Genetics of Type 2 Diabetes- A Review Article

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Abstract

Objective: Type 2 diabetes (T2D) as a complex disease is the result of genetically heterogeneous factors and environmental issues interaction. Linkage and small-scale candidate gene studies were successful in identification of genetic susceptibilities of monogenic form of diseases. However, they were largely unsuccessful while applying to the more common forms of disease. By designing Genome Wide Association studies (GWAs), the new windows open to genetic approaches. So far, around 153 variant were discovered for T2D and missing rare variants are waiting to be discovered. The new findings are beneficial to explain molecular signaling and pathways responsible for pathophysiology of T2D, which offered opportunities for the development of novel therapeutic and preventive tactics. The GWAs findings need to be confirmed in on going researches. In this review, we address, genetic susceptibilities related to T2D since 2007. Also challenge advantages and disadvantages of GWAs and discuss about the next confirmatory approaches need to be done.

Keywords: Genome Wide Association Studies, T2D, Insulin resistance, High blood glucose, Re-sequencing.

Introduction

Type 2 diabetes (T2D) is a worldwide concern. Based on International Diabetes Federation, 285 million adults aged 20–79 years suffered from diabetes in 2010. About 60% of them located in Asia. Almost 80% of people with diabetes live in developing countries. Around 95% of diabetic patients suffer from T2D (1-3).Worryingly, new findings show decrease in the onset age of T2D. The disease is more frequently reported among young Africans and Pima Indians (4). T2D in Asia differs from the other world regions; since it has developed in younger age group, and in people with much lower body-

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mass index (BMI) (5). This review will highlight the genetic discoveries of T2D.

T2D and Metabolic traits

T2D is a complex metabolic disease (6). Complex disease like T2D and cancers are the results of both environmental and genetic risk factors and also intrauterine environment. However they do not follow a Mendelian pattern of inheritance and cannot be described by a single gene disorder, so this hypothesis "common illnesses common variants" help to understanding mechanisms of these kind of diseases (7,8).

Environmental factors are largely responsible for T2D. Decreased physical activity and increased fat consumption lead to augmentation of nutrient storage. This kind of Long-term fatty diet is associated not only with the progress of obesity but also with reductions in insulin release (9). Environmental factors will be bolded while the genetic abnormalities already exist. Moreover, changes in the amounts of dietary carbohydrate and fat can affect both insulin sensitivity and insulin release in three days, while obesity does not exist (10). Other environmental condition that should be considered is in utero environment. Poor diet can modify metabolisms, results in a tissue adaptation that favors the storage of nutrients (11). Entirely, these environmental changes and genetic risk factors are responsible for developing T2D.

Studies of first-degree relatives highlight that Insulin resistance and impaired beta cell function are the main complication of diabetes, which leads to high blood glucose (12). Normal glucose homeostasis is conserved by a fine balance between insulin secretion and insulin sensitivity of the peripheral tissues. Insulin resistance is a key feature of the metabolic syndrome and often progresses to T2D. Also Insulin resistance is the main connection between obesity and T2D. Insulin resistance in both of these conditions is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output (13).

Genetics of T2D before GWAs

Uncovering genetic risk factor provided better vision of underlying mechanisms. Genetic studies of T2D before the GWA revolution could be divided in 4 groups; studying the pattern of inheritance, linkage studies, association studies on candidate genes and microarray studies.

The genes involved in monogenic form of diabetes mellitus (MODY, Neonatal diabetes, mitochondrial diabetes and syndromes of severe insulin resistance) were discovered by studying pattern of inheritance. The discovered genes related to beta cell dysfunction in MODY diabetes are; *HNF4A (14-16)*, *GCK (15)*, *PDX1 (16)*, *TCF2 (17)*, *NEUROD1 (18)* and *KLF11 (19)*. The genes; *KCNJ11 (20)*, *ABCC8 (21)*, *EIF2AK3 (20)*, *PLAGL1 (22)*, *HYMA1 (23)*, *PTF1A (24)* and *INS (25)* are reported in monogenic form of Neonatal diabetes which cause beta cell dysfunction. *INSR(26)*and *ACT2* are monogenic cause of insulin resistance in severe insulin resistance syndrome.

