaction was tested as a gene-environment interaction term (GxE).

RESULTS

In our genotyped population, we identified 524 B12 deficiency cases, and 3509 controls.

SNP rs492602-T associates with higher risk of B12 deficiency (OR=1.40, p=5.1e-7), and with abnormally low plasma B12 levels (OR=1.35, p=3.1e-7).

We found associations between 3 of the 4 medical conditions and B12 deficiency, and we did not find an interaction with rs492602-C and any of the medical conditions.

We also tested B12 deficiency and these medical conditions adjusted with rs492602, but none of the new ORs or p-values dramatically changed.

ACKNOWLEDGMENTS

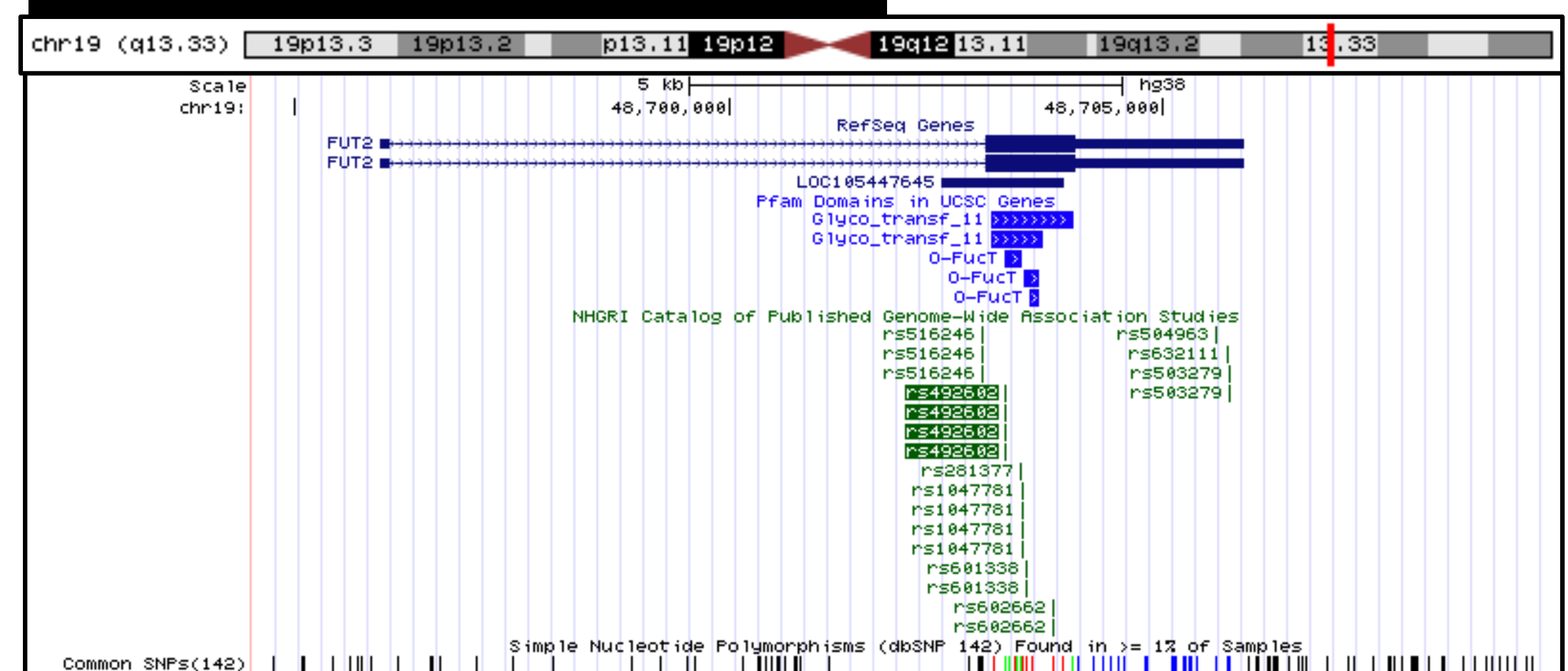
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FOR MORE INFORMATION

