OBJECTIVE—MBL2 encodes the mannose-binding lectin, which is a key player in the innate immune system and has recently been found to play a role in insulin resistance and development of type 1 diabetes and gestational diabetes mellitus. To assess the role of MBL2 in diabetes susceptibility, this gene was analyzed in the Pima Indian population, which has a high prevalence of type 2 diabetes.

RESEARCH DESIGN AND METHODS—Nineteen tag single nucleotide polymorphisms (SNPs) were genotyped in a population-based sample of 3,501 full-heritage Pima Indians, and selected SNPs were further genotyped in independent samples of Native American (n = 3,723) and Old Order Amish (n = 486) subjects.

RESULTS—Two variants, a promoter SNP (rs11003125) at −550 bp with a risk allele frequency of 0.77 and a Gly54Asp (rs1800450) with a risk allele frequency of 0.83, were associated with type 2 diabetes in the full-heritage Pima Indians (odds ratio 1.30 per copy of the G allele for rs11003125, P = 0.0007, and 1.30 per copy of the glycine allele for rs1800450, P = 0.002, adjusted for age, sex, birth year, and family membership). These associations replicated in an independent Native American sample (1.19, P = 0.04, for rs11003125) and a Caucasian sample, the Old Order Amish (1.51, P = 0.004, for rs11003125 and 2.38, P = 0.003, for rs1800450). Among Pima Indians with normal glucose tolerance, the diabetes risk allele glycine of Gly54Asp was associated with a decreased acute insulin response to an intravenous glucose bolus infusion (P = 0.004, adjusted for age, sex, percent body fat, glucose disposal under physiological insulin stimulation, and family membership).

CONCLUSIONS—Our data suggest that the functional variants in MBL2 contribute to type 2 diabetes susceptibility in both Native Americans and the Old Order Amish. Diabetes 59: 2080–2085, 2010

Mannose-binding lectin (MBL) is a liver-derived serum lectin involved in the innate immune defense. Upon binding to specific carbohydrate structures on various microorganisms, MBL may utilize MBL serine protease (MASP)-2 to activate the third pathway of complement (lectin pathway) and thereby opsonophagocytosis (1).

Serum MBL levels have been shown to be strongly correlated with the presence of variants within the MBL2 gene. Missense polymorphisms at codon 54 (resulting in a glycine to aspartic acid), codon 57 (resulting in a glycine to glutamic acid), and codon 52 (resulting in an arginine to cysteine) impair oligomer formation, leading to reduced serum levels of functional MBL. In addition, three promoter polymorphisms at position −550 bp G > C (H/A), −221 bp G > C (Y/X) and +4 bp C > T (P/Q) influence the expression of MBL2 (1–3).

Deficiency of MBL has been associated with immunodeficiency, autoimmune disorders such as systemic lupus erythematosus, and rheumatoid arthritis (4,5). Recent studies have further implicated MBL deficiency in the development of type 1 diabetes (6), gestational diabetes mellitus (7), diabetic nephropathy (8), and insulin resistance and obesity (9). Based on the biological role of MBL2, this gene was investigated as a potential susceptibility gene for type 2 diabetes in Pima Indians.

RESEARCH DESIGN AND METHODS—Subjects in the present study are part of a longitudinal study of the etiology of type 2 diabetes among the Gila River Indian Community in Arizona, where most of the residents are Pima Indians or of the closely related Tohono O’odham tribe. Diabetes status was determined by an oral glucose tolerance test according to the criteria of the World Health Organization (10). The initial genetic study was conducted in a population-based sample of full-heritage Pima Indians (n = 3,501), where 1,561 subjects had type 2 diabetes (37% male, age at the last exam 49 ± 14 years, and BMI 39 ± 8 kg/m²) and 1,940 subjects were nondiabetic (46% male, age at the last exam 31 ± 15 years, and BMI 36 ± 8 kg/m²). Independent replication was assessed in 3,723 subjects from the same longitudinal study who were of mixed Native American heritage (reported heritage, on average, was one-half Pima and three-quarters Native American). The replication sample had 750 subjects with type 2 diabetes (41% male, age at the last exam 42 ± 14 years, and BMI 38 ± 9 kg/m²) and 2,973 nondiabetic subjects (47% male, age at the last exam 24 ± 11 years, and BMI 34 ± 8 kg/m²). Additional replication was assessed in a case-control sample from the Old Order Amish (139 diabetic subjects and 347 subjects with normal glucose tolerance) as previously described (11).