Candidate genes, based on their indirect physiologic role, seem to contribute to the disease. Studying variations in candidate genes instead of discovering new pathways leading toT2D, verifies the defined role of genes. These surveys usually have been based on linkage analysis. Since 2006, three studies reported by linkage analysis; amino acid substitution in the nuclear receptor and adipo-genic transcription factors, *PPARγ* (27), Glu23Lys variant in the *KCNJ11* gene associated with insulin signaling(28), polymorphism (K121Q) in the insulin action inhibitor *ENPP1* and *IRS1*, *IRS2* and phosphatidylinositol 3- kinase (29-31). One of the outstanding exception gene discovery by linkage studies is *TCF7L2* that confirmed in later studies (32).

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Table 1. Genetic susceptibilities related to type 2 diabetes since 2007

Year	Locus
2007	IGF2BP2 (47,48), CDKAL1 (47,49,50), SLC30A8 (46-48), CDKN2A/2B (47,49,50), HHEX (46,47), FTO (48,50-52), HNF1B (53), PPARG (47,48), WSF1 (54), TCF7L2 (46-51,55), KCNJ11 (47,48,50)
2008	NOTCH2 (56,57), THADA (56,57), ADAMSTS9 (56,57), JAZF1 (56,57), CDC123/CAMK1D (56,57), TSPAN8/ LGR5 (56,57), WSF1 (56), TCF7L2 (57), KCNQ1 (58), DCD (57), MC4R (59,60), FTO (57)
2009	IRS1 (61), HCCA2 (62), SFRS10 (63), WSF1 (61), CDKAL1 (64), SLC30A8 (64), CDKN2A/2B (64), HHEX (64), TCF7L2 (64,65), KCNJ11 (65), KCNQ1 (64), MTNR1B (66), MC4R (63), FTO (65)
2010	DUSP9 (67), GCKR (68) ,BCL11A (67), G6PC2 (68), ADCY5 (68,69), WFS1 (67), ZBED3 (67), DGKB/TMEM195 (68), GCK (68), KLF14 (67), TP53INP1 (67), GLIS3 (68), TLE4 (CHCHD9) (67), ADRA2A (68,70), CENTD2 (67), CRY2 (68), FADS1 (68), MTNR1B (67,71), HMGA2 (67), HNF1A (67), IGF1 (68), C2CD4A/B (72), PRC1 (67), ZFAND6 (67), PTPRD (71), SRR (71), PROX1 (68), RBMS1/ITGB6 (73), FAM148B (68), PPARG (67), UBE2E2 (72), CDKAL1 (67), JAZF1 (67), SLC30A8 (67,68), CDKN2A/2B (67,72), CDC123/CAMK1D (74), HHEX (67), TCF7L2 (67), KCNQ1 (67,70), SPRY2 (74), FTO (67)
2011	ST6GAL1 (75), C6orf57 (76),VPS26A (75), ARAP1 (77), MADD (77), HNF1A (78), AP3S2 (75), HMG20A (75), VPS13C/C2CD4A/B (77), HNF4A (75)
2012	MACF1 (79), BCL11A (6), GRB14 (6,75), RND3 (80), THADA (81),TMEM163 (82), IGF2BP2 (83), PPARG (81), PSMD6 (84), MAEA (84,85), ANKRD55 (6), CDKAL1 (86), KCNK16 (84), ZFAND3 (84), DGKB (6), GCC1-PAX4 (84), JAZF1 (81), ANK1 (6,85), SLC30A8 (86), CDKN2A/2B (86), GLIS3 (84), TLE1 (6), HHEX (86), TCF7L2 (86), ZMIZ1 (6), KCNQ1 (6), CCND2 (6), HMGA2 (81), KLHDC5 (6), HMG20A (6,86), BCAR1 (6), LAMA1 (86), MC4R (6), CATAD2A/CILP2 (6,81), GIPR (6), PEPD (84), SUGP1/CILP2 (6,81), FITM2-R3HDML-HNF4A (84), FTO (86)
2013	COBLL1 (79), CDKAL1 (87), CDKN2A/B (87), KCNQ1 (87), CDC123/CAMK1D (87), GLIS3 (87), HNF1B (87), DUSP9 (87), GRK5 (87), RASGRP1 (87), SGCG (88), FAM58A (87)
2014	*FAF1 (89), LPP (89), TMEM154 (89), ARL15 (89), HLA-B (90), POU5F1-TCF19 (89), SSR1-RREB1 (89), INS-IGF2 (90), MPHOSPH9 (89)*