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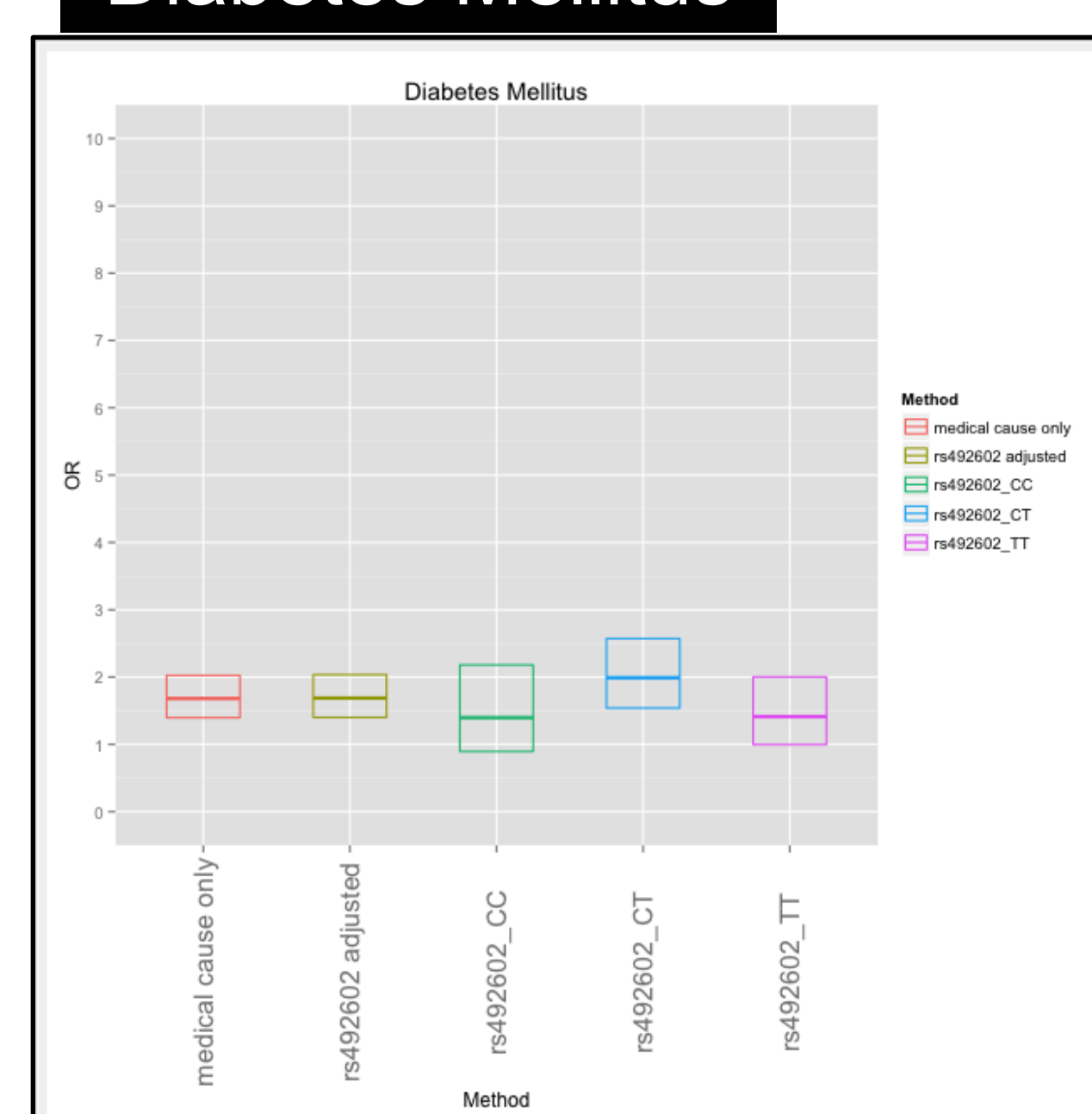
FUT2 and SNPs in GWAS Cat.



