Review

Korean Diabetes J 2010;34:10-15
doi: 10.4093/kdj.2010.34.1.10
pISSN 1976-9180 · eISSN 2093-2650

kdj
KOREAN DIABETES JOURNAL

The Epidemiology of Diabetes in Korea: From the Economics to Genetics

Nam H. Cho

Department of Preventive Medicine, Ajou University School of Medicine, Suwon, Korea

To determine the factors responsible for the dramatic increase in the prevalence of diabetes in Korea. A computerized literature survey was conducted to evaluate the risk factors for Type 2 diabetes mellitus (T2DM) in Korea, including genome-wide association studies. National Statistics gross national income data was integrated with the reported prevalence of diabetes to evaluate the relationship between diabetes and the economic growth. The strength of the association was evaluated using measures of effect size, such as odds ratio and relative risks. The putative risk factors identified in Korean studies are very similar to the risk factors identified from the other countries, including genetic background. Genome-wide association studies reported relative risks of 1.5 or less, indicating that no single gene is associated with the risk of T2DM. The scientific evidence suggests that the dramatic increase in the incidence and prevalence of T2DM in Korea is related to the economic development of Korea, which has a direct influence on health policy, as well as an individual's health behaviors. We expect to observe the current diabetes incidence rates until the key risk factors are present for long enough in our society, at which point we would expect to start observing a more gradual increase in both the incidence and prevalence of T2DM in Korea.

Keywords: Epidemiology; Economy; Genetics

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major health problem affecting more than 170 million people worldwide, with a major increase expected in Asia in the next 20 years, as indicated by the predicted doubling of the diabetic populations in India and China [1]. In the USA, more than 13% of adults over the age of 20 years have been diagnosed with T2DM [2]. T2DM is also a major chronic disease and public health problem in Korea. The prevalence of diabetes mellitus in Korea increased from less than 1% in 1960 to 6-9% by the end of the 1990s [3,4]. The rapid rise in the prevalence of diabetes and cardiovascular disease in Korea may be related to an increasingly Westernized diet, decreased physical activity, an increasing obese population, and genetic background [5]. The putative risk factors for T2DM in the Korean population include (but are not limited to) increasing age, urban living, female gender, obesity, smoking, family history of diabetes, impaired liver function, metabolic syndrome, elevated blood pressure, and increased triglycerides. For a better understanding of T2DM in Korea, the magnitude of the prevalence, incidence, and risk factors still needs to be evaluated.

The most recent report from a large size community cohort prospective study revealed the age, gender, and resident specific annual incidence of T2DM was 1.33%, 1.55%, 1.68%, and 2.35% in 40-year-old rural female, urban female, rural male, and urban male, respectively. In 50-year-old the rate increased to 1.48% in rural female, 1.65% in rural male, 2.3% in urban female, and 3.18% in urban male. In 60-year-old, 1.85% in rural male, 2.05% in rural female, 4.1% in urban female, and 4.55% in urban male. In 70-year-old, the rate increased to 3.08% in rural female, 3.93%

Corresponding author: Nam H. Cho
Department of Preventive Medicine, Ajou University School of Medicine,
5 Woncheon-dong, Youngtong-gu, Suwon, Gyeonggi 443-721, Korea
E-mail: chnaha@ajou.ac.kr

in rural male, 5% in urban female, and 5% in urban male. The incidence rates stratified by age and gender in rural subjects showed 'J' shaped pattern, but linear pattern was observed in urban subjects.

The prevalence of T2DM was 5.2%, 5.4%, 7.5%, and 10% in 40-year-old urban women, rural women, rural men, and urban men, respectively. In 50-year-old, the prevalence increased to 10.9% in urban women, 13.5% in rural women, 14.9% in rural men, and 16.5% in urban men. In 60-year-old, the prevalence was 16.5% in rural men, 17.5% in rural women, 17.5% in urban women, and 24.8% in urban men. A relatively higher prevalence was observed in the urban and male populations [6].

ECONOMY AND DIABETES

Korea has experienced a dramatic increase in the prevalence of diabetes since the early 1990s; however, the rapid increase in the prevalence of chronic disease could be the result of various artifacts, rather than being the consequence of risk factors. The artifacts responsible for dramatic changes of the prevalence and incidence of chronic disease in Korea include:

1) Changes in diagnostic methods and criteria,
2) Changes in national health policy and the health insurance system,
3) Promotion of disease awareness, and
4) A sudden change or increased exposure to key risk factors.

