Genetics of Type 2 Diabetes: Advances and Future Prospect

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Abstract
Type 2 diabetes (T2D) is a complex metabolic disorder with an increasing incidence worldwide. The disease is characterized by a combination of impairment in insulin secretion from pancreatic beta cells and insulin resistance of peripheral tissues, especially muscle and liver, resulting from interaction between multiple environmental and genetic factors. Life-style changes and obesity are the major causes for the current epidemic of T2D. The rapidly increasing prevalence of Type 2 diabetes makes it a major healthcare problem worldwide. In the developing nations this poses a serious health care burden. In recent years there has been a swing in the onset to younger age group. To date, Genome-Wide Association Scan (GWAS) studies have identified more than 65 common genetic variants associated with T2D or glucose/insulin levels. The recently discovered genes by GWAS suggest a shift from genes involved in insulin action to those involved in insulin secretion, indicating pivotal role of beta-cell dysfunction in the pathogenesis of T2D. However, in most cases the causal variants are not known. Also, the molecular mechanism of the patho-physiology of the disease is still obscure. Functional studies will be required to identify the mechanisms by which the associated signals impair islet function and increase risk of T2D. Understanding the pathophysiology of T2D will provide new and useful information(s) for prevention of the disease and development of new drugs for the treatment of T2D. Pharmacogenetics is another promising clinical application of the genetic findings for T2D. Also, efforts are being made to understand the genetic basis of differences in disease susceptibility by studying the genetic variations among different populations, an area that is important for the future of medicine.

Keywords: Type 2 Diabetes; Genome-wide association scan; Single nucleotide polymorphism; Genetics; Minor allele frequency

Introduction
The more typical, common and multi-factorial form of Type 2 diabetes results from the interaction between environmental risk factors and predisposing genotype (a combination of genetic variants). (T2D) is characterized by insulin resistance in peripheral tissues like muscle, fat and liver coupled with effects of aging, obesity and reduced exercise [1] and dysregulated insulin secretion by pancreatic beta-cells. In T2D, the pancreatic beta cells become progressively less able to secrete sufficient insulin to maintain normal carbohydrate and lipid homeostasis [2].

By the year 2030, Type 2 diabetes is expected to affect an estimated 366 million people of world’s population [3]. The presence of diabetes mellitus is associated with a range of vascular complications such as myocardial infarction, stroke, heart failure, renal failure, angina, and retinopathy leading to a reduced life expectancy and a reduced quality of life. Increasing morbidity and mortality due to type 2 diabetes makes it a major burden on society worldwide. The potential for modifying risk through adequate treatments and lifestyle alterations make the identification of methods for the early detection of persons at greater risk an important public health challenge.

Several risk factors for type 2 diabetes have been identified, including family history, history of gestational diabetes mellitus, age, sex, obesity, central obesity, low physical activity, smoking, diet, ethnicity, elevated blood pressure, dyslipidemia, stress and different drug treatments. Genetic factors are known to play an important part in the development of T2D, as exemplified by rare monogenic subtypes (MODY) [4-7], the difference in concordance rates between monozygotic and dizygotic twins [8-11] and the high prevalence in particular ethnic groups, and its modification by genetic admixture. Ethnic variation of T2D represents strong evidence for the genetic basis of this disease. The maximum prevalence is recorded in Pima Indians from USA and South Sea Island populations (such as Naurus in Polynesia) where it now reaches ~50% [12,13]. However, the role of genetics in the development of diabetes is poorly understood.

Advances in genotyping technology during the last 7 years have facilitated rapid progress in large-scale genetic studies. The progress in the genetic studies of more common forms of T2D had been slow initially. Recently, a number of genes have been reproducibly associated with T2D risk in multiple genome-wide association studies (GWAS) each making a modest contribution to the overall risk. All identified alleles associated with type 2 diabetes risk are common (minor allele frequency \( \text{MAF} > 5\% \)) and have a low penetrance (OR<1.5) in the general population. The role(s) of many of them still needs to be confirmed, and for the majority, the biological and molecular mechanisms are far from being clearly understood.

Although GWAS have greatly improved our understanding of the genetic basis of T2D, most of these studies have been performed in Europeans, and therefore current type 2 diabetes genetic risk models are not likely to be applicable to all populations. The studies involving South Asians are very limited. Inter-population differences in allele frequencies and effect sizes have yielded the discovery of new loci in different populations. There is growing evidence that Asian Indians are at a high risk for T2D compared to other populations. In recent years, India has become ‘diabetes capital’ of the world [14]. According to latest estimates, 61 million people in India alone are currently

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afflicted with T2D, and their number is projected to increase to 101 million by 2030 [3]. The relatively unexplored and high-risk Indian population provides an opportunity for genetic dissection of T2D and other metabolic disorders. Also, India represents one of the largest human diversity, consisting of 4635 culturally and anthropologically well-defined populations with little or no gene flow between them [15].