Metabolic quantitative traits. Among the full-heritage Pima Indians, 415 subjects (58% male, age 27 ± 6 years, and BMI 34 ± 8 kg/m²) had undergone detailed metabolic testing for risk factors that predict type 2 diabetes. These individuals were determined to be nondiabetic, and acute insulin response was only analyzed in subjects who had normal glucose tolerance. Glucose tolerance was determined by a 75-g oral glucose tolerance test (OGTT) with measurements of fasting and 30, 60, 120, and 180-min plasma glucose and insulin levels.
insulin concentrations (12). The acute insulin response to intravenous glucose was measured on a separate day from the OGTT. Blood samples were collected prior to a 25-g glucose intravenous bolus infusion and at 3, 4, 5, 6, 8, and 10 min after infusion. The acute insulin response was calculated as the mean increase in plasma insulin concentrations from 3–5 min (13). Insulin sensitivity was assessed using the hyperinsulinenemic-euglycemic clamp technique as previously described (12,13). Body composition was estimated by underwater weighing until January 1996 and by dual-energy X-ray absorptiometry (DXP-1; Lunar Radiation) thereafter (14).

SNP identification and genotyping. DNA from 24 Pima Indians (12 non-diabetic and aged $\sim$45 years; 12 diabetic with onset age $<25$ years) was sequenced using a Big Dye terminator (Applied Biosystems) on an automated DNA capillary sequencer (model 3730; Applied Biosystems). Genotyping was done using the SNPlex genotyping system 48-plex (Applied Biosystems) on an automated DNA capillary sequencer (model 3730; Applied Biosystems) for the Native American samples and Taqman genotyping assays (Applied Biosystems) for the Old Order Amish samples.

Statistical analysis. In the Pima study, statistical analyses were performed using the software of the SAS Institute (Cary, NC). The general association of genotypes with type 2 diabetes was assessed by logistic regression analysis and was adjusted for covariates (age, sex, and birth year). The model was fit with a generalized estimating equation technique to account for correlation among siblings. Genotype was analyzed as a numeric variable representing the number (0, 1, 2) of copies of a given allele. The association of quantitative traits with genotypes was analyzed by linear regression using the generalized estimating equation procedure to account for correlation among siblings. $P$ values were adjusted for potential confounding covariates. In the replication study, which included individuals of mixed ancestry, the individual estimate of European admixture was also used as a covariate. These estimates were derived by the method of Hanis et al. (15) from 39 informative markers with large differences in allele frequency between populations (16). Linkage disequilibrium (LD) and haplotype blocks were estimated by Haplovie (version 3.32).

For the Amish study, the odds ratio (OR) is derived from a logistic regression model, while the $P$ value is based on the normal-liability threshold model implemented in SOLAR to account for relationships among individuals. CIs (and the approximate SE) are test based (17,18).

RESULTS AND DISCUSSION

Sequencing of the $MBL2$ gene (all four exons, three introns, and $\sim$2 kb of the upstream region) in 24 Pima Indians identified 37 variants. Three were previously known variants which predicted missense substitutions—rs5030737 (Arg52Cys), rs1800450 (Gly54Asp), and rs1800451 (Gly57Glu)—which predicted missense substitutions—rs5030737 and rs11003125 (intron 2). The $MBL2$ gene (all four exons, three introns, and 7 flanking) were sequenced in 24 Pima Indians (12 nondiabetic and aged $\sim$45 years; 12 diabetic with onset age $<25$ years) was sequenced using a Big Dye terminator (Applied Biosystems) on an automated DNA capillary sequencer (model 3730; Applied Biosystems). Genotyping was done using the SNPlex genotyping system 48-plex (Applied Biosystems) on an automated DNA capillary sequencer (model 3730; Applied Biosystems) for the Native American samples and Taqman genotyping assays (Applied Biosystems) for the Old Order Amish samples.