However, it is almost impossible for exposure of a large population to a key risk factor to result in a such dramatic increasing pattern of chronic diseases. For example, chronic diseases, such as diabetes, are the consequence of exposure to multiple risk factors over a long period of time. In other words, exposure to multiple risk factors from the environment, lifestyle, and habitual factors results in the progression of disease at different rates among individuals and in a gradual pattern. Therefore, the onset of diabetes occurs based on the individual's susceptibility, immunity, and exposure amount, as well as on the duration of the risk factors and incubation period. Thus, the dramatic change in the patterns of incidence and prevalence of diabetes are related to economic changes of individual nations, as well as the individual's health behavior.

As shown in Fig. 1, Korea has experienced both steady economic growth and an increasing prevalence of diabetes. In the early 1970s, epidemiologic studies from Korea reported a T2DM prevalence of less than 2%; however, a log linear increase in prevalence was observed, starting in 1987. This is an unusual pattern if the prevalence is the result of the risk exposure, as one would expect a gradual linear increase if the prevalence is related to risk exposure. The Korean government implemented a universal health insurance system in 1987, and the prevalence of diabetes clearly reflects a "seeking of disease" concept. This hypothesis is further supported by the fact that the Korean gross national income is curtailing the prevalence pattern of diabetes (Fig. 1). Diabetes awareness campaigns, individuals' health care attitudes and interest, screening programs, and national health care coverage are relate to the higher prevalence of diabetes and contribute to the logarithmic prevalence pattern. The most recent study from the National Health Insurance Corporation and the Bureau of National Statistics indicated a total of 2 million people with diabetes in Korea [7]. However, this report did not include asymptomatic cases, which are present in about the same amount as known cases. If we include asymptomatic cases, as well as impaired glucose tolerance cases, we would estimate somewhere around 4-5 million people with T2DM or at high risk for T2DM in Korea [8].

We suggested that the rapid rise in both incidence and prevalence of diabetes in Korea is largely due to national health policy; however, to some degree, the rise is due to exposure to multiple risk factors. Thus, let us evaluate the risk factors of the T2DM in Korea and the magnitude of these risk factors.

RISK FACTORS

The putative risk factors for T2DM in the Korean population include (but are not limited to) old age, urban living, female gender, obesity, smoking, family history of diabetes, impaired liver function, metabolic syndrome, elevated blood pressure, and increased triglycerides. Although some risk factors have yet to be identified, the aforementioned variables are the key risk factors for diabetes mellitus in Koreans. Most of these risk factors have also been identified as key risk factors in other locations, including Europe, South and North America, and Africa. Moreover, seventy percent of identified risk factors are modifiable. For example, smoking is a habitual behavior and is modifiable. Several prospective studies have demonstrated the risk association between cigarette smoking and diabetes in both Caucasian and Asian populations [9-14]. In the 21,068-participant U.S. Physicians' Health Study, both former and current smokers had an increased risk of self-reported diabetes in a