Table 2. Related genetic susceptibility associated with glycemic traits

Locus	Trait
SNX7	Fasting proinsulin levels adjusted for fasting glucose (77)
LYPLAL1	Fasting insulin (91)
DPYSL5	Fasting glucose (91)
GIPR	2hglucose/Insulinogenic index/AUCins/gluc/2-h insulin, adjusted for 2h glucose/T2D (69)
IRS1	Fasting glucose/ HOMA-IR, Fasting insulin, CAD (68,91)
SLC2A2	Fasting glucose/ HOMA B/HBA1C (68)
TAF11	Fasting insulin (91)
GRB10	FG, FI (83)
LARP6	Fasting proinsulin levels (77)
SGSM2	Fasting proinsulin levels (77)
VPS13C	2h- glucose/ 2h- insulin, adjust for 2h-glocuse (69)
PDX1-AS1	Fasting glucose (91)
PCSK1	Fasting proinsulin levels/ fasting glucose (77,91)
PDGFC	Fasting insulin (91)
MSMO1	Fasting insulin, insulin resistance (92)
HECTD4/C12orf51	1-h plasma glucose (93)
OR4S1	Fasting glucose (91)
MADD	Fasting glucose/ Fasting proinsulin/HOMA B (68,77)
TCERG1L	Fasting insulin, insulin resistance (92)
PPP1R3B	Fasting glucose (91)
FOXA2/LINC00261	Fasting glucose (91)

Microarray approach is another way of defining genetic variation in T2D. Two discoveries since 2006 are covering here. One of them is defects in skeletal muscle of T2D patients related to decrease in the expression of nuclear-encoded genes (*PGC- 1α* and *PGC-1β*) involved in mitochondrial oxidative phosphorylation (33). The other one is transcription factor *ARNT/Hif1b* that influenced on the expression of many other genes related to insulin pathway and glucose sensing (34).

Overview of GWA studies

Before 2005, family linkage and SNPs-based studies were available for discovering genomic loci having influence on complex disease and traits; however on 2005, a new generation of

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association survey on the entire human genome is called Genome Wide Association study or GWAs founded by National Institutes of Health to cover hundreds to thousands of genotyping (35,36).By 2013, the catalog of published GWAs include near two thousand papers (37).

GWAs, usually are held as case control study and assaying fewer than 100,000 SNPs to more than one million, commonly by the Affymetrix 500k and Illumina HumanHap300 arrays. The accepted threshold for statistical significance in GWAs is $<5*10^{-8}$ (38-40). A precise maps of usual single nucleotide polymorphisms (SNPs) all over the genome and also patterns of linkage disequilibrium, which accomplished by International Hap Map project and affordable High-throughput genotyping technologies and map of copy number variants are the primary requirements for GWA studies (41,42).

GWA studies not only identify genetic associations with observable traits, but also demonstrate gene-gene interactions. It also could be carried out for quantitative traits, which explain underlying physiology of disease (43,44).

Genetic risk factor of T2D:

GWAs have both confirmed known genes and discovered many new susceptible genes for T2D since 2007 (45). The first GWAs for T2D was conducted in French population composed of 661 cases of T2D and 614 non-diabetic controls were genotyped on two genotyping platforms. In total, 392,935 SNPs were analyzed for association with T2D. This study revealed novel and reproducible association signals at *SLC30A8* and *HHEX* and confirmed the famous association at *TCF7L2*. However, *LOC387761, EXT2* associations were not reproducible in follow-up studies (46). Till now around 153 variants, more than 120 loci were identified to be associated with T2D or related traits and many new hints are waiting to be discovered. The summery of GWAs and meta-analysis related to T2D since 2007 are listed in Table 1. There are many other loci, reported to be associated with T2D complication that were listed in Table 2.

Confirmatory of GWAs

However, the loci identified in GWAs range from 10 to 100 kb, did not cover causal variants and genes. Further techniques, including re-sequencing of associated regions can be essential to entirely understand associations (94). In addition, data gathering from different GWAs should be confirmed in re-sequencing, genotyping and bioinformatics studies to elucidate that the results are reproducible in diverse population group and also the function of susceptible new candidate gene become clear (95-97).

Pros and cons of GWAs

Although several predominant limitations of using GWAs exist, GWAs methodologies are used for both monogenic and complex genetic disease. The benefits of GWAs are listed.