To determine whether the association with type 2 diabetes in the full-heritage Pima Indians could be replicated in other Native Americans, rs1800450 and rs11003125 were further genotyped in a nonoverlapping sample of 3,723 subjects who were predominately of mixed Native American heritage. The promoter SNP rs11003125 reproducibly associated with type 2 diabetes ($P = 0.04$, adjusted for age, sex, birth year, and heritage) (Table 1). Combining the initial and replication samples ($n = 7,224$) provided the strongest evidence for association with type 2 diabetes for rs11003125 ($P = 9.2 \times 10^{-6}$) (Table 1). The combined sample also showed a significant association for rs1800450 ($P = 0.001$) (Table 1), but this significant association was largely driven by the initial full-heritage Pima sample, with only a nonsignificant association in the same direction ($P = 0.18$) identified in the largely mixed-heritage replication group.

To determine whether variants in $MBL2$ had a significant effect on diabetes in non–Native American populations, rs1800450 and rs11003125 were genotyped in an Amish sample of 139 diabetic subjects and 347 subjects with normal glucose tolerance. Consistent with the Native American samples, rs11003125 was associated with type 2 diabetes in the Amish (OR 1.51; $P = 0.004$, adjusted for age, sex, and family structure) (Table 2), but the frequency of risk allele G was lower in the Amish than in Pima Indians (0.45 vs. 0.77, respectively). The SNP rs1800450 (Gly54Asp) was also associated with type 2 diabetes in the Amish (OR 2.38, adjusted $P = 0.003$) (Table 2), but the frequency of risk allele Glycine was comparable in the Amish and Pima Indians (0.87 vs. 0.83). In contrast, these associations do not appear to replicate in the large Caucasian Diabetes Genetics Replication and Meta-analysis (DIAGRAM) (19). Neither of these SNPs were directly genotyped in genome-wide association (GWA) studies from the Diabetes Genetics Initiative (DGI) and the Wellcome Trust Case Control Consortium (WTCCC), which are two of the three large studies from which the meta-analysis was derived; however, a proxy, rs1838065, which we determined to have an $R^2 = 1$ with rs11003125 (based on our genotyping of 90 Caucasians), was not associated with type 2 diabetes in DIAGRAM ($P = 0.35$, Table 2).

Combining the negative DIAGRAM data together with the positive Amish and Native American data rendered the overall combined association nonsignificant ($P = 0.17$) (Table 2).

Data across a larger genomic region encompassing $MBL2$ could also be obtained from prior GWA studies in Pima Indians (20), DGI (21), WTCCC (22), and DIAGRAM (19). For example, a $\sim$400 kb region encompassing the $\sim$8.3 $Mb$ $MBL2$ (chromosome 10: 54007027–54401287) yielded 101 SNPs that were previously genotyped in a GWA study of Pima Indians. Only one GWA study SNP (rs1838065) was located within $MBL2$ (intron 2). The pairwise LD pattern of these 101 SNPs and their association with early-onset type 2 diabetes in Pima subjects who were analyzed in this prior GWA study (300 early-onset diabetes case and 334 control subjects) are shown in supplementary Fig. 2A and B. GWA study SNP rs1838065, which is in near-perfect LD with the promoter rs11003125 ($R^2 = 0.99$), was associated with early-onset type 2 diabetes (defined as diabetes onset $\leq 25$ years of age) in the GWA study (adjusted $P = 0.0006$), as were several nearby GWA study SNPs (adjusted $P = 0.0007–0.005$) (supplementary Fig. 2), which were in high LD among themselves ($R^2 = 0.66–0.99$) but in low LD with rs1838065 ($R^2 = 0.30–0.37$). In
contrast with rs1838065, these additional GWA study SNPs (tagged by rs920727) had only a borderline association therefore uninformative in full-heritage Pima Indians, while SNP rs11003132, which had a borderline significance with type 2 diabetes in Pima Indians (Table 1), was not associated with type 2 diabetes in Pima Indians (Table 1).

