Novel Insights Into the Etiology of Diabetes From Genome-Wide Association Studies

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The flood of confirmed genes for type 2 diabetes arising from genome-wide association (GWA) studies has started to raise questions as to the value of such research. Objections stem from the low individual allelic effect sizes (1.1–1.5) and from the recent observations that allele-counting summaries of the current known variants do not add much to the predictive models for type 2 diabetes (1). It has also been suggested that such a large number of variants of this effect size would be required to explain the known heritable component for diabetes that almost every gene could eventually be identified as a type 2 diabetes gene. If this did turn out to be the case, what would be the value of this knowledge (2)? These grumbles come despite the fact that prior to 2007, genetic research in common complex disease had made very little substantive progress either in the realms of candidate gene studies or in the previous generation of genome-wide studies that used microsatellite markers in a linkage paradigm. As noted by Rich, Norris, and Rotter in a commentary last year (3), the results from GWA studies have quickly turned from a trickle to a flood (4–16), and the most immediate advances from this are not disease prediction but, rather, in leading to a better understanding of etiopathogenesis together with identification of novel gene products and pathways as targets for intervention (17).

While the road to drug discovery on such a basis is undoubtedly long and rocky, in terms of disease etiology per se, we are uncovering a wealth of additional knowledge regarding the pathoetiology of type 2 diabetes. First, we are finding that the majority of genetic loci involved in type 2 diabetes are firmly rooted in the biology of the pancreatic β-cell and only associated with insulin resistance to a minor degree (18). This is epitomized by the seminal discovery of variants in the *SLC30A8* gene, which appears to be involved in the uptake of zinc, which is in this case required for the production of insulin (13). This clearly may have an important role in determining some of the priorities in future diabetic research. While some genetic loci are very elusive to further study and point the finger at multiple genes encoding poorly understood gene products, many of these gene loci implicate the involvement of known pathways that may or may not have been greatly appreciated as important in type 2 diabetes. Obviously, the discovery that an obesity gene, *FTO*, also predisposes individuals to type 2 diabetes was a gratifying and sensible observation (5); however, the discovery that this gene is predominantly a behavioral gene involved in appetite/food choice has major implications for future pathways for weight reduction/diabetes prevention interventions (19).

In a less obvious fashion, the characterization of the melatonin receptor (*MNTR1B*) as a modulator of glycemic control and type 2 diabetes susceptibility has brought to the fore previous epidemiological observations regarding sleep patterns/melatonin levels and their role in type 2 diabetes (4,10,20,21). In this case, the genetic effect provides a logical anchor point to suggest the direct causality of poor sleep, melatonin levels, and disease susceptibility (22). In type 1 diabetes, a focus on a viral trigger for this disease has been strengthened by the discovery of a key viral defense gene, *IFIH1*, as playing a role in susceptibility to type 1 diabetes (23). In contrast, a novel uric acid transporter has been identified from GWA study approaches that harbors variants that predispose to gout (24). These variants have no associations with type 2 diabetes susceptibility or other features of the metabolic syndrome, suggesting that high uric acid levels seen in type 2 diabetes and the metabolic syndrome are not disease causing but may arise as a result of the metabolic disturbances apparent in type 2 diabetes. The use of GWA studies has also highlighted a common etiology of different diseases/phenotypes, with certain genes being involved in both cancer and diabetes—most interestingly, the opposing roles of *TCF2* polymorphisms in prostate cancer and type 2 diabetes lend further support to previous epidemiology suggesting that type 2 diabetes confers protection from prostate cancer (6). In addition, *JAZF1*, a known oncogene (25), has also been show to harbor variants that modulate susceptibility to prostate cancer and diabetes (15,26,27). It is well established that shorter stature is associated with type 2 diabetes; however, the potential environmental/socioeconomic confounders limit the interpretation of this data. There is now a convergence between the list of genes associated with height in GWA studies and those affecting type 2 diabetes risk, with the *JAZF1* locus associated with height, type 2 diabetes susceptibility, and fasting glucose in nondiabetic individuals, thus confirming a causal role for stature/growth phenotypes in type 2 diabetes susceptibility (28). In a similar fashion, a gene widely studied as a drug target for metabolic disease, *PPARD*, has also recently been shown to contain variants that modulate height (29).