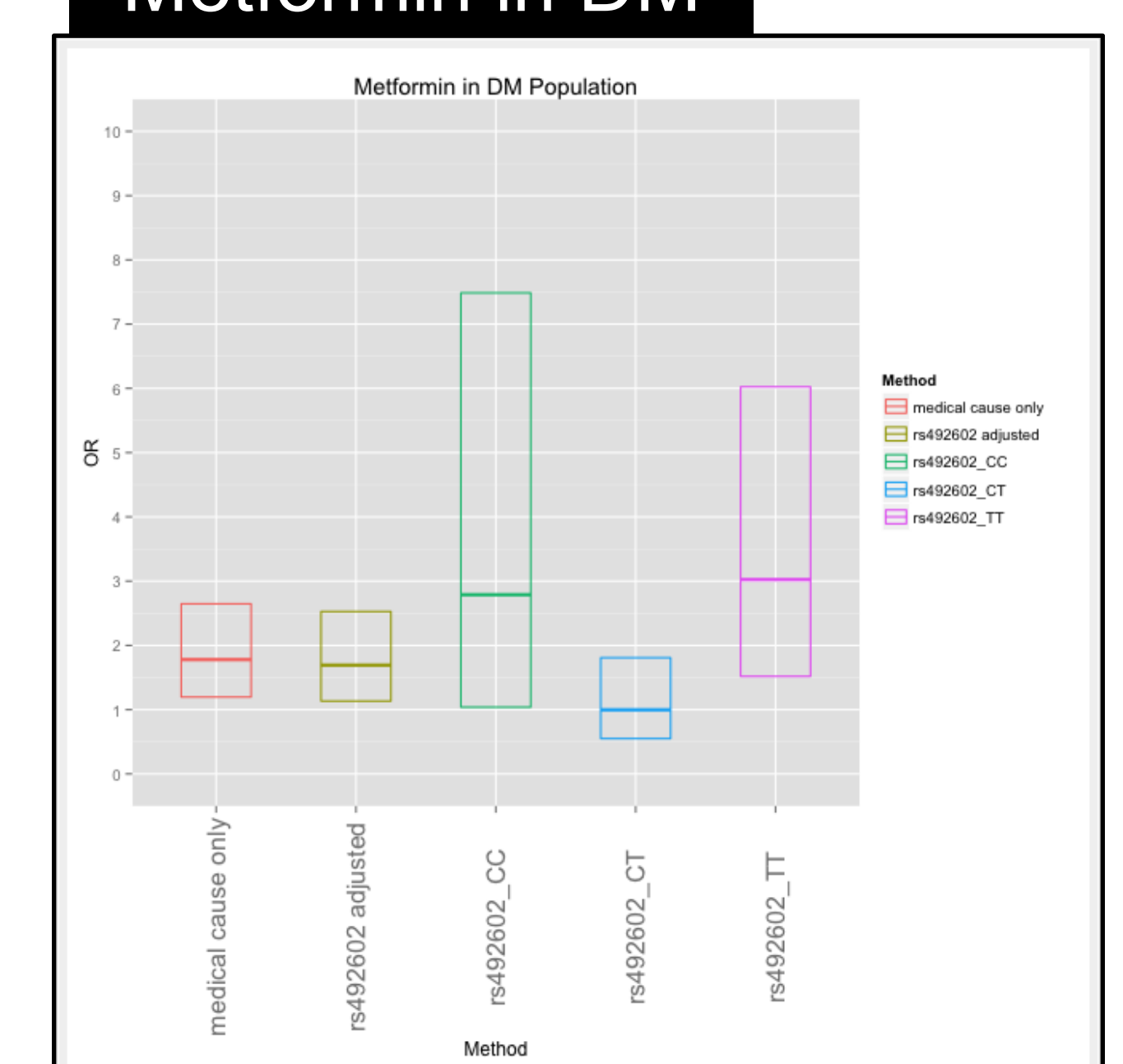
Medical Causes of Vit B12 Deficiency

	OR	p-value	GxE OR	GxE p-value
Diabetes mellitus	1.64	1.4e-6	1.05	0.73
Thyroid diseases	1.29	0.012	0.98	0.86
PPI use	1.32	0.07	1.07	0.76
Metformin (in DM patients)	1.83	0.0028	0.86	0.60