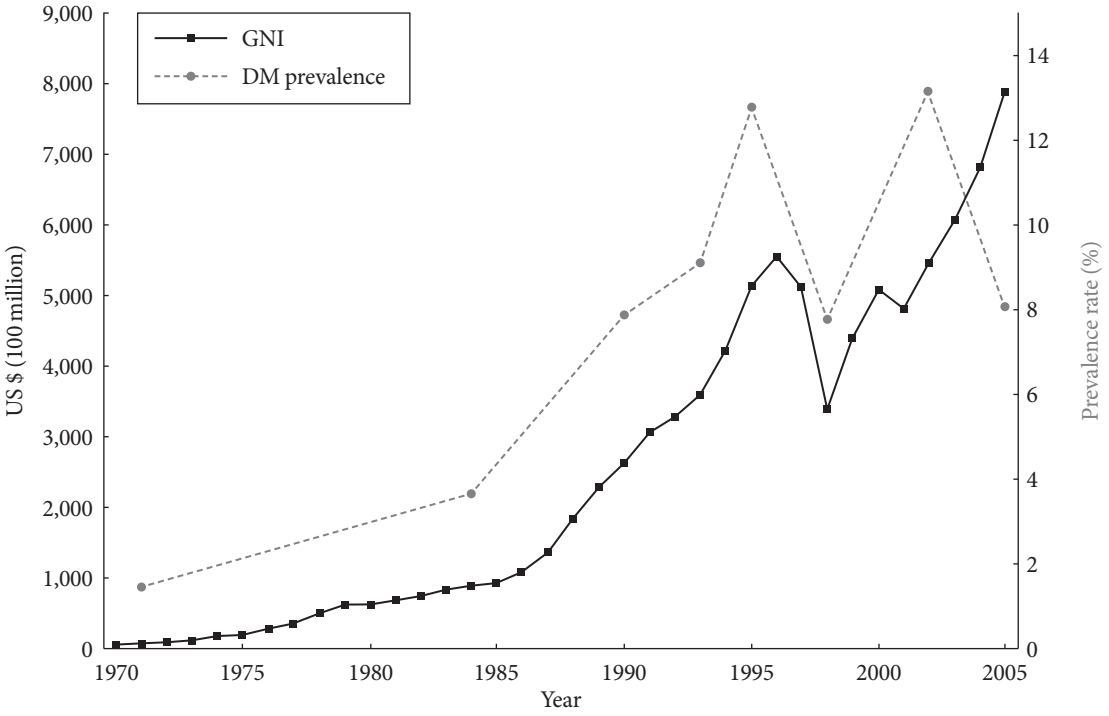

Fig. 1. The prevalence of diabetes and gross national income (GNI).

dose-response relationship. Similarly, in the Nurses' Health Study, a dose-dependent relationship between smoking and diabetes incidence among 114,247 female nurses had been reported [15]. Although these dose-relationships were not always consistent, this may be due to differences in study design, participant characteristics, and measurement methods [10,16,17]. In a study from Korea, smokers (ex- and current) had a higher incidence of diabetes mellitus than never-smokers (6.3% vs. 5.1%, $P < 0.05$). The incidence of diabetes was 5.1%, 8.3%, 5.1%, and 6.8% in never-smokers, ex-smokers, current smokers, and heavy smokers, respectively ($P < 0.05$). In this study, compared to never smokers, the ex- and heavy smokers had a 2-fold increased risk of diabetes, while current smokers had a 1.5-fold increased risk. Furthermore, the population attributable risk of smoking for diabetes was 14% (95% confidence interval [CI], 4.4% to 23.6%) [18]. In other words, if no smokers were present in Korea, then 14% of the cases of diabetes could be prevented. In, addition, urban living, obesity, impaired liver function, metabolic syndrome, elevated blood pressure, and increased triglycerides are all modifiable risk factors and all independently contribute to the risk of diabetes. The relationship between liver function and T2DM has been investigated in numerous clinical and epidemiologic studies. In a study in Korea, ALT levels had a dose-dependent effect on the prevalence of T2DM at baseline examination from 3.2%, 4.1%. 6.3%, and 12.5% ($\chi^2 = 256.8$; $P < 0.001$) in lowest to highest quartile groups, respectively. However, at the follow-up evaluation, the incidence of T2DM was 2.5%, 2.3%, 4.0%, and 7.1% for the respective quartile groups. The relative risks were 0.9 (95% CI, 0.55 to 1.53; P = ns), 1.67 (1.06 to 2.6; $P < 0.05$), and 3 (1.97 to 4.7; $P < 0.001$), when compared to the lowest quartile group. Furthermore, a multiple logistic regression analysis revealed that age-adjusted relative risk was 1.34 (95% CI, 0.98 to 1.85; $P = 0.07$) in the 2nd quartile, 1.91 (1.41 to 2.59; $P < 0.001$) in the 3rd quartile, and 2.95 (2.17 to 4.0; $P < 0.001$) in the 4th quartile group, when compared to the lowest quartile group [19].

The rise of diabetes incidence and prevalence in Korea is a result of both health policy change and exposure to putative risk factors. In the past 10 years, genetic susceptibility has emerged as a new key risk factor for T2DM. We will now evaluate the strength of genetics as a risk factor of T2DM.