Another interesting finding from GWA studies further changes our understanding of the way we view A1C as a measure of glycemic control. Recent studies from the Women's Health Study have identified common genetic variation in hexokinase 1 as a robust modifier of A1C in

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FIG. 1. Fava beans: Individuals with defective erythrocyte glucose handling (generally *G6PD* mutations) are sensitive to Fava beans, resulting in hemolytic anemia. The finding that HK1 variants modulate A1C levels through such an anemic mechanism, rather than by systemic glycemic control, reminds us of the widespread nature of such glucose handling defects in malarial endemic countries.

nondiabetic populations (9). In this issue of *Diabetes*, Bonnefond et al. (30) have shown that modulation of A1C levels by variants in the *HK1* gene is not via a role in systemic glucose homeostasis or, thus, in type 2 diabetes etiology and remind us that A1C is also modulated by anemia independently of glucose control. It would appear that this may be due to local glucose handling in the erythrocyte, potentially affecting erythrocyte turnover. Importantly, HK1 is the predominant hexokinase in the erythrocyte that provides phosphorylated glucose as a precursor for both glycolysis and the pentose shunt in the erythrocyte. Mutations in HK1 (31) and in downstream activities involved in both glycolysis (pyruvate kinase) and the pentose shunt (glucose-6-phosphate dehydrogenase) are common causes of inherited hemolytic anemia and are known to affect A1C levels (32,33). Erythrocytes rely on glycolysis exclusively for ATP production, and the pentose shunt is the only mechanism by which erythrocytes can provide NADH for the reduction of glutathione, the major defense against oxidative stress in these cells. Genetic defects in this pathway are generally seen in the next step, glucose-6-phosphate dehydrogenase, which results in extreme sensitivity to environmental insults, leading to hemolytic anemia (32). Environmental stressors, which provoke anemia in individuals with a defective pentose shunt, include Fava beans (favism) or drugs such as primaquine. These genetic defects are highly prevalent in populations that have historically been highly exposed to malarial infection, such as Africa, India, the Middle East, and southern Europe; therefore, in studies of A1C, it will be very important to control for these defects (or indeed other hemoglobinopathies such as sickle cell) if study populations have a significant proportion of ancestry from these regions (Fig. 1).

So, despite the grumbles regarding GWA studies and disease prediction, it is clear that these insights demonstrate the immense value of the GWA studies performed during the last 3 years to diabetes research. We also have to realize that this is only the start of the genomic revolution. Indeed, the current reports are based on genotyping chips that query only the most common variation in the genome and represent a mere scratch on the surface of the genetic architecture of human complex disease. The use of new genotyping platforms with increased genetic content, the completion of the 1,000 genome project, and widespread adoption of whole-genome sequencing should provide another quantum jump in our understanding of interindividuality in disease processes and will hopefully allow us to provide truly personalized medicine in type 2 diabetes.

