

Association of the Common Genetic Variant Upstream of *INSIG2* Gene with Obesity Related Phenotypes in Chinese Children and Adolescents¹

HAI-JUN WANG^{#, †}, HENG ZHANG^{*}, SHI-WEI ZHANG^{*}, YONG-PING PAN[§], AND JUN MA^{*2}

[#] Department of Maternal and Child Health, School of Public Health, Peking University, Beijing 100191, China; ^{*} Institute of Child and Adolescent Health, Peking University, Beijing 100191, China; [†] Key Laboratory of Epidemiology, Ministry of Education, China; [§] Dongcheng School Health Care Institute, Beijing 100005, China

Objective To study the association between the rs7566605 variant of *INSIG2* and obesity-related phenotypes in Chinese children and adolescents. **Methods** The study sample consisted of two independent cohorts of Chinese children and adolescents. Anthropometric indices, lipids, blood pressure, fasting glucose, insulin and percentage of fat mass were determined. PCR with restriction fragment length polymorphism analysis was performed for genotyping the rs7566605 variant. **Results** In each of the two independent cohorts, no significant association was observed between rs7566605 and obesity under additive, dominant or recessive model. We also did not detect any difference in the genotype frequency between all the obese children and controls. Furthermore, we did not find evidence of an association between body composition indices and metabolic phenotypes in all children. However, the triglyceride level of CC homozygotes was significantly higher than that of GG+GC genotypes in obese children ($P=0.022$). Additionally, we observed a non-significant trend of severe obesity in a *post-hoc* test. **Conclusion** *INSIG2* rs7566605 variant is not associated Chinese childhood obesity in two independent cohorts. Further study is needed to verify the effect of rs7566605 on triglyceride in obese children.

Key words: *INSIG2* gene; Obesity-related phenotypes; Children and adolescents

REFERENCES

1. Hill J O, Catenacci V, Wyatt H R (2005). Obesity: overview of an epidemic. *Psychiatr Clin North Am* **28**, 1-23.
2. Herbert A, Gerry N P, McQueen M B, *et al.* (2006). A common genetic variant is associated with adult and childhood obesity. *Science* **312**(5771), 279-283.
3. Rankinen T, Zuberi A, Chagnon Y C, *et al.* (2006). The human obesity gene map: the 2005 update. *Obesity (Silver Spring)* **14**(4), 529-644.
4. Dina C, Meyre D, Samson C, *et al.* (2007). Comment on "A common genetic variant is associated with adult and childhood obesity". *Science* **315**(5809), 187.
5. Loos R J, Barroso I, O'rahilly S, *et al.* (2007). Comment on "A common genetic variant is associated with adult and childhood obesity". *Science* **315**(5809), 187.
6. Hall D H, Rahman T, Avery P J, *et al.* (2006). *INSIG-2* promoter polymorphism and obesity related phenotypes: association study in 1428 members of 248 families. *BMC Med Genet* **7**, 83.
7. Feng Y, Dong H, Xiang Q, *et al.* (2007). Lack of association between rs7566605 and obesity in a Chinese population. *Hum Genet* **120**(5), 743-745.
8. Kumar J, Sunkishala R R, Karthikeyan G, *et al.* (2007). The common genetic variant upstream of *INSIG2* gene is not associated with obesity in Indian population. *Clin Genet* **71**(5), 415-418.
9. Smith A J, Cooper J A, Li L K, *et al.* (2007). *INSIG2* gene polymorphism is not associated with obesity in Caucasian, Afro-Caribbean and Indian subjects. *Int J Obes (Lond)* **31**(11), 1753-1755.
10. Pollex R L, Ban M R, Young T K, *et al.* (2007). Association between the -455T>C promoter polymorphism of the APOC3 gene and the metabolic syndrome in a multi-ethnic sample. *BMC Med Genet* **8**, 80.
11. Kuzuya M, Ando F, Iguchi A, *et al.* (2007). No association between rs7566605 variant and being overweight in Japanese. *Obesity (Silver Spring)* **15**(11), 2531-2534.
12. Tabara Y, Kawamoto R, Osawa H, *et al.* (2008). No association between *INSIG2* Gene rs7566605 polymorphism and being overweight in Japanese population. *Obesity (Silver Spring)*

¹This research was supported by the grant from National Natural Science Foundation of China (30700668), Specialized Research Fund for the Doctoral Program of Higher Education (20070001811), and the Major State Basic Research and Development Program of China (973 program) (2006CB503900).