GENETICS AND DIABETES

The genome-wide association (GWA) approach is an emerging methodology that enables us to identify genetic variants with

specific loci predisposing individuals to complex traits and diseases [20]. Several genes identified through linkage scans or the candidate gene approach have been confirmed to be associated with T2DM (e.g., *PPARG*, *KCNJ11*, *HNF4A*, and *CAPN10*). Furthermore, under the common variant-common disease hypothesis, several GWA studies on T2DM have been conducted in large-scale case-control samples. Seven novel genes (*TCF7L2*, *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A* and *CDKN2B*, *IGF2BP2*, and *FTO*) have been reproducibly demonstrated to have a modest association with T2DM (odds ratio [OR], 1.12 to 1.37) in multiple populations of European ancestry [21-25]. While many of the genes are implicated in the insulin production/secretion pathway (*TCF7L2*, *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A/B* and *IGF2BP2*), *FTO* is associated with T2DM through its regulation of adiposity [25,26]. Moreover, a region near CDKN2A/B is associated with risk of both T2DM and cardiovascular diseases [27,28]. Despite consistent associations among Europeans, the contributions of these genetic variants in other ethnic groups are unclear. Given the differences in environmental factors (e.g., lifestyle), risk factor profiles (body composition and insulin secretion/resistance patterns), and genetic background (linkage disequilibrium pattern and risk allele frequencies) between Europeans and Asians, it is important to understand the role of these genes in Asians.

Recent GWA studies have been performed in a Chinese population in Hong Kong (involving 6,795 T2DM cases and non-diabetic controls) and two Korean populations. The risk alleles were consistent among the three Asian populations and were consistent with those reported in Europeans [21-25]. *TCF7L2* (rs7903146) showed the strongest effect (OR, 1.34), followed by *CDKN2A/B* (rs10811661), *CDKAL1* (rs7754840 and rs7756992), *HHEX* (rs1111875, rs5015480 and rs7923837), *SLC30A8* (rs13266634), *IFG2BP2* (rs4402960), and *FTO* (rs8050136). Haplotype analyses did not reveal a more significant association than single-marker analyses. Interestingly, multiple single nucleotide polymorphisms at *CDKAL1* and *HHEX* were significantly associated with T2DM risk. However, only rs10811661 near *CDKN2A/B* was highly significant for association with T2DM.

Since the reported T2DM genes may be implicated in different metabolic pathways, subset analyses were performed by dividing the T2DM patients into non-obese (body mass index [BMI] <25 kg/m^2) and obese subgroups using the Asian guideline for the definition of obesity [28]. The study found that the associations for T2DM were significantly higher in the non-obese subgroup, as compared to the obese subgroup in the combined samples for *CDKAL1* (rs7754840) and *CDKN2A/B* (rs10811661) (OR, 1.29 vs. 1.15 and 1.39 vs. 1.20 in non-obese and obese subgroups, respectively, heterogeneity $P < 0.05$). The former association in non-obese diabetes was also observed in an Icelandic population [24]. On the other hand, *FTO* showed a stronger association in the obese subgroup (OR, 1.06 vs. 1.27 in non-obese vs. obese subgroups, heterogeneity $P < 0.05$). The result for *FTO* is consistent with the finding that the T2DM association was lost after adjustment for BMI (OR, 1.18; $P = 0.003$ vs. OR, 1.09; $P = 0.126$ before and after adjustment for BMI, respectively). Moreover, the risk allele of *FTO* was highly associated with increased BMI in the combined samples ($P = 1.7 \times 10^{-6}$). Taken together, *FTO* alters the risk for T2DM, primarily through effects on adiposity, which is consistent with reported findings in Europeans [25,26,29]. In addition to BMI, the risk alleles for *SLC30A8* (rs13266634) and *HHEX* (rs1111875) were significantly associated with diagnosis at an earlier age [30].

These studies provide important insight into the impact of the new T2DM genes identified through genome-wide association studies. However, the strength of the effect size is not as strong as some of the risk factors, such as family history of diabetes. Therefore, we are inclined to believe that the link between diabetes and genetic susceptibility is genuine, but, however, is not a key risk factor for T2DM.