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REFERENCES

1. van Hoek M, Dehghan A, Witteman JC, van Duijn CM, Uitterlinden AG, Oostra BA, Hofman A, Sijbrands EJ, Janssens AC. Predicting type 2 diabetes based on polymorphisms from genome-wide association studies: a population-based study. Diabetes 2008;57:3122–3128
2. Goldstein DB. Common genetic variation and human traits. N Engl J Med 2009;360:1696–1698
3. Rich SS, Norris JM, Rotter JI. Genes associated with risk of type 2 diabetes identified by a candidate-wide association scan: as a trickle becomes a flood. Diabetes 2008;57:2915–2917
4. Bouatia-Naji N, Bonnefond A, Cavalcanti-Proenca C, Sparso T, Holmkvist J, Marchand M, Delplanque J, Lobbens S, Rocheleau G, Durand E, De Graeve F, Chèvre JC, Borch-Johnsen K, Hartikainen AL, Ruokonen A, Tichet J, Marre M, Weill J, Heude B, Tauber M, Lemaire K, Schuit F, Elliott P, Jørgensen T, Charpentier G, Hadjadj S, Cauchi S, Vaxillaire M, Sladek R, Visvikis-Siest S, Balkau B, Lévy-Marchal C, Pattou F, Meyre D, Blakemore AI, Jarvelin MR, Walley AJ, Hansen T, Dina C, Pedersen O, Froguel P. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. Nat Genet 2009;41:89–94
5. 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;316:889–894
6. Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, Rafnar T, Gudbjartsson D, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Blondal T, Stacey SN, Helgason A, Gunnarsdottir S, Olafsdottir A, Kristinsson KT, Birgisdottir B, Ghosh S, Thorlacius S, Magnusdottir D, Stefansdottir G, Kristjansson K, Bagger Y, Wilensky RL, Reilly MP, Morris AD, Kimber CH, Adeyemo A, Chen Y, Zhou J, So WY, Tong PC, Ng MC, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Tres A, Fuertes F, Ruiz-Echarri M, Asin L, Saez B, van Boven E, Klaver S, Swinkels DW, Aben KK, Graif T, Cashy J, Suarez BK, van Vierssen Trip O, Frigge ML, Ober C, Hofker MH, Wijmenga C, Christiansen C, Rader DJ, Palmer CN, Rotimi C, Chan JC, Pedersen O, Sigurdsson G, Benediktsson R, Jonsson E, Einarsson GV, Mayordomo JI, Catalona WJ, Kiemeney LA, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat Genet 2007;39:977–983
7. Helgadottir A, Thorleifsson G, Magnusson KP, Gretarsdottir S, Steinthorsdottir V, Manolescu A, Jones GT, Rinkel GJ, Blankensteijn JD, Ronkainen A, Jääskeläinen JE, Kyo Y, Lenk GM, Sakalihasan N, Kostulas K, Gottsäter A, Flex A, Stefansson H, Hansen T, Andersen G, Weinsheimer S, Borch-Johnsen K, Jorgensen T, Shah SH, Quyyumi AA, Granger CB, Reilly MP, Austin H, Levey AI, Vaccarino V, Palsdottir E, Walters GB, Jonsdottir T, Snorradottir S, Magnusdottir D, Gudmundsson G, Ferrell RE, Sveinbjornsdottir S, Hernesniemi J, Niemelä M, Limet R, Andersen K, Sigurdsson G, Benediktsson R, Verhoeven EL, Teijink JA, Grobbee DE, Rader DJ, Collier DA, Pedersen O, Pola R, Hillert J, Lindblad B, Valdimarsson EM, Magnadottir HB, Wijmenga C, Tromp G, Baas AF, Ruigrok YM, van Rij AM, Kuivaniemi H, Powell JT, Matthiasson SE, Gulcher JR, Thorgeirsson G, Kong A, Thorsteinsdottir U, Stefansson K. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. Nat Genet 2008;40:217–224
8. Lindgren CM, Heid IM, Randall JC, Lamina C, Steinthorsdottir V, Qi L, Speliotes EK, Thorleifsson G, Willer CJ, Herrera BM, Jackson AU, Lim N, Scheet P, Soranzo N, Amin N, Aulchenko YS, Chambers JC, Drong A, Luan J, Lyon HN, Rivadeneira F, Sanna S, Timpson NJ, Zillikens MC,