TABLE 2
Association of promoter rs11003125 and rs1800450 (Gly54Asp) with type 2 diabetes in Pima Indian, Amish, and DIAGRAM subjects

| SNP      | Location | Risk/ non-risk | OR (95% CI) | P     | P_{het} | OR (95% CI) | P     | P_{het} |
|----------|----------|----------------|-------------|-------|---------|-------------|-------|---------|
| rs1800450| Gly54Asp (A/C) | G/A          | 0.83 (1.10–1.53) | 0.002 | 0.83 (1.09–1.40) | 0.18 | 1.24 (1.09–1.40) | 0.001 |
| rs5030737 | Arg52Cys (A/D) | C/T          | 0.99 (0.47–8.06) | 0.35  | 0.91 (0.80–1.39) | 0.69 | 1.13 (0.91–1.41) | 0.28  |
| rs7095891 | Promoter (P/Q) | C/T          | 0.97 (0.88–1.88) | 0.19  | 0.91 (0.80–1.39) | 0.69 | 1.13 (0.91–1.41) | 0.28  |
| rs7096206 | Promoter (Y/X) | G/C*         | 0.99 (0.92–5.21) | 0.07  | 0.68 (1.01–1.41) | 0.04 | 1.25 (1.12–1.40) | 9.2 × 10^{-5} |

Nineteen tag SNPs (R^2 ≥ 0.8) were selected from 57 SNPs that span MBL2 (~8.3 kb) and approximately 25 kb flanking each side of the gene. Allele frequency (AF) is presented as frequency of the risk allele. OR is expressed as per copy of the risk allele (and thus, by definition, is >1). The risk allele is underlined where the P value is ≤ 0.05. *Genotypes were determined according to the reverse strand of the SNP database sequence. Sequences flanking the two novel SNPs are as follows: novel: promoter, tttcatggatgggtgtgtgc; novel: 3’UTR, catgactgcagtagtact [g/a]ctgtttataaacattgtat.
The observation that specific MBL2 SNPs had replicated associations with type 2 diabetes in Native Americans and a small group of Amish subjects, who are of European descent but were not associated with diabetes in the large DIAGRAM, is unexpected. It is possible that the association in the Amish is a false positive. Alternatively, both the Pima Indians and the Old Order Amish represent far more homogeneous populations compared with the study population of DIAGRAM. It is also possible that susceptibility genes for common diseases may have larger effects in these populations compared with others as a result of segregation of high-penetrance alleles that are rare or nonexistent in the general population, gene-gene or gene-environment interactions, or the absence of other susceptibility genes whose effects could mask other genes.

To aid in validating the positive associations with type 2 diabetes, we further investigated whether these variants in MBL2 were associated with metabolic risk factors that predict type 2 diabetes among 415 nondiabetic, full-heritage Pima Indians. For both rs11003125 and rs1800450, the allele associated with higher risk for diabetes (G and glycine, respectively) was associated with a higher 2-h plasma glucose concentration (adjusted \( P = 0.0005 \) and 0.04, respectively) and higher 2-h plasma insulin concentration (adjusted \( P = 0.0008 \) and 0.003, respectively) during an oral glucose tolerance test (Table 3). The risk allele glycine for rs1800450 was additionally associated with a lower acute insulin response to an intravenous glucose bolus infusion (adjusted \( P = 0.004 \)) among subjects who had normal glucose tolerance (\( n = 281 \)) (Table 3). However, neither SNP was associated with insulin-stimulated glucose uptake.

Previous functional studies have shown that serum MBL levels are greatly influenced by variants within the MBL2 gene. Three promoter variants (rs11003125 [H/A], rs7096206 [Y/X], and rs7095891 [P/Q]) and three missense variants (rs5030737 [A/D], rs1800450 [A/B], and rs1800451 [A/C]) were previously associated with MBL deficiency (3,23). Several of these variants are in high LD, so a limited number of haplotypes are present in humans. HTPA (G-G-C-Gly) haplotype carriers have the highest serum concentration of MBL, typically from 1,400 to 2,500 \( \mu \)g/l, whereas LYPB (C-G-C-Asp) haplotype carriers have the lowest serum concentration: 20–400 \( \mu \)g/l (3,20). Since rs7096206 (Y/X) and rs7095891 (P/Q) are very rare in Pima Indians (minor allele frequency <0.03), these high versus low serum level haplotypes can essentially be determined from a two-SNP haplotype of the promoter rs11003125 (H/I) and missense rs1800450 (A/B) in Pima Indians.