Studies on non-European populations, especially those with unique demographic and cultural histories, are important for identifying population-specific Linkage Disequilibrium (LD) patterns and environmental factors that may modulate disease risk or protection. Given the existence of marked genetic variability among South Asian communities, in addition to diversity in culture, language, caste system, physical appearance, and diet, they do not constitute a single homogeneous community [16]. Although recent GWAS found T2D associated loci largely similar across populations, a few loci still show differential association/protection in populations with different genetic and racial background [17-20]. Therefore, screening populations with a different genetic and racial background or environmental exposures may improve insights about the disease and genetic risk factors.

Genetics of Type 2 Diabetes

Before GWAS studies

Only a few of genetic variants had been shown to be clearly associated with T2D before Genome-Wide Association Scan (GWAS) studies. These loci were identified via family-based linkage studies and candidate gene analyses. For the common form of T2D, the discovery of Calpain10 (CAPN10) in a Mexican-American population was the first reported success of linkage-positional cloning strategy for the disease. However, the association could not be reliably replicated in other ethnic groups [21-25]. The genome-wide linkage approach also led to the identification of several other loci associated with T2D, the most prominent being the TCF7L2 (transcription factor 7 like 2) gene on chromosome 10q25.3 [26]. Several T2D associated SNPs have been identified in a region of strong linkage disequilibrium within TCF7L2 (odds ratio for T2D of ~1.4 fold per allele).

The starting point for the candidate gene approach is the selection of a particular gene that may have potential implications on a biological function or disease. Defects in genes encoding proteins that play a role in pathways involved in insulin control and glucose homeostasis are excellent candidates for type 2 diabetes mellitus. The candidate gene approach led to the identification of a few genes of which two T2D genes are now considered widely replicated: peroxisome proliferator-activated receptor gamma (PPARG) [27-29], and potassium inwardly rectifying channel, subfamily J, member 11 (KCNJ11) the β-cell potassium channel (Kir6.2) gene [30-32]. Among all T2D susceptibility genes studied before 2006, only two were found to be convincingly associated, P12A variant in PPARG gene (encoding the target for the thiazolidinedione class of drugs used to treat T2D) by Altshuler et al. [28] and E23K in KCNJ11 (which encodes part of the target for another class of diabetes drug, the sulphonylureas) by Gloyn et al. [30]. But these have only modest effect on disease risk (odds ratio ~1.2).

In 2006, deCODE genetics identified common variation in the TCF7L2 gene to have a substantial effect on T2D susceptibility [33]. TCF7L2 encodes a transcription factor that is active in the Wnt-signalling pathway and had no track record as a candidate for T2D. TCF7L2 has been replicated in almost every population examined and, with an OR of about 1.4, represents the strongest T2D susceptibility gene identified so far. The association of TCF7L2 with T2D has been demonstrated in US and Danish subjects [33-35]. The association has also been replicated in diverse subjects of UK [36,37], Amish [38], Finnish [39], French [40], Japanese [41,42], Mexican American [43] origin. Replication of significant associations of ENPP1 with risk of obesity and T2D in some [44,45] but not all [46-49] is intriguing. Further, from large-scale candidate pathway studies two more loci were found to be associated with T2D i.e., WFS1 (Wolfram syndrome1) and HNF1- beta (Hepatocyte nuclear factor 1-beta, also known as TCF2). Common variants in Wolfran syndrome1 (WFS1) gene have been found to confer risk of T2D [50]. Also, variants in HNF1-beta (a transcription factor implicated in pancreatic islet development and function) have been found to be associated to T2D [51].

GWAS studies and beyond

A major breakthrough has been the introduction of the use of genome-wide association scan (GWAS) studies in the year 2007. Substantial advances have been made in the past few years, with genome-wide association scans (GWAS) now allowing unprecedented progress to be made in the understanding of the genetic etiology of several complex diseases, including type 2 diabetes. Initial studies identified T2D-associated variants in loci harboring genes such as solute carrier family 30 (zinc transporter), member 8 (SLC30A8), and two linkage disequilibrium (LD) blocks: insulin degrading enzyme-kinase factor11-hematopoietically expressed homeobox (IDF-KIF11-HHEX) and exostoses (multiple) 2 (EXT2-ALX) [52,53]. Further, association with CDK5 regulatory subunit associated protein 1-like 1 (CDKA1L), insulin like growth factor 2 mRNA-binding protein 2 (IGFBP2), and cyclin-dependent kinase inhibitor 2A/2B (CDKN2A/2B) was also found [54-57]. The strong association found with variants in TCF7L2, CDKAL1 and CDKN2A/2B to that of T2D implicate wnt-signaling pathway and cell-cycle control in the pathogenesis of T2D [58]. Replication of the above six entirely novel T2D susceptibility loci was done in studies involving individuals of both European [59] and Asian [60-63] origin.