Zhao JH, Almgren P, Bandinelli S, Bennett AJ, Bergman RN, Bonnycastle LL, Bumpstead SJ, Chanock SJ, Cherkas L, Chines P, Coin L, Cooper C, Crawford G, Doering A, Dominiczak A, Doney AS, Ebrahim S, Elliott P, Erdos MR, Estrada K, Ferrucci L, Fischer G, Forouhi NG, Gieger C, Grallert H, Groves CJ, Grundy S, Guiducci C, Hadley D, Hamsten A, Havulinna AS, Hofman A, Holle R, Holloway JW, Illig T, Isomaa B, Jacobs LC, Jameson K, Jousilahti P, Karpe F, Kuusisto J, Laitinen J, Lathrop GM, Lawlor DA, Mangino M, McArdle WL, Meitinger T, Morken MA, Morris AP, Munroe P, Narisu N, Nordström A, Nordström P, Oostra BA, Palmer CN, Payne F, Peden JF, Prokopenko I, Renström F, Ruokonen A, Salomaa V, Sandhu MS, Scott LJ, Scuteri A, Silander K, Song K, Yuan X, Stringham HM, Swift AJ, Tuomi T, Uda M, Vollenweider P, Waeber G, Wallace C, Walters GB, Weedon MN; Wellcome Trust Case Control Consortium, Witteman JC, Zhang C, Zhang W, Caulfield MJ, Collins FS, Davey Smith G, Day IN, Franks PW, Hattersley AT, Hu FB, Jarvelin MR, Kong A, Kooner JS, Laakso M, Lakatta E, Mooser V, Morris AD, Peltonen L, Samani NJ, Spector TD, Strachan DP, Tanaka T, Tuomilehto J, Uitterlinden AG, van Duijn CM, Wareham NJ, Hugh Watkins; Procardis Consortia, Waterworth DM, Boehnke M, Deloukas P, Groop L, Hunter DJ, Thorsteinsdottir U, Schlessinger D, Wichmann HE, Frayling TM, Abecasis GR, Hirschhorn JN, Loos RJ, Stefansson K, Mohlke KL, Barroso I, McCarthy MI; Giant Consortium. Genome-wide association scan meta-analysis identifies three Loci influencing adiposity and fat distribution. PLoS Genet 2009;5:e1000508

