Genetics of Diabetes: An Overview

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CHAPTER OUTLINE

INTRODUCTION

Diabetes mellitus is a heterogeneous disease