Another study using meta-analysis of T2D data found further T2D-associated variants in loci harbouring genes including juxtaposed with another zinc finger gene 1 (JAZF1), cell division cycle 123, calcium/calmodulin-dependent protein kinase 1D (Cdk123, CAMK1D), tetraspanin 8, leucine-rich repeat-containing G protein-coupled receptor 5 (TSPAN8, LGGR5), thyroid adenoma associated thyroid adenoma associated (THADA), ADAM metallopeptidase with thrombospondin type 1 motif, 9 (ADAMT59), and notch gene homolog 2 (NOTCH2) [64,65].

After GWAS in thousands of samples from various populations, enormous amount of data has been generated. The parallel meta-analysis of large association studies was also able to add a few more loci which showed statistical significance with T2D and its traits. The largest meta-analysis for T2D so far was DIAGRAM meta-analysis. The combined genome-wide association data from eight cohorts of European descent for 8130 T2D cases and 38,987 controls was analysed. Overall, 14 signals achieved genome-wide significance, of which, twelve novel associations were identified at BCL11A, ZBED3, KLFL14, TSPAN16, CDCHD9, KCNQ1, CENTD2, HMGA2, HNF1A, ZFAND6, PRC1, DUSP9 and two had been previously reported MTNR1B, IRS1 [66]. With the shift from GWAS to GWAS meta-analysis the number of independent loci showing genome-wide significant associations with T2D was raised from 19 to 44 loci in various populations across the world at the end of year 2011. Genome-Wide Association Studies (GWAS) and subsequent meta-analyses have identified ~65 susceptibility loci for T2D by the end of 2012 that collectively explains only 10% of the disease risk.
T2D loci have also been identified through GWAS of related traits. GWAS analysis of fasting glucose concentrations conducted by the meta-analyses of glucose and insulin-related traits consortium (MAGIC) demonstrated association of adenylate cyclase-5 (ADCY5), prospero-related homeobox-1 (PROX1), glucokinase (GCK), glucokinase regulatory protein (GCKR), and diacylglycerol kinase (DGKB) transmembrane protein-195 (TMEM195) with T2D [67]. Further, GWAS of fasting glucose concentrations have discovered a variant in melatonin receptor 1B (MTNR1B), which was also subsequently found to be associated with T2D [68-70]. Additionally, GWAS for obesity has clearly shown association with fat mass and obesity-associated protein, FTO [71,72]. The advent of GWAS has transformed gene discovery in Type 2 diabetes, with a number of loci identified to date [73-75]. These loci have been identified and confirmed through several GWAS analyses (Table 1). Consistent with the complex nature of physiologic defects in T2D, the genetics of the disorder involves a large number of susceptibility genes each with a relatively small effect. However, interaction with other susceptibility loci and/or environmental factors may result in more substantial effects.

Much work is still needed to translate knowledge of these genes into benefits for the patients. There is need to shift the focus from gene discovery to the questions of epigenetic modifications, the transcriptome, protein structure/function and protein interactions.