- No need to know the biological pathway of disease
- Documents specific genetic associations
- It is likely to discover new candidate genes that is difficult to reach by other approaches
- Provides strong data on sequence and copy-number variations

However, there are some limitations in GWAs

- Detects association related to disease not their causation
- Identifies a specific location in genome not a specific gene. So it could be the coding sequence of protein or sequence between genes that yet dose not assumed to be related to disease. These variants are hard to check by biochemically experimental works (98).
- Defines common variations in society (more that 5% frequency) not rare ones
- Unable to release all interactions between SNPs and SNPs-environment.

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- Requires large sample size to studied and the results need to be reproducible in other populations (98).

Post-GWAs prioritization

Many GWAs have been directed, with the consumption of high-through put and affordable genotyping and next generation sequencing platforms. Therefore, many DNA variants associated with complex traits have been discovered but these are just small proportion of heritability related to these diseases. Variants with frequencies less than 5% and variants with small effect size that sharply influence the mechanisms of disease are undiscovered. So many chips are design to fine map certain genomic region. Also a number of whole exome sequencing created to find rare variant. To raise the power, meta-analysis studies are designed. In this way so many other gaps are discovered (99,100).

Comment and conclusion

Since 2007, GWAs have critical role to uncover genetic risk factors associated toT2D. Around 120 loci related to the disease are discovered. However, much of the risk factors still remain unexplained. This could be due to, not covering every variant in GWA studies. Rare variant may have relatively large effects on T2D which is missing in this kind of studies. And also some risk factors are due to epigenetic mechanisms that do not make any changes on genome sequences. Therefore, better understanding T2D not only needs applying many GWAs on different populations and doing meta-analysis on them but also needs knowledge of heritability and studying rare variants in different populations. Identification of such rare variants, will require re-sequencing of the entire genome of type 2 diabetes cases and controls. However, the much more important part is to validate GWAs results by re-sequencing on different groups of same population and also diverse population. It seems that discovering mechanisms of complex diseases need a wide-range of further studies.

References

1. Atlas D. International diabetes federation. Hallado en: http://www.idf org/diabetesatlas/5e/es/prologo. 2000.
2. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon K-H, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. Jama. 2009;301(20):2129-40.
3. 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(5):1047-53.
4. Wheeler E, Barroso I. Genome-wide association studies and type 2 diabetes. Briefings in functional genomics. 2011;10(2):52-60.
5. He J, Klag MJ, Whelton PK, Chen J-Y, Qian M-C, He G-Q. Body mass and blood pressure in a lean population in southwestern China. American journal of epidemiology. 1994;139(4):380-9.
6. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segre AV, Steinthorsdottir V, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nature genetics. 2012;44(9):981.
7. Feero WG, Guttmacher AE, Manolio TA. Genomewide association studies and assessment of the risk of disease. New England Journal of Medicine. 2010;363(2):166-76.
8. Riancho JA. Genome-wide association studies (GWAS) in complex diseases: advantages and limitations. Reumatología Clínica (English Edition). 2012;8(2):56-7.
9. Kaiyala KJ, Prigeon RL, Kahn SE, Woods SC, Porte D, Schwartz MW. Reduced β-cell function contributes to impaired glucose tolerance in dogs made obese by high-fat feeding. American Journal of Physiology-Endocrinology And Metabolism. 1999;277(4):E659-E67.
10. Chen M, Bergman R, Porte Jr D. Insulin Resistance and β-Cell Dysfunction in Aging: The Importance of Dietary Carbohydrate. The Journal of Clinical Endocrinology & Metabolism. 1988;67(5):951-7.
11. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. 1992;35(7):595-601.
12. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes research and clinical practice. 2010;87(1):4-14.
13. Reaven GM. Pathophysiology of insulin resistance in human disease. Physiological reviews. 1995;75(3):473-86.
14. Pearson E, Pruhova S, Tack C, Johansen A, Castleden H, Lumb P, et al. Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4α mutations in a large European collection. Diabetologia. 2005;48(5):878-85.