Haplotype analysis for rs11003125 and rs1800450 was performed in the combined sample of 7,224 predominately Pima Indians. The haplotype G-glutamine (HA), carrying both the G nucleotide (designated H allele) of the promoter rs11003125 and glycine (designated A allele) of rs1800450, was associated with increased risk for type 2 diabetes in Pima Indians (haplotype frequency of G-glutamine 0.78 in diabetic vs. 0.71 in nondiabetic; OR 1.25 [95% CI 1.12–1.33], \( P = 0.0001 \), adjusted for age, sex, and birth year [heritage estimate in the replication group]). Because this haplotype G-glutamine is highly concordant with the G (H) allele of rs11003125 \( (R^2 = 0.99) \), it is difficult to statistically distinguish the single genotypic versus haplotypic effects. When both SNPs are included in a single model, there is a significant association with rs11003125 (OR 1.29 [95% CI 1.08–1.54]; \( P = 0.005 \)) conditional on the effect at rs1800450, but there is little association with rs1800450.
conditional on the effect at rs1103125 (0.94 [0.77–1.16]; P = 0.61). It thus appears that the promoter rs11003125 is the stronger predictor of diabetes, with little additional information from rs1800450.

The prevalence of type 2 diabetes was plotted in the full-heritage Pima Indian (n = 3,081) (Fig. 1A) and the replication Native American (n = 3,504) (Fig. 1B) groups according to the genotypes of rs11003125 and rs1800450. Ordering the genotypic groups according to their association with serum MBL levels showed that subjects homozygous for both G and glycine alleles had a higher prevalence of diabetes than did subjects homozygous for the C allele and either homozygous or heterozygous for the aspartic acid alleles (P_trend = 8.4 × 10^{-5} in the combined analysis of 6,585 predominately Pima subjects, adjusted for age, sex, and birth year, and in the replication group, heritage). In Caucasians, Eskimos, Africans, South Americans, and Native Americans, the G-glycine (HA) haplotype is associated with higher MBL serum level (3,24–26).

The present study demonstrates that an allele for MBL2, which arises predominately from the promoter SNP rs11003125 (G allele), predicts a higher serum level of MBL2 and is associated with increased risk for type 2 diabetes, increased 2-h plasma glucose and 2-h plasma insulin, and decreased insulin secretion in some populations. Consistent with our observations, high MBL2 levels have recently been reported to be associated with high A1C levels in the Strong Heart Study, a longitudinal study of cardiovascular disease among Native Americans (26). SNP rs11003125 is in high LD with other SNPs that map within intron 2 and a flanking region of MBL2; therefore, the contribution of other functional SNPs cannot be ruled out. Nevertheless, both high LD and diabetes association were restricted to the region in and near MBL2, suggesting that evidence for association with type 2 diabetes is more likely derived from MBL2 rather than other genes in the region.

Although the physiologic mechanisms underlying the association of MBL2 levels with diabetes are unknown, it has previously been shown that MBL2 plays a dual role in modifying inflammatory responses (27). Deficiency of MBL has been linked to increased risk of developing type 1 diabetes (6), insulin resistance, and obesity (9) as a result of a chronic infectious state or low-grade inflammation. MBL2 could also affect metabolic pathways through stimulating fatty acid oxidation in skeletal muscle (28) or reducing release of tumor necrosis factor-α, interleukin-1, and interleukin-6 (29). In contrast, increased MBL levels could lead to an overly activated complement system, thereby inducing inflammatory damage or interweaving a complex autoimmune process (30). Consistent with the latter effect, high MBL levels have been associated with increased risk for insulin resistance in pregnancy (31) and late-onset of rheumatoid arthritis (5). However, our study indicates that MBL2 variants are more likely to influence type 2 diabetes via an effect on insulin secretion rather than on insulin action, suggesting that inflammatory damage in pancreatic β-cell function may be involved. Additional studies are needed to investigate the impact of this gene on specific type 2 diabetes related–pathways and disease susceptibility in non–Native American groups.

**ACKNOWLEDGMENTS**

This work was supported by the intramural research program of the National Institute of Diabetes and Digestive and Kidney Disease, the National Institutes of Health. The Amish study was supported by National Institutes of Health grants R01 DK54261 and P30 DK072488 (to the Clinical Nutrition Research Unit of Maryland) and P60 DK079637 (to the Baltimore Diabetes Research and Training Center). Li Bian was supported by an ADA mentor grant awarded to Clifton Bogardus.