<table>
<thead>
<tr>
<th>Year of discovery</th>
<th>Gene/ SNP</th>
<th>Name of the gene(s)</th>
<th>Allele</th>
<th>Chromosome loci</th>
<th>Disease Mechanism</th>
<th>Study</th>
<th>OR (95% CI) Reference</th>
</tr>
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<tbody>
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<td>2000</td>
<td>PPARG/ rs18012824</td>
<td>Peroxisome proliferative activated receptor-v gene</td>
<td>C/G</td>
<td>3p25.2</td>
<td>Insulin sensitivity</td>
<td>GWAS</td>
<td>1.14 (1.08–1.20)</td>
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<td>2003</td>
<td>KCNJ11/ ABCB8/ rs5219 / rs757110</td>
<td>Potassium inwardly-rectifying channel, subfamily J, member 11</td>
<td>T/C G/T</td>
<td>11p15.1</td>
<td>Beta-cell dysfunction</td>
<td>GWAS</td>
<td>1.15 (1.09–1.21)</td>
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<td>T/C</td>
<td>10q25.2</td>
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<td>1.37 (1.28–1.47)</td>
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<td>1.20 (1.14–1.25)</td>
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<td>GWAS</td>
<td>1.12 (1.08–1.16)</td>
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<td>10q23.33</td>
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<td>GWAS</td>
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<td>Insulin-like growth factor 2 binding protein 2</td>
<td>T/G</td>
<td>3q28</td>
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<td>2008</td>
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<td>10p13</td>
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<td>JAZF1/ rs864745</td>
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<td>DGKB-TMEM195/ rs2191349</td>
<td>Diacylglycerol kinase beta-Alkylglycerol monoxygenase</td>
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<td>7p21.2</td>
<td>Decreased β-cell function, increased fasting glucose</td>
<td>GWAS</td>
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</table>
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| Year | Locus | Description | SNP | rs Number | Gene | Chrm | Position | Beta-Cell Dysfunction | Insulin Sensitivity | Function | Analysis | P-value | Study
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<td>12q14.3</td>
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<td>2010</td>
<td>HNF1A</td>
<td>Hepatocyte nuclear factor 1-alpha</td>
<td>T/A</td>
<td>7557197</td>
<td>Hnf1a</td>
<td>12q24.31</td>
<td>Pancreatic and liver transcriptional regulator</td>
<td>GWAS meta-analysis</td>
<td>1.07 (1.05–1.10)</td>
<td>[66]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>ZFAND5</td>
<td>AN1-type zinc finger protein 6</td>
<td>G/A</td>
<td>11634397</td>
<td>Zfand5</td>
<td>15q25.1</td>
<td>Beta-cell dysfunction</td>
<td>GWAS meta-analysis</td>
<td>1.06 (1.04–1.08)</td>
<td>[66]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2010</td>
<td>PRC1</td>
<td>Protein regulator of cytokinesis 1</td>
<td>A/C</td>
<td>8042680</td>
<td>Prc1</td>
<td>15q26.1</td>
<td>Unknown (Cytokinesis regulator)</td>
<td>GWAS meta-analysis</td>
<td>1.07 (1.05–1.09)</td>
<td>[66]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2010</td>
<td>MTNR1B</td>
<td>Melatonin receptor type 1B</td>
<td>G/C</td>
<td>10830963</td>
<td>Mtnr1b</td>
<td>11q14.3</td>
<td>Decreased beta-cell function, increased fasting glucose</td>
<td>GWAS meta-analysis</td>
<td>1.09 (1.06–1.12)</td>
<td>[66,68-70]</td>
<td></td>
<td></td>
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**Table 1:** T2D loci reaching statistical significance identified by GWAS and GWAS meta-analysis.

Current Status in Indian Population

Several lines of evidence from population based studies suggest that Indians are apparently genetically more prone to diabetes and insulin resistance. Also, Asian Indians are more susceptible to developing truncal obesity, which might account for their tendency to insulin resistance referred to as "Asian Indian phenotype" [81-85].

Among all the association studies with T2D in Indian populations [86], TCF7L2 has been shown to be most promising in south Indian [87] and western Indian [88,89] populations, where intronic SNP (rs12255372, rs7903146) show association with T2D. The rs1055080 and (TCC)n repeat polymorphisms of FOXA2 independently influence the risk of type 2 diabetes and affect metabolic traits, with opposing effects, in North India [90]. They have identified common and rare genetic variants with T2D in north-western Indian populations showing higher effect size compared to European populations. We have also shown higher effect size compared to European populations of two of the well established genetic variants in eastern Uttar Pradesh population of India [91].

First GWAS on Indian population for T2D in 12,535 Indians, revealed a new type 2 diabetes associated locus at 2q21, with the lead signal being rs6723108 (odds ratio 1.31; P=3.3x10^-10). Imputation analysis refined the signal to rs998451 (odds ratio 1.56; P=6.3x10^-13) within TMEM163 that encodes a probable vesicular transporter in nerve terminals. TMEM163 variants also showed association with developmental and physiological pathways and systems biology as routes to the application of this knowledge for direct patient benefits. Different bioinformatic and proteomic analysis have found shared molecular pathogenesis with a wide variety of other disorders e.g. neurological disorders [76-78]. Some of the genes found to be associated with T2D also appear to be key players in cancer pathogenesis [79,80]. Thus, we find that high throughput methods like GWAS, bioinformatic and system biology approaches help to generate novel hypotheses and illuminate new aspects of biology.
decreased fasting plasma insulin and homeostatic model assessment of insulin resistance, indicating a plausible effect through impaired insulin secretion. Forty-nine of 36 previously reported signals showed consistency in direction with similar effect sizes in Indians and other previous studies, and 25 of them were also found to be associated (P<0.05) to T2D. Known loci and the newly identified 2q21 locus altogether explained 7.65% variance in the risk of T2D in Indians [19]. The study suggests that common susceptibility variants for T2D are largely same across populations, and also reveals a population specific locus providing further insights into genetic architecture and etiology of T2D.