9. Pare G, Chasman DI, Parker AN, Nathan DM, Miletich JP, Zee RY, Ridker PM. Novel association of HK1 with glycated hemoglobin in a non-diabetic population: a genome-wide evaluation of 14,618 participants in the Women's Genome Health Study. PLoS Genet 2008;4:e1000312
10. Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, Thorleifsson G, Loos RJ, Manning AK, Jackson AU, Aulchenko Y, Potter SC, Erdos MR, Sanna S, Hottenga JJ, Wheeler E, Kaakinen M, Lyssenko V, Chen WM, Ahmadi K, Beckmann JS, Bergman RN, Bochud M, Bonnycastle LL, Buchanan TA, Cao A, Cervino A, Coin L, Collins FS, Crisponi L, de Geus EJ, Dehghan A, Deloukas P, Doney AS, Elliott P, Freimer N, Gateva V, Herder C, Hofman A, Hughes TE, Hunt S, Illig T, Inouye M, Isomaa B, Johnson T, Kong A, Krestyaninova M, Kuusisto J, Laakso M, Lim N, Lindblad U, Lindgren CM, McCann OT, Mohlke KL, Morris AD, Naitza S, Orrù M, Palmer CN, Pouta A, Randall J, Rathmann W, Saramies J, Scheet P, Scott LJ, Scuteri A, Sharp S, Sijbrands E, Smit JH, Song K, Steinthorsdottir V, Stringham HM, Tuomi T, Tuomilehto J, Uitterlinden AG, Voight BF, Waterworth D, Wichmann HE, Willemsen G, Witteman JC, Yuan X, Zhao JH, Zeggini E, Schlessinger D, Sandhu M, Boomsma DI, Uda M, Spector TD, Penninx BW, Altshuler D, Vollenweider P, Jarvelin MR, Lakatta E, Waeber G, Fox CS, Peltonen L, Groop LC, Mooser V, Cupples LA, Thorsteinsdottir U, Boehnke M, Barroso I, Van Duijn C, Dupuis J, Watanabe RM, Stefansson K, McCarthy MI, Wareham NJ, Meigs JB, Abecasis GR. Variants in MTNR1B influence fasting glucose levels. Nat Genet 2009;41:77–81
11. 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;316:1331–1336
12. 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;316:1341–1345
13. 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;445:881–885
14. 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;39:770–775
15. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, de Bakker PI, Abecasis GR, Almgren P, Andersen G, Ardlie K, Boström KB, Bergman RN, Bonnycastle LL, Borch-Johnsen K, Burtt NP, Chen H, Chines PS, Daly MJ, Deodhar P, Ding CJ, Doney AS, Duren WL, Elliott KS, Erdos MR, Frayling TM, Freathy RM, Gianniny L, Grallert H, Grarup N, Groves CJ, Guiducci C, Hansen T, Herder C, Hitman GA, Hughes TE, Isomaa B, Jackson AU, Jørgensen T, Kong A, Kubalanza K, Kuruvilla FG, Kuusisto J, Langenberg C, Lango H, Lauritzen T, Li Y, Lindgren CM, Lyssenko V, Marvelle AF, Meisinger C, Midthjell K, Mohlke KL, Morken MA, Morris AD, Narisu N, Nilsson P, Owen KR, Palmer CN, Payne F, Perry JR, Pettersen E, Platou C, Prokopenko I, Qi L, Qin L, Rayner NW, Rees M, Roix JJ, Sandbaek A, Shields B, Sjögren M, Steinthorsdottir V, Stringham HM, Swift AJ, Thorleifsson G, Thorsteinsdottir U, Timpson NJ, Tuomi T, Tuomilehto J, Walker M, Watanabe RM, Weedon MN, Willer CJ; Wellcome Trust Case Control Consortium, Illig T, Hveem K, Hu FB, Laakso M, Stefansson K, Pedersen O, Wareham NJ, Barroso I, Hattersley AT, Collins FS, Groop L, McCarthy MI, Boehnke M, Altshuler D. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet 2008;40:638–645
16. 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;316:1336–1341
17. Hirschhorn JN. Genomewide association studies: illuminating biologic pathways. N Engl J Med 2009;360:1699–1701
18. Florez JC. Newly identified loci highlight beta cell dysfunction as a key cause of type 2 diabetes: where are the insulin resistance genes? Diabetologia 2008;51:1100–1110
19. Cecil JE, Tavendale R, Watt P, Hetherington MM, Palmer CNA. An obesity-associated FTO gene variant and increased energy intake in children. N Engl J Med 2008; 359:2558–2566
20. Lyssenko V, Nagorny CL, Erdos MR, Wierup N, Jonsson A, Spégel P, Bugliani M, Saxena R, Fex M, Pulizzi N, Isomaa B, Tuomi T, Nilsson P, Kuusisto J, Tuomilehto J, Boehnke M, Altshuler D, Sundler F, Eriksson JG, Jackson AU, Laakso M, Marchetti P, Watanabe RM, Mulder H, Groop L. Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. Nat Genet 2009;41:82–88
21. Staiger H, Machicao F, Schafer SA, Kirchhoff K, Kantartzis K, Guthoff M, Silbernagel G, Stefan N, Haring HU, Fritsche A. Polymorphisms within the novel type 2 diabetes risk locus MTNR1B determine beta-cell function. PLoS One 2008;3:e3962
22. Willyard C. Hungry for sleep. Nat Med 2008;14:477–480
23. Nejentsev S, Walker N, Riches D, Egholm M, Todd JA: Rare variants of IFIH1, a gene implicated in antiviral responses, protect against type 1 diabetes. Science 2009;324:387–389
24. Vitart V, Rudan I, Hayward C, Gray NK, Floyd J, Palmer CN, Knott SA, Kolcic I, Polasek O, Graessler J, Wilson JF, Marinaki A, Riches PL, Shu X, Janicijevic B, Smolej-Narancic N, Gorgoni B, Morgan J, Campbell S, Biloglav Z, Barac-Lauc L, Pericic M, Klaric IM, Zgaga L, Skaric-Juric T, Wild SH, Richardson WA, Hohenstein P, Kimber CH, Tenesa A, Donnelly LA, Fairbanks LD, Aringer M, McKeigue PM, Ralston SH, Morris AD, Rudan P, Hastie ND, Campbell H, Wright AF. SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. Nat Genet 2008;40:437–442
25. Koontz JI, Soreng AL, Nucci M, Kuo FC, Pauwels P, van Den Berghe H, Dal Cin P, Fletcher JA, Sklar J. Frequent fusion of the JAZF1 and JJAZ1 genes in endometrial stromal tumors. Proc Natl Acad Sci U S A 2001;98:6348–6353
26. Frayling TM, Colhoun H, Florez JC. A genetic link between type 2 diabetes and prostate cancer. Diabetologia 2008;51:1757–1760
27. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, Yu K, Chatterjee N, Welch R, Hutchinson A, Crenshaw A, Cancel-Tassin G, Staats BJ, Wang Z, Gonzalez-Bosquet J, Fang J, Deng X, Berndt SI, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cussenot O, Valeri A,

