Genomics Proteomics Bioinformatics 15 (2017) 405–406

Genomics Proteomics Bioinformatics

www.elsevier.com/locate/gpb
www.sciencedirect.com

LETTER TO THE EDITOR

Comments on "Vitamin Pharmacogenomics: New Insight into Individual Differences in Diseases and Drug Responses"

Tom Greenfield [a]

International College of Generative Medicine, Canterbury, Kent CT1 1BL, United Kingdom

Received 18 April 2017; accepted 22 September 2017
Available online 7 October 2017

Dear Editor,

I would like to offer some comments on the excellent article by Hai-Yan He and colleagues published in *Genomics, Proteomics & Bioinformatics* on 1st April 2017 [1]. The authors include, in the list of genetic polymorphisms that have an effect on vitamins, the low concentrations of cellular and plasma vitamin B_{12} in GG carriers of SNP rs602662 (772 G > A) in the gene encoding fucosyltransferase 2 (*FUT2*).

The G allele of *FUT2* rs602662 is the ancestral allele, and as reviewed in the article by He and colleagues, has been recognised in various genome-wide association study (GWAS) analyses as linked with lower plasma levels of vitamin B_{12} [1]. This SNP is in strong linkage disequilibrium with the FUT2 W143X nonsense variant (rs601338) [2], which is known as the primary allele for non-secretor status of ABH blood group antigens [3]. The ancestral (G) allele of SNP rs601338 allows for normal translation of *FUT2* (ABH secretor), whereas the variant A allele, linked with the missense variant rs602662(A), results in a premature stop codon in *FUT2* and a truncated, dysfunctional FUT2 enzyme, leading to the ABH non-secretor phenotype.

The association between *FUT2* and vitamin B_{12} is likely to result from ABH non-secretor status, as the association between plasma vitamin B_{12} concentration and the *FUT2* rs492602 (in perfect linkage disequilibrium with rs601338) is found to be stronger than that for rs602662 [3].

The secretor phenotype was originally believed to be associated with reduced plasma B_{12} due to an association with *Helicobacter pylori*-induced gastritis [4], but this was refuted in a later study by Oussalah and colleagues which investigates the influence of *FUT2* polymorphism on *H. pylori* serologic status [5]. A subsequent paper by Chery et al suggests that FUT2 phenotype worsens B_{12} status by decreasing gastric intrinsic factor (GIF) secretion via a mechanism related to H-type fucosylation, particularly in the presence of *GIF* mutations, and is unrelated with *H. pylori*-induced gastritis [6].

Interestingly, a recent GWAS analysis by Nongmaithem and colleagues based on Indians in the Pune Maternal Nutrition Study has identified allele-specific differences for rs78060698 in *FUT6* [7]. This variant is found to differentially influence the binding affinity of hepatocyte nuclear factor 4α (HNF4α), and the knockdown of *HNF4α* may repress the expression of *FUT3*, *FUT5*, and *FUT6*. This in turn would affect production of the fucose moiety in the glycan structure secreted in the intestinal tract, which has an important role in maintaining host-microbial interaction, as well as microbial abundance and diversity. Thus, the rs78060698 variant could play a part in mediation of intestinal host-microbial interaction, leading to alteration of plasma B_{12} concentrations. Given the influence of the *FUT2* ABH non-secretor variant on plasma B_{12} levels, and also the difference between vegetarians and non-vegetarians [8], this seems entirely feasible. Nongmaithem et al also consider the possibility of an influence of FUTs on B_{12} concentrations, which may be mediated through

E-mail: tom@greenfieldsclinic.co.uk (Greenfield T).
[a] ORCID: 0000-0003-1762-009X.
DOI of original article: 10.1016/j.gpb.2016.10.005.
Peer review under responsibility of Beijing Institute of Genomics, Chinese Academy of Sciences and Genetics Society of China.

https://doi.org/10.1016/j.gpb.2017.09.001

the glycosylation of B_{12}-binding proteins and their receptors including transcobalamin I, GIF, cubilin, and CD320. The authors state however that the mechanism through which the FUTs act upon these B_{12}-binding proteins and their receptors is unclear and needs to be investigated further.

Competing interests

The author has declared that no competing interests exist.

References

[1] He HY, Liu MZ, Zhang YL, Zhang W. Vitamin pharmacogenomics: new insight into individual differences in diseases and drug responses. Genomics Proteomics Bioinformatics 2017;15:94–100.
[2] Hazra A, Kraft P, Selhub J, Giovannucci EL, Thomas G, Hoover RN, et al. Common variants of *FUT2* are associated with plasma vitamin B_{12} levels. Nat Genet 2008;40:1160–2.
[3] Kelly RJ, Rouquier S, Giorgi D, Lennon GG, Lowe JB. Sequence and expression of a candidate for the human *Secretor* blood group alpha(1,2)fucosyltransferase gene (*FUT2*). Homozygosity for an enzyme- inactivating nonsense mutation commonly correlates with the non-secretor phenotype. J Biol Chem 1995;270:4640–9.
[4] Hazra A, Kraft P, Lazarus R, Chen C, Chanock SJ, Jacques P, et al. Genome-wide significant predictors of metabolites in the one-carbon metabolism pathway. Hum Mol Genet 2009;18:4677–87.
[5] Oussalah A, Besseau C, Chery C, Jeannesson E, Guéant-Rodriguez RM, Anello G, et al. *Helicobacter pylori* serologic status has no influence on the association between fucosyltransferase 2 polymorphism (*FUT2* 461 G > A) and vitamin B_{12} in Europe and West Africa. Am J Clin Nutr 2012;95:514–21.
[6] Chery C, Hehn A, Mrabet N, Oussalah A, Jeannesson E, Besseau C, et al. Gastric intrinsic factor deficiency with combined *GIF* heterozygous mutations and *FUT2* secretor variant. Biochimie 2013;95:995–1001.
[7] Nongmaithem SS, Joglekar CV, Krishnaveni GV, Sahariah SA, Ahmad M, Ramachandran S, et al. GWAS identifies population-specific new regulatory variants in *FUT6* associated with plasma B_{12} concentrations in Indians. Hum Mol Genet 2017;26:2551–64.
[8] Tanwar VS, Chand MP, Kumar J, Garg G, Seth S, Karthikeyan G, et al. Common variant in *FUT2* gene is associated with levels of vitamin B(12) in Indian population. Gene 2013;515:224–8.