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15. Pruhova S, Ek J, Lebl J, Sumnik Z, Saudek F, Andel M, et al. Genetic epidemiology of MODY in the Czech republic: new mutations in the MODY genes HNF-4α, GCK and HNF-1α. Diabetologia. 2003;46(2):291-5.
16. Shih DQ, Stoffel M. Molecular etiologies of MODY and other early-onset forms of diabetes. Current diabetes reports. 2002;2(2):125-34.
17. Horikawa Y, Iwasaki N, Hara M, Furuta H, Hinokio Y, Cockburn BN, et al. Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. Nature genetics. 1997;17(4):384-5.
18. Kristinsson S, Thorolfsdottir E, Talseth B, Steingrimsson E, Thorsson A, Helgason T, et al. MODY in Iceland is associated with mutations in HNF-1α and a novel mutation in NeuroD1. Diabetologia. 2001;44(11):2098-103.
19. Neve B, Fernandez-Zapico ME, Ashkenazi-Katalan V, Dina C, Hamid YH, Joly E, et al. Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(13):4807-12.
20. Sagen JV, Ræder H, Hathout E, Shehadeh N, Gudmundsson K, Bævre H, et al. Permanent Neonatal Diabetes due to Mutations in KCNJ11 Encoding Kir6. 2 Patient Characteristics and Initial Response to Sulfonylurea Therapy. Diabetes. 2004;53(10):2713-8.
21. Proks P, Arnold AL, Bruining J, Girard C, Flanagan SE, Larkin B, et al. A heterozygous activating mutation in the sulphonylurea receptor SUR1 (ABCC8) causes neonatal diabetes. Human molecular genetics. 2006;15(11):1793-800.
22. Kamiya M, Judson H, Okazaki Y, Kusakabe M, Muramatsu M, Takada S, et al. The cell cycle control gene ZAC/PLAGL1 is imprinted—a strong candidate gene for transient neonatal diabetes. Human molecular genetics. 2000;9(3):453-60.
23. Wintergerst KA, Hargadon S, Hsiang HY. Continuous subcutaneous insulin infusion in neonatal diabetes mellitus. Pediatric diabetes. 2004;5(4):202-6.
24. Sellick GS, Barker KT, Stolte-Dijkstra I, Fleischmann C, Coleman RJ, Garrett C, et al. Mutations in PTF1A cause pancreatic and cerebellar agenesis. Nature genetics. 2004;36(12):1301-5.
25. Lindsay RS, Kobes S, Knowler WC, Bennett PH, Hanson RL. Genome-wide linkage analysis assessing parent-of-origin effects in the inheritance of type 2 diabetes and BMI in Pima Indians. Diabetes. 2001;50(12):2850-7.
26. Pessin JE, Saltiel AR. Signaling pathways in insulin action: molecular targets of insulin resistance. The Journal of clinical investigation. 2000;106(2):165-9.
27. Beamer BA, Chung-Jen Y, Andersen RE, Muller D. Association of the Pro12Ala variant in the peroxisome proliferator-activated (receptor-gamma2) gene with obesity in two caucasian populations. Diabetes. 1998;47(11):1806.
28. Barroso I, Luan Ja, Middelberg RP, Harding A-H, Franks PW, Jakes RW, et al. Candidate gene association study in type 2 diabetes indicates a role for genes involved in β-cell function as well as insulin action. PLoS Biol. 2003;1(1):e20.
29. Almind K, Inoue G, Pedersen O, Kahn CR. A common amino acid polymorphism in insulin receptor substrate-1 causes impaired insulin signaling. Evidence from transfection studies. Journal of Clinical Investigation. 1996;97(11):2569.
30. Almind K, Delahaye L, Hansen T, Van Obberghen E, Pedersen O, Kahn CR. Characterization of the Met326Ile variant of phosphatidylinositol 3-kinase p85α. Proceedings of the National Academy of Sciences. 2002;99(4):2124-8.
31. Pizzuti A, Frittitta L, Argiolas A, Baratta R, Goldfine ID, Bozzali M, et al. A polymorphism (K121Q) of the human glycoprotein PC-1 gene coding region is strongly associated with insulin resistance. Diabetes. 1999;48(9):1881-4.
32. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nature genetics. 2006;38(3):320-3.
33. Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, et al. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1. Proceedings of the National Academy of Sciences. 2003;100(14):8466-71.
34. Gunton JE, Kulkarni RN, Yim S, Okada T, Hawthorne WJ, Tseng Y-H, et al. Loss of ARNT/HIF1β mediates altered gene expression and pancreatic-islet dysfunction in human type 2 diabetes. Cell. 2005;122(3):337-49.
35. Pearson TA, Manolio TA. How to interpret a genome-wide association study. Jama. 2008;299(11):1335-44.
36. Klein RJ, Zeiss C, Chew EY, Tsai J-Y, Sackler RS, Haynes C, et al. Complement factor H polymorphism in age-related macular degeneration. Science. 2005;308(5720):385-9.
37. Hindorff LA, Junkins HA, Hall P, Mehta J, Manolio T. A catalog of published genome-wide association studies. 2011.
38. Manolio TA, Brooks LD, Collins FS. A HapMap harvest of insights into the genetics of common disease. The Journal of clinical investigation. 2008;118(5):1590-605.