Recently, replication of Type 2 Diabetes candidate genes variations in three geographically unrelated Indian population groups has been conducted. The study suggests TCF7L2, HHEX, IDE, ENPP1 and FTO as commonly associated T2D susceptibility genes in the three Indian populations. Interaction analyses have shown an increased effect in associations suggesting the importance of gene and pathway based interaction between multiple functionally important genes [92]. Combined meta-analysis in Sikh population (n=7,329; 3,354 case subjects) from India revealed a novel locus associated with T2D at 13q12 represented by a directly genotyped intronic SNP (rs9552911, P=1.82x10^-8) in the SGCG gene. This finding provides new evidence supporting population-specific signal in relation to T2D. This may provide additional insights into T2D pathogenesis [20].

Conclusion
Type 2 Diabetes mellitus is rapidly becoming substantial health issue and therefore a burden on current society. Evidence from several studies indicates that diabetes is a heterogeneous disease. The major issue to address in diabetes biology is to identify the genetic changes in the disease and their occurrence in different populations. Uncovering these genetic changes in diabetes are important in several ways, specifically, (a) defining the mechanistic and functional role of specific genetic alterations; (b) developing potential biomarkers to differentiate high risk from low risk; and (c) testing and designing genetic based strategies against a specific genetic alteration.

Significant advances have been made in recent years in relation to the pathogenesis of T2D. This has significantly improved our knowledge of one of the most serious global health threats, allowing identification of genes and pathways involved in the development and progression of the disease. However, due to the multifactorial nature of the disease, how the identified genes and pathways impact on T2D still remain largely unknown. Understanding the pathogenesis of T2D is necessary to enable the identification of prognostic and predictive biomarkers, as well as new therapeutic targets, which in turn should lead to improved outcomes in affected patients.

A number of studies have demonstrated that common variants with low penetrance have little predictive power [93-98]. In contrast, it has been proposed that accumulation of rare variants with a mildly deleterious effect may substantially increase the relative risk at the individual level. Indeed, with the next generation of sequencing technologies, rare variants may be identified. Such results together with the known common susceptibility variants may increase the discriminative value of genetic risk factors and push the limit towards a threshold acceptable for clinical utility.

Future Perspective
Since 2007, genome-wide association studies (GWAS) have identified more than 65 genetic variants that increase the risk of type 2 diabetes by 10–30% [99,100]. However, the challenge is to investigate the functional consequences of these variants as most of these variants are noncoding variants. Many of the variants identified to date regulate insulin secretion and not insulin action in insulin-sensitive tissues indicating role of beta-cell (dys)function in the pathogenesis of T2D [17-18,57,59,101-103].

Identification of a large number of novel genetic variants increasing susceptibility to type 2 diabetes and related traits opened up opportunity, to translate this genetic information to the clinical practice and possibly improve risk prediction. Genetic testing for the prediction of type 2 diabetes in high risk individuals is currently of little value in clinical practice [104]. The investigations in this direction face limitations in genetic modelling. These limitations include (a) effect size of the genetic loci are usually small, (b) the ability of genetic tests to discriminate are low, (c) the added value of genetic information is smaller compared to the clinical risk factors, (d) clinical relevance of some of the genetic variants in disease prediction is questionable, and (e) appropriate model systems for studying gene-gene and gene-environment interactions in the risk prediction is still lacking. Use of new high-throughput sequencing techniques may be useful in identification of low-frequency and rare variants with large effect size. Investigations in non-European ancestry populations will be more useful in identification of new variants critical in T2D prediction, since for genetic risk prediction and for targeted disease therapy how much genetic risk loci can be translated between different ethnicities is vital. Also, epigenetic and structural variation studies can identify new variants that may be important in T2D disease prediction. There is urgent need of developing new statistical methods that can be applied in gene-gene and gene-environment interaction studies in large populations [98].

In a systematic review by Maruthur et al. [105], based on 34 articles on the pharmacogenetics of diabetes medications, evidence of biologically plausible pharmacogenetic interactions for metformin, sulfonylureas, repaglinide, pioglitazone, rosiglitazone, and acarbose, were identified with several studies reporting statistically significant interactions between genetic variants and medications for glycemic outcomes. These results require confirmation in future studies to determine if an individual’s genetic information can be used to individualize the choice of prediabetes and diabetes pharmacologic management.

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