Andriole GL, Crawford ED, Tucker M, Gerhard DS, Fraumeni JF Jr, Hoover R, Hayes RB, Hunter DJ, Chanock SJ. Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet 2008;40:310–315
28. Johansson A, Marroni F, Hayward C, Franklin CS, Kirichenko AV, Jonasson I, Hicks AA, Vitart V, Isaacs A, Axenovich T, Campbell S, Dunlop MG, Floyd J, Hastie N, Hofman A, Knott S, Kolcic I, Pichler I, Polasek O, Rivadeneira F, Tenesa A, Uitterlinden AG, Wild SH, Zorkoltseva IV, Meitinger T, Wilson JF, Rudan I, Campbell H, Pattaro C, Pramstaller P, Oostra BA, Wright AF, van Duijn CM, Aulchenko YS, Gyllensten U; EUROSPAN Consortium. Common variants in the JAZF1 gene associated with height identified by linkage and genome-wide association analysis. Hum Mol Genet 2009;18:373–380
29. Burch LR, Zhou K, Donnelly LA, Doney AS, Brady J, Goddard C, Morris AD, Hansen MK, Palmer CNA. A single nucleotide polymorphism on exon-4 of the gene encoding PPARdelta is associated with reduced height in adults and children. J Clin Endocrinol Metab 2009;94:2587–2593
30. Bonnefond A, Vaxillaire M, Labrune Y, Lecoeur C, Chèvre J-C, Bouatia-Naji N, Cauchi S, Balkau B, Marre M, Tichet J, Riveline J-P, Hadjadj S, Gallois Y, Czernichow S, Hercberg S, Kaakinen M, Wiesner S, Charpentier S, Lévy-Marchal C, Elliott P, Jarvelin M-R, Horber F, Dina C, Pedersen O, Sladek R, Meyre D, Froguel P. Genetic variant in *HK1* is associated with a proanemic state and A1C but not other glycemic control–related traits. Diabetes 2009;58:2687–2697
31. Valentine WN, Oski FA, Paglia DE, Baughan MA, Schneider AS, Naiman JL. Hereditary hemolytic anemia with hexokinase deficiency: role of hexokinase in erythrocyte aging. N Engl J Med 1967;276:1–11
32. Beutler E. G6PD deficiency. Blood 1994;84:3613–3636
33. Keitt AS. Pyruvate kinase deficiency and related disorders of red cell glycolysis. Am J Med 1966;41:762–785