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39. Barrett JC, Cardon LR. Evaluating coverage of genome-wide association studies. Nature genetics. 2006;38(6):659-62.
40. Pe'er I, de Bakker PI, Maller J, Yelensky R, Altshuler D, Daly MJ. Evaluating and improving power in whole-genome association studies using fixed marker sets. Nature genetics. 2006;38(6):663-7.
41. Consortium IH. A haplotype map of the human genome. Nature. 2005;437(7063):1299-320.
42. Redon R, Ishikawa S, Fitch KR, Feuk L, Perry GH, Andrews TD, et al. Global variation in copy number in the human genome. nature. 2006;444(7118):444-54.
43. Reiman EM, Webster JA, Myers AJ, Hardy J, Dunckley T, Zismann VL, et al. GAB2 alleles modify Alzheimer's risk in APOE ε4 carriers. Neuron. 2007;54(5):713-20.
44. Lyssenko V, Nagorny CL, Erdos MR, Wierup N, Jonsson A, Spégel P, et al. Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. Nature genetics. 2009;41(1):82-8.
45. Han X, Luo Y, Ren Q, Zhang X, Wang F, Sun X, et al. Implication of genetic variants near SLC30A8, HHEX, CDKAL1, CDKN2A/B, IGF2BP2, FTO, TCF2, KCNQ1, and WFS1 in type 2 diabetes in a Chinese population. BMC medical genetics. 2010;11(1):1.
46. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature. 2007;445(7130):881-5.
47. Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science. 2007;316(5829):1331-6.
48. Zeggini E, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, Lango H, et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science. 2007;316(5829):1336-41.
49. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, Benediktsson R, Jonsdottir T, Walters GB, et al. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. Nature genetics. 2007;39(6):770-5.
50. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. science. 2007;316(5829):1341-5.
51. Burton PR, Clayton DG, Cardon LR, Craddock N, Deloukas P, Duncanson A, et al. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447(7145):661-78.
52. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007;316(5826):889-94.
53. Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nature genetics. 2007;39(8):977-83.
54. Sandhu MS, Weedon MN, Fawcett KA, Wasson J, Debenham SL, Daly A, et al. Common variants in WFS1 confer risk of type 2 diabetes. Nature genetics. 2007;39(8):951-3.
55. Salonen JT, Uimari P, Aalto J-M, Pirskanen M, Kaikkonen J, Todorova B, et al. Type 2 diabetes whole-genome association study in four populations: the DiaGen consortium. The American Journal of Human Genetics. 2007;81(2):338-45.
56. Lyssenko V, Jonsson A, Almgren P, Pulizzi N, Isomaa B, Tuomi T, et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. New England Journal of Medicine. 2008;359(21):2220-32.
57. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, et al. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nature genetics. 2008;40(5):638-45.
58. Yasuda K, Miyake K, Horikawa Y, Hara K, Osawa H, Furuta H, et al. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. Nature genetics. 2008;40(9):1092-7.
59. Willer CJ, Sanna S, Jackson AU, Scuteri A, Bonnycastle LL, Clarke R, et al. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. Nature genetics. 2008;40(2):161-9.
60. Chambers JC, Elliott P, Zabaneh D, Zhang W, Li Y, Froguel P, et al. Common genetic variation near MC4R is associated with waist circumference and insulin resistance. Nature genetics. 2008;40(6):716-8.
61. Rung J, Cauchi S, Albrechtsen A, Shen L, Rocheleau G, Cavalcanti-Proença C, et al. Genetic variant near IRS1 is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. Nature genetics. 2009;41(10):1110-5.
62. Kong A, Steinthorsdottir V, Masson G, Thorleifsson G, Sulem P, Besenbacher S, et al. Parental origin of sequence variants associated with complex diseases. Nature. 2009;462(7275):868-74.
63. Thorleifsson G, Walters GB, Gudbjartsson DF, Steinthorsdottir V, Sulem P, Helgadottir A, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nature genetics. 2009;41(1):18-24.