No potential conflicts of interest relevant to this article were reported.

Yunhua L. Muller researched data, wrote manuscript. Robert L. Hanson reviewed/edited manuscript, contributed to discussion. Li Bian researched data, contributed to discussion. Janel Mack researched data, contributed to discussion. William

**FIG. 1. Prevalence of type 2 diabetes in the full-heritage Pima Indian group (A) (n = 3,081) and the replication mixed heritage group (B) (n = 3,504) according to genotypes of promoter rs11003125 and rs1800450 (Gly54Asp). *Either homozygous or heterozygous for the Asp alleles.**
C. Knowler reviewed/edited manuscript, contributed to discussion. Clifton Bogardus reviewed/edited manuscript, contributed to discussion. Leslie J. Baier wrote manuscript, contributed to discussion.

REFERENCES

1. Dommett RM, Klein N, Turner MW. Mannose-binding lectin in innate immunity: past, present and future. Tissue Antigens 2006;68:193–209
2. Turner MW. The role of mannose-binding lectin in health and disease. Mol Immunol 2003;40:423–429
3. Madsen HO, Garred P, Thielsch JA, Lammi LU, Ryder LP, Sveigaard A. Interplay between promoter and structural gene variants control basal serum level of mannan-binding protein. J Immunol 1995;155:3013–3020
4. Davies EH, Teh LS, Ordí-Ros J, Snowden N, Hillyard MC, Hajeer A, Donn R, Perez-Peñen P, Villardell-Tarres M, Oller W. A dysfunctional allele of the mannose binding protein gene associated with systemic lupus erythematosus in a Spanish population. J Rheumatol 1997;24:485–48
5. Garred P, Madsen HO, Marquart H, Hansen TM, Sørensen SF, Petersen J, Volck B, Sveigaard A, Graudal NA, Rudd PM, Dewk RA, Sin RB, Andersen V. Two edged role of mannose binding lectin in rheumatoid arthritis: a cross sectional study. J Rheumatol 2000;27:26–34
6. Araújo J, Brandão LA, Guimarães RL, Santos S, Falcão EA, Milanesi M, Segur L, Souza PR, de Lima Filho JI, Crovella S. Mannose binding lectin gene polymorphisms are associated with type 1 diabetes in Brazilian children and adolescents. Hum Immunol 2007:68:739–743
7. Megia A, Gallart L, Fernández-Real JM, Vendrell J, Simón I, Gutiérrez C, Richart C. Mannose-binding lectin gene polymorphisms are associated with gestational diabetes mellitus. J Clin Endocrinol Metab 2004;89:5081–5087
8. Østergaard J, Thiel S, Gadjeva M, Hansen TK, Rasch R, and Flyvbjerg A. Mannose-binding lectin deficiency attenuates renal changes in a streptozotocin-induced model of type 1 diabetes in mice. Diabetologia 2007;50:1541–1549
9. Fernández-Real JM, Straczkowski M, Vendrell J, Soriguer F, Pérez Del Pulgar S, Gallart L, López-Bermejo A, Kowalska I, Manco M, Cardona F, García-Gil MM, Mingrone G, Richart C, Ricart W, Zorzano A. Protection from inflammatory disease in insulin resistance: the role of mannose-binding lectin. Diabetologia 2006;49:2402–2411
10. World Health Organization. Report of a WHO Study Group: Diabetes Mellitus. Geneva, Switzerland. Technical Report Series, No. 727, 1985
11. Rampersaud E, Damcott CM, Fu M, Shen H, McArdle P, Shi X, Shelton J, Segat L, Souza PR, de Lima-Filho JL, Crovella S. Mannose binding lectin gene polymorphisms are associated with type 1 diabetes in Brazilian populations. Diabetes 2007;56:3053–3062
12. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus: prospective studies of Pima Indians. N Engl J Med 1993;329:1898–1902
13. Lillioja S, Bogardus C. Obesity and insulin resistance: lessons learned from the Pima Indians. Diabetes/Metab Rev 1988;4:517–540
14. Norman RA, TatRARanni PA, Pratley R, Thompson DB, Hansen RL, Prochazka M, Baier L, Ehn MG, Sacchi H, Foroud T, Garvey WT, Burns D, Knowler WC, Bennett PH, Bogardus C, Ravussin E. Autosomal genomic scan for loci linked to obesity and energy metabolism in Pima Indians. Am J Hum Genet 1998;62:659–68