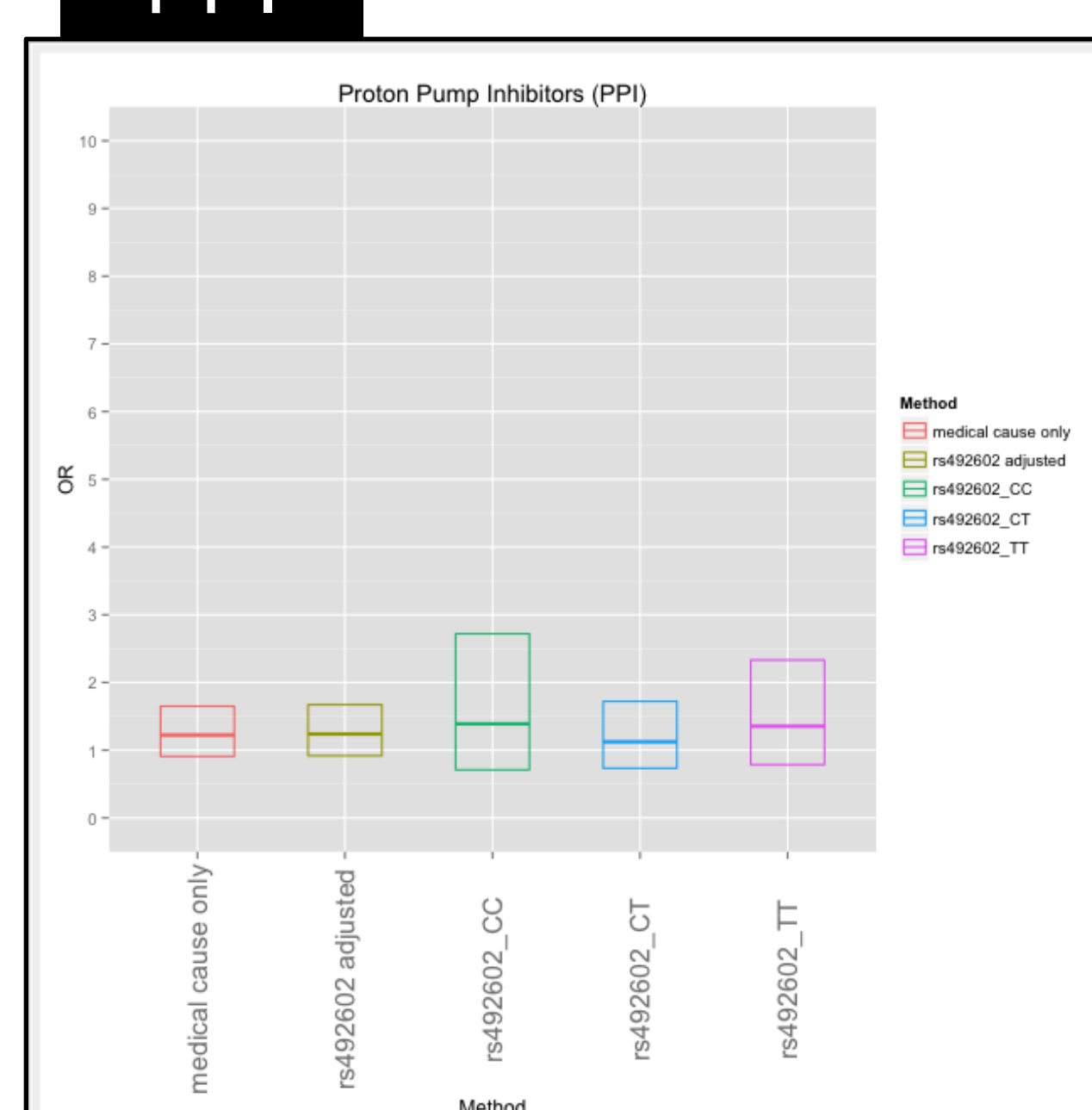
Diabetes Mellitus



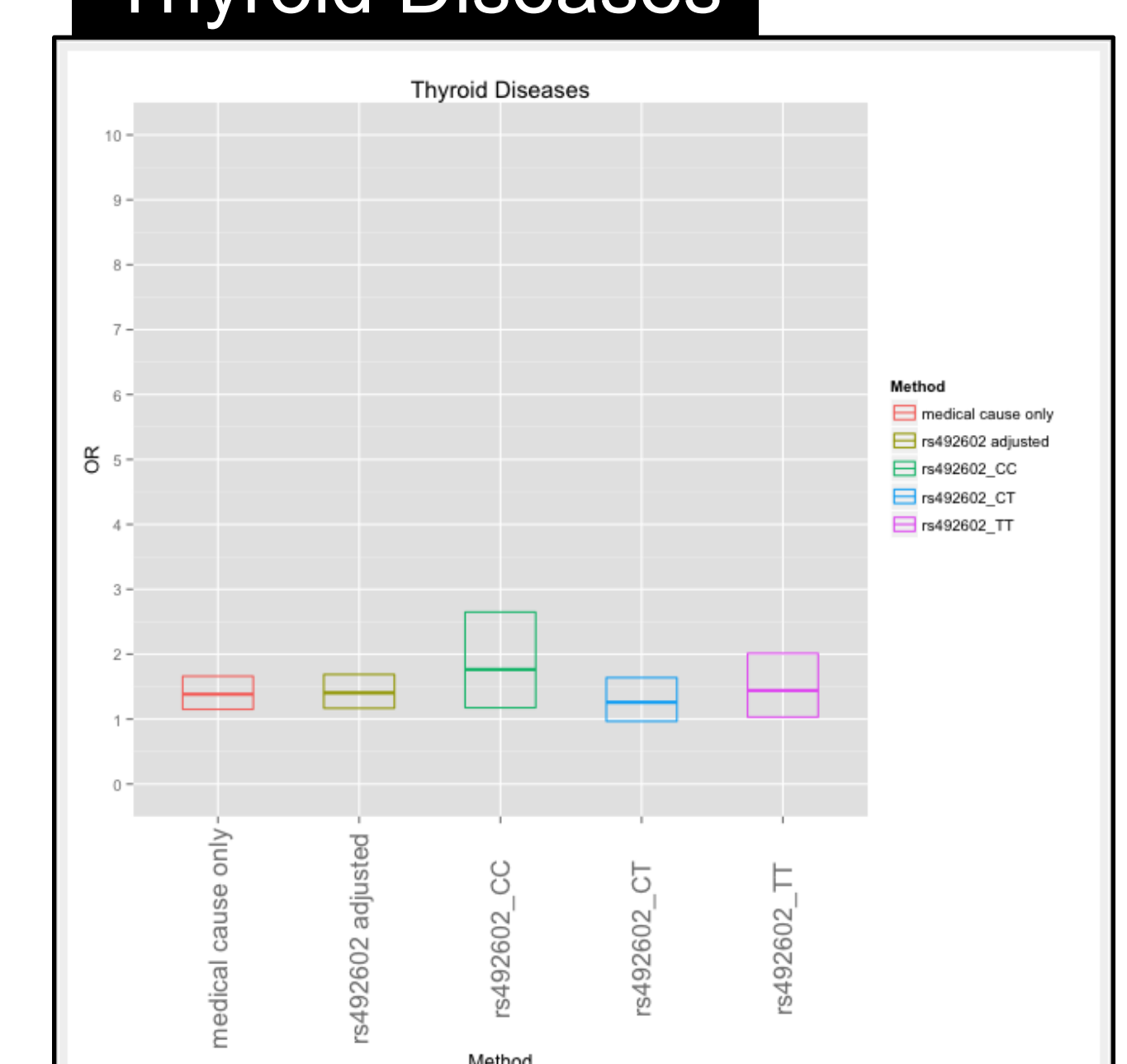
Metformin in DM



PPI



Thyroid Diseases



(The boxes show the estimated odd ratios [OR] and their 95% confidence intervals [CI])