SUMMARY

Numerous epidemiologic studies from Korea have revealed a high rate of diabetes. Although the effect sizes are different, the putative risk factors identified from Korean studies are very similar to the risk factors identified from the other countries. Furthermore, the genes identified through genome-wide association studies conducted in both Asian and Caucasian populations revealed a lower effect size. These genetic studies reported a relative risk of 1.5 or less, indicating that no single gene is associated with the risk of T2DM; however, a strong interaction between genetic factors and lifestyle, diet, and habitual factors was suggested. In addition, relative risk (RR) and OR are statistics that only describe an association, not causation. RR and OR also refer to a population and not to an individual patient. Furthermore, studies of small groups are more likely to find an association that might actually be due to chance, while larger groups are less likely to show an association between a risk factor and an outcome. Finally, when the incidence of an outcome

of interest in the study population is low (<10%), the OR is close to the RR; the more frequent the outcome becomes, the more the OR will overestimate the RR when OR is greater than 1 or underestimate the RR when OR is less than 1.

In conclusion, the high incidence and prevalence of T2DM in Korea is related to economic development, which has a direct influence on health policy, as well as an individual's health behaviors, and which is associated with a high rate of T2DM. Environmental and genetic factors very likely contribute to some degree to the high rate of diabetes in Korea. Finally, although genetic factors are independently associated with an onset of T2DM, the strength of an association is less than that of the environmental risk factors that have been reported. Therefore, we expect to observe the current diabetes rates until the key risk factors incubate long enough in our society, at which point we would expect to start observing a more gradual increase in both the incidence and prevalence of T2DM in Korea.

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.
2. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, Williams DE, Gregg EW, Bainbridge KE, Saydah SH, Geiss LS. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. Diabetes Care 2009;32:287-94.
3. Park Y, Lee H, Koh CS, Min H, Yoo K, Kim Y, Shin Y. Prevalence of diabetes and IGT in Yonchon County, South Korea. Diabetes Care 1995;18:545-8.
4. Kim YI, Choi CS, Kim SW, Lee JS, Kim HH, Lee MS, Lee SI, Park JY, Hong SK, Lee KU. Prevalence of diabetes mellitus and impaired glucose tolerance in Korean adults living in Jungup district, South Korea. J Korean Diabetes Assoc 1998;22:363-71.
5. Cho NH. Prevalence of diabetes and management status in Korean population. Korean J Med 2005;68:1-3.
6. Cho NH. Longitudinal epidemiologic study of diabetes mellitus: community cohort based genome project. National Institute of Health Annual Reports 2001-2009.
7. Kang SK, Kim KW, Cho NH, Hur CW, Kim HK, Choi RY, Park HR. Nationwide diabetes epidemiology study. Seoul: Korean Diabetes Association; 2004.
8. Kang SK, Kim KW, Cho NH, Hur CW, Kim HK, Choi RY, Park HR. Nationwide diabetes epidemiology study. Seoul: Korean Diabetes Association; 2003.
9. Manson JE, Ajani UA, Liu S, Nathan DM, Hennekens CH. A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. Am J Med 2000;109:538-42.
10. Wannamethee SG, Shaper AG, Perry IJ; British Regional Heart Study. Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. Diabetes Care 2001;24:1590-5.
11. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. BMJ 1995;310:555-9.
12. Foy CG, Goff DC, Bell RA, Wagenknecht LE, Farmer DF. Smoking and incidence of diabetes among U.S. adults: findings from the Insulin Resistance Atherosclerosis Study. Diabetes Care 2005;28:2501-7.
13. Sawada S, Lee I, Muto T, Matuszaki K, Blair S. Cardiorespiratory fitness and the incidence of type 2 diabetes: prospective study of Japanese men. Diabetes Care 2003;26:2918-22.
14. Shai I, Jiang R, Manson JE, Stampfer MJ, Willett WC, Colditz GA, Hu FB. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care 2006;29:1585-90.
15. Rimm EB, Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, Hennekens CH, Speizer FE. Cigarette smoking and the risk of diabetes in women. Am J Public Health 1993;83:211-4.
16. Keen H, Jarrett RJ, McCartney P. The ten-year follow-up of the Bedford survey (1962-1972): glucose tolerance and diabetes. Diabetologia 1982;22:73-8.
17. Wilson PW, Anderson KM, Kannel WB. Epidemiology of diabetes mellitus in the elderly: the Framingham Study. Am J Med 1986;80:3-9.
18. Cho NH, Chan JC, Jang HC, Lim S, Kim HL, Choi SH. Cigarette smoking is an independent risk factor for type 2 diabetes: a four-year community-based prospective study. Clin Endocrinol (Oxf) 2009;71:679-85.
19. Cho NH, Jang HC, Choi SH, Kim HR, Lee HK, Chan JC, Lim S. Abnormal liver function test predicts type 2 diabetes: a community-based prospective study. Diabetes Care 2007;30:2566-8.
20. Frazer KA, Murray SS, Schork NJ, Topol EJ. Human genetic variation and its contribution to complex traits. Nat Rev Genet 2009;10:241-51.
21. Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research, Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker

PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Boström K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjögren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 2007;316:1331-6.

22. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU, Prokunina-Olsson L, Ding CJ, Swift AJ, Narisu N, Hu T, Pruim R, Xiao R, Li XY, Conneely KN, Riebow NL, Sprau AG, Tong M, White PP, Hetrick KN, Barnhart MW, Bark CW, Goldstein JL, Watkins L, Xiang F, Saramies J, Buchanan TA, Watanabe RM, Valle TT, Kinnunen L, Abecasis GR, Pugh EW, Doheny KF, Bergman RN, Tuomilehto J, Collins FS, Boehnke M. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 2007;316:1341-5.
23. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, Balkau B, Heude B, Charpentier G, Hudson TJ, Montpetit A, Pshezhetsky AV, Prentki M, Posner BI, Balding DJ, Meyre D, Polychronakos C, Froguel P. A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature 2007;445:881-5.
24. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, Benediktsson R, Jonsdottir T, Walters GB, Styrkarsdottir U, Gretarsdottir S, Emilsson V, Ghosh S, Baker A, Snorradottir S, Bjarnason H, Ng MC, Hansen T, Bagger Y, Wilensky RL, Reilly MP, Adeyemo A, Chen Y, Zhou J, Gudnason V, Chen G, Huang H, Lashley K, Doumatey A, So WY, Ma RC, Andersen G, Borch-Johnsen K, Jorgensen T, van Vliet-Ostaptchouk JV, Hofker MH, Wijmenga C, Christiansen C, Rader DJ, Rotimi C, Gurney M, Chan JC, Pedersen O, Sigurdsson G, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. Nat Genet 2007;39:770-5.
25. Zeggini E, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, Lango H, Timpson NJ, Perry JR, Rayner NW, Freathy RM, Barrett JC, Shields B, Morris AP, Ellard S, Groves CJ, Harries LW, Marchini JL, Owen KR, Knight B, Cardon LR, Walker M, Hitman GA, Morris AD, Doney AS; Wellcome Trust Case Control Consortium (WTCCC), McCarthy MI, Hattersley AT. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science 2007;316:1336-41.
26. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007;316:889-94.
27. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Jonasdottir A, Sigurdsson A, Baker A, Palsson A, Masson G, Gudbjartsson DF, Magnusson KP, Andersen K, Levey AI, Backman VM, Matthiasdottir S, Jonsdottir T, Palsson S, Einarsdottir H, Gunnarsdottir S, Gylfason A, Vaccarino V, Hooper WC, Reilly MP, Granger CB, Austin H, Rader DJ, Shah SH, Quyyumi AA, Gulcher JR, Thorgeirsson G, Thorsteinsdottir U, Kong A, Stefansson K. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science 2007;316:1491-3.
28. McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio LA, Tybjaerg-Hansen A, Folsom AR, Boerwinkle E, Hobbs HH, Cohen JC. A common allele on chromosome 9 associated with coronary heart disease. Science 2007;316:1488-91.
29. Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J, Najjar S, Nagaraja R, Orrú M, Usala G, Dei M, Lai S, Maschio A, Busonero F, Mulas A, Ehret GB, Fink AA, Weder AB, Cooper RS, Galan P, Chakravarti A, Schlessinger D, Cao A, Lakatta E, Abecasis GR. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet 2007;3:e115.
30. Ng MC, Park KS, Oh B, Tam CH, Cho YM, Shin HD, Lam VK, Ma RC, So WY, Cho YS, Kim HL, Lee HK, Chan JC, Cho NH. Implication of genetic variants near TCF7L2, SLC30A8, HHEX, CDKAL1, CDKN2A/B, IGF2BP2, and FTO in type 2 diabetes and obesity in 6,719 Asians. Diabetes 2008;57:2226-33.