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64. Takeuchi F, Serizawa M, Yamamoto K, Fujisawa T, Nakashima E, Ohnaka K, et al. Confirmation of multiple risk Loci and genetic impacts by a genome-wide association study of type 2 diabetes in the Japanese population. Diabetes. 2009;58(7):1690-9.
65. Timpson NJ, Lindgren CM, Weedon MN, Randall J, Ouwehand WH, Strachan DP, et al. Adiposity-related heterogeneity in patterns of type 2 diabetes susceptibility observed in genome-wide association data. Diabetes. 2009;58(2):505-10.
66. Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, Thorleifsson G, et al. Variants in MTNR1B influence fasting glucose levels. Nature genetics. 2009;41(1):77-81.
67. Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nature genetics. 2010;42(7):579-89.
68. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, et al. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nature genetics. 2010;42(2):105-16.
69. Saxena R, Hivert M-F, Langenberg C, Tanaka T, Pankow JS, Vollenweider P, et al. Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. Nature genetics. 2010;42(2):142-8.
70. Rosengren AH, Jokubka R, Tojjar D, Granhall C, Hansson O, Li D-Q, et al. Overexpression of alpha2A-adrenergic receptors contributes to type 2 diabetes. Science. 2010;327(5962):217-20.
71. Tsai F-J, Yang C-F, Chen C-C, Chuang L-M, Lu C-H, Chang C-T, et al. A genome-wide association study identifies susceptibility variants for type 2 diabetes in Han Chinese. PLoS Genet. 2010;6(2):e1000847.
72. Yamauchi T, Hara K, Maeda S, Yasuda K, Takahashi A, Horikoshi M, et al. A genome-wide association study in the Japanese population identifies susceptibility loci for type 2 diabetes at UBE2E2 and C2CD4A-C2CD4B. Nature genetics. 2010;42(10):864-8.
73. Qi L, Cornelis MC, Kraft P, Stanya KJ, Kao WL, Pankow JS, et al. Genetic variants at 2q24 are associated with susceptibility to type 2 diabetes. Human molecular genetics. 2010;19(13):2706-15.
74. Shu XO, Long J, Cai Q, Qi L, Xiang Y-B, Cho YS, et al. Identification of new genetic risk variants for type 2 diabetes. PLoS Genet. 2010;6(9):e1001127.
75. Kooner JS, Saleheen D, Sim X, Sehmi J, Zhang W, Frossard P, et al. Genome-wide association study in individuals of South Asian ancestry identifies six new type 2 diabetes susceptibility loci. Nature genetics. 2011;43(10):984-9.
76. Sim X, Ong RT-H, Suo C, Tay W-T, Liu J, Ng DP-K, et al. Transferability of type 2 diabetes implicated loci in multi-ethnic cohorts from Southeast Asia. PLoS Genet. 2011;7(4):e1001363.
77. Strawbridge RJ, Dupuis J, Prokopenko I, Barker A, Ahlqvist E, Rybin D, et al. Genome-wide association identifies nine common variants associated with fasting proinsulin levels and provides new insights into the pathophysiology of type 2 diabetes. Diabetes. 2011;60(10):2624-34.
78. Parra E, Below J, Krithika S, Valladares A, Barta J, Cox N, et al. Genome-wide association study of type 2 diabetes in a sample from Mexico City and a meta-analysis of a Mexican-American sample from Starr County, Texas. Diabetologia. 2011;54(8):2038-46.
79. Albrechtsen A, Grarup N, Li Y, Sparsø T, Tian G, Cao H, et al. Exome sequencing-driven discovery of coding polymorphisms associated with common metabolic phenotypes. Diabetologia. 2013;56(2):298-310.
80. Palmer ND, McDonough CW, Hicks PJ, Roh BH, Wing MR, An SS, et al. A genome-wide association search for type 2 diabetes genes in African Americans. PloS one. 2012;7(1):e29202.
81. Saxena R, Elbers CC, Guo Y, Peter I, Gaunt TR, Mega JL, et al. Large-scale gene-centric meta-analysis across 39 studies identifies type 2 diabetes loci. The American Journal of Human Genetics. 2012;90(3):410-25.
82. Tabassum R, Chauhan G, Dwivedi OP, Mahajan A, Jaiswal A, Kaur I, et al. Genome-wide association study for type 2 diabetes in Indians identifies a new susceptibility locus at 2q21. Diabetes. 2012:DB_120406.
83. Scott RA, Lagou V, Welch RP, Wheeler E, Montasser ME, Luan Ja, et al. Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. Nature genetics. 2012;44(9):991-1005.
84. Cho YS, Chen C-H, Hu C, Long J, Ong RTH, Sim X, et al. Meta-analysis of genome-wide association studies identifies eight new loci for type 2 diabetes in east Asians. Nature genetics. 2012;44(1):67-72.
85. Imamura M, Maeda S, Yamauchi T, Hara K, Yasuda K, Morizono T, et al. A single-nucleotide polymorphism in ANK1 is associated with susceptibility to type 2 diabetes in Japanese populations. Human molecular genetics. 2012;21(13):3042-9.
86. Perry JR, Voight BF, Yengo L, Amin N, Dupuis J, Ganser M, et al. Stratifying type 2 diabetes cases by BMI identifies genetic risk variants in LAMA1 and enrichment for risk variants in lean compared to obese cases. PLoS Genet. 2012;8(5):e1002741.
87. Li H, Gan W, Lu L, Dong X, Han X, Hu C, et al. A genome-wide association study identifies GRK5