15. Hanis CL, Chakraborty R, Ferrell RE, Schull WJ. Individual admixture estimates: disease associations and individual risk of diabetes and gallbladder disease among Mexican-Americans in Starr County, Texas. Am J Phys Anthropol 1986;70:433–441
16. Tian C, Hinds DA, Shigeta R, Adler SG, Lee A, Pahl MV, Silva G, Belmont JW, Hanson RL, Knowler WC, Gregersen PK, Ballinger DG, Seldin MF. A genomewide single-nucleotide-polymorphism panel for Mexican American admixture mapping. Am J Hum Genet 2007;80:1014–1023
17. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. Am J Hum Genet 1998;62:1198–1211
18. Danziger CT, Pollin TI, Reinhart LJ, Ott SH, Shen H, Silver KD, Mitchell BD, Shuldiner AR. Polymorphisms in the transcription factor 7-like 2 (TCF7L2) gene are associated with type 2 diabetes in the Amish: Replication and evidence for a role in both insulin resistance and insulin secretion. Diabetes 2006;55:2654–2659
19. Zeggini E, Scott L, Saxena R, Voight BF, for the Diabetes Genetics Replication and Meta-analysis (DAGRAM) Consortium: 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
20. Hanson RL, Bogardus C, Duggan D, Kubes S, Knowlton M, Infante AM, Marovich L, Benitez D, Baier LJ, Knowler WC. A search for variants associated with young-onset type 2 diabetes in American Indians in a 100K genotyping array. Diabetes 2007;56:3045–3052
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, Burt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Alshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Bostrom K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Spielhofer E, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmquist J, Laurila E, Sjogren 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, Soungze C, Gage D, Nizami M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purell S. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 2007;316:1333–1336
22. Zeggini E, Weedon MN, Lidgren CM, Frayling TM, Elliott KS, Lango H, Timpson NJ, Perry JR, Rayner NW, Freathy RM, Barrett JC, Shields B, Morris AP, Eillard S, Groves CJ, Harries LW, Marchini JL, Owen CR, Knight B, Cardon LR, Walker M, Hittman GA, Morris AD, Doney AS, the 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
23. Turner MW. Mannose-binding lectin: the pluripotent molecule of the innate immune system. Immunol Today 1996;17:532–540
24. Kilpatrick DC. Mannan-binding lectin: clinical significance and applications. Biochim Biophys Acta 2002;1572:401–413
25. Madsen HO, Satl MI, Hogh B, Sveigaard A, Garred P. Different molecular events result in low protein levels of mannose-binding lectin in populations from southeast Africa and South America. J Immunol 1998;161:3169–3175
26. Best LG, Pfeuﬀe RE, Decroos S, North KE, Macauley JW, Zhang Y, Lee ET, Howard BV, Unans J, Palmieri V, Garred P. Genetic and other factors determining mannose-binding lectin levels in American Indians: the Strong Heart Study. BMC Med Genet 2009;10:5
27. Garred P, Harboe M, Oettinger T, Koch C, Sveigaard A. Dual role of mannose-binding protein in infections: another case of heterosis? Eur J Immunogenet 1998;24:125–131
28. Pruehs J, Tsao TS, Jaremche S, Ebbets-Reed D, Erickson MR, Yen FT, Bihain BE, Lodish HF. Proteolytic cleavage product of 30-kDa adipocyte mannan-binding protein in infections: another case of heterosis? Eur J Immunogenet 1994;21:125–131
29. Soell M, Lett E, Holveck F, Schoeller M, Wachsmann D, Klein JP. Activation mediated by CD14 antigen, and mannan binding protein inhibits TNF-alpha of human monocytes by streptococcal rhamnose glucose polymers is mediated by CD14 antigen, and mannan binding protein inhibits TNF-alpha release. J Immunol 1996;154:851–860
30. Turner MW, Hannus RM. Mannose-binding lectin: structure, function, genetics and disease associations. Rev Immunogenet 2000;2:305–322
31. Kilpatrick DC. Mannan-binding lectin concentration during normal human pregnancy. Hum Reprod 2000;15:941–943