²Correspondence should be addressed to Jun MA, Institute of Child and Adolescent Health, Peking University, 38 Xueyuan Road, Beijing 100191, China. Tel: 86-10-82801624. Fax: 86-10-82801178. E-mail: majunt@bjmu.edu.cn

Biographical note of the first author: Hai-Jun WANG, female, born in 1973, Ph.D., associate professor at Department of Maternal and Child Health, School of Public Health, Peking University, majoring in maternal and child health, especially genetics of childhood obesity.

- 16(1), 211-215.
13. Ciullo M, Nutile T, Dalmasso C, *et al.* (2008). Identification and replication of a novel obesity locus on chromosome 1q24 in isolated populations of Cilento. *Diabetes* **57**(3), 783-790.
 14. Boes E, Kollerits B, Heid I M, *et al.* (2008). INSIG2 polymorphism is neither associated with BMI nor with phenotypes of lipoprotein metabolism. *Obesity (Silver Spring)* **16**(4), 827-833.
 15. Krapivner S, Popov S, Chernogubova E, *et al.* (2008). Insulin-induced gene 2 involvement in human adipocyte metabolism and body weight regulation. *J Clin Endocrinol Metab* **93**(5), 1995-2001.
 16. Yang L, Wu Y, Li H, *et al.* (2008). Potential association of INSIG2 rs7566605 polymorphism with body weight in a Chinese subpopulation. *Eur J Hum Genet* **16**(6), 759-761.
 17. Roskopf D, Bornhorst A, Rimbach C, *et al.* (2007). Comment on "A common genetic variant is associated with adult and childhood obesity". *Science* **315**(5809), 187.
 18. Lyon H N, Emilsson V, Hinney A, *et al.* (2007). The association of a SNP upstream of *INSIG2* with body mass index is reproduced in several but not all cohorts. *PLoS Genet* **3**(4), e61.
 19. Zhang J, Lin R, Wang F, *et al.* (2008). A common polymorphism is associated with body mass index in Uyghur population. *Diabetes Res Clin Pract* [Epub ahead of print]
 20. Hotta K, Nakamura M, Nakata Y, *et al.* (2008). *INSIG2* gene rs7566605 polymorphism is associated with severe obesity in Japanese. *J Hum Genet* [Epub ahead of print]
 21. Wang H J, Ma J, Yin Z D, *et al.* (2007). Study on the Relationship Between Obesity and Metabolic Syndrome in Adolescents. *Chin J Sch Health* **28**(10), 878-882. (In Chinese)
 22. Ma J, Zhang S W, Wu S X, *et al.* (2008). Prevalence of metabolic syndrome among children with different nutritional status in Beijing]. *Chin J Sch Health* **29**(2), 103-105. (In Chinese)
 23. Group of China Obesity Task Force (2004). Body mass index reference norm for screening overweight and obesity in Chinese children and adolescents. *Chin J Epidemiol* **25**(2), 97-102. (In Chinese)
 24. Lohmueller K E, Pearce C L, Pike M, *et al.* (2003). Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Gene* **33**(2), 177-182.
 25. Yabe D, Brown M S, Goldstein J L (2002). Insig-2, a second endoplasmic reticulum protein that binds SCAP and blocks export of sterol regulatory element-binding proteins. *Proc Natl Acad Sci U S A* **99**(20), 12753-12758.
 26. Takaishi K, Duplomb L, Wang M Y, *et al.* (2004). Hepatic insig-1 or -2 overexpression reduces lipogenesis in obese Zucker diabetic fatty rats and in fasted/refed normal rats. *Proc Natl Acad Sci U S A* **101**(18), 7106-11.
 27. Engelking L J, Liang G, Hammer R E, *et al.* (2005). Schoenheimer effect explained--feedback regulation of cholesterol synthesis in mice mediated by Insig proteins. *J Clin Invest* **115**(9), 2489-2498.
 28. Oki K, Yamane K, Kamei N, *et al.* (2008). The single nucleotide polymorphism upstream of insulin-induced gene 2 (*INSIG2*) is associated with the prevalence of hypercholesterolaemia, but not with obesity, in Japanese American women. *Br J Nutr* [Epub ahead of print]

(Received July 20, 2008 Accepted October 19, 2008)