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and RASGRP1 as type 2 diabetes loci in Chinese Hans. Diabetes. 2013;62(1):291-8.
88. Saxena R, Saleheen D, Been LF, Garavito ML, Braun T, Bjonnes A, et al. Genome-wide association study identifies a novel locus contributing to type 2 diabetes susceptibility in Sikhs of Punjabi origin from India. Diabetes. 2013;62(5):1746-55.
89. Mahajan A, Go MJ, Zhang W, Below JE, Gaulton KJ, Ferreira T, et al. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nature genetics. 2014;46(3):234-44.
90. Ng MC, Shriner D, Chen BH, Li J, Chen W-M, Guo X, et al. Meta-analysis of genome-wide association studies in African Americans provides insights into the genetic architecture of type 2 diabetes. PLoS Genet. 2014;10(8):e1004517.
91. Manning AK, Hivert M-F, Scott RA, Grimsby JL, Bouatia-Naji N, Chen H, et al. A genome-wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance. Nature genetics. 2012;44(6):659-69.
92. Chen G, Bentley A, Adeyemo A, Shriner D, Zhou J, Doumatey A, et al. Genome-wide association study identifies novel loci association with fasting insulin and insulin resistance in African Americans. Human molecular genetics. 2012:dds282.
93. Go MJ, Hwang J-Y, Kim YJ, Oh JH, Kim Y-J, Kwak SH, et al. New susceptibility loci in MYL2, C12orf51 and OAS1 associated with 1-h plasma glucose as predisposing risk factors for type 2 diabetes in the Korean population. Journal of human genetics. 2013;58(6):362-5.
94. Turnpenny PD, Ellard S. Emery's Elements of Medical Genetics: Elsevier/Churchill Livingstone; 2012.
95. Reddy MPL, Wang H, Liu S, Bode B, Reed JC, Steed RD, et al. Association between type 1 diabetes and GWAS SNPs in the southeast US Caucasian population. Genes and immunity. 2011;12(3):208-12.
96. Capasso M, Diskin SJ, Totaro F, Longo L, De Mariano M, Russo R, et al. Replication of GWAS-identified neuroblastoma risk loci strengthens the role of BARD1 and affirms the cumulative effect of genetic variations on disease susceptibility. Carcinogenesis. 2012:bgs380.
97. Ioannidis JP, Thomas G, Daly MJ. Validating, augmenting and refining genome-wide association signals. Nature Reviews Genetics. 2009;10(5):318-29.
98. Ward LD, Kellis M. Interpreting noncoding genetic variation in complex traits and human disease. Nature biotechnology. 2012;30(11):1095-106.
99. Trynka G, Hunt KA, Bockett NA, Romanos J, Mistry V, Szperl A, et al. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. Nature genetics. 2011;43(12):1193-201.
100. Hou L, Zhao H. A review of post-GWAS prioritization approaches. Front Genet. 2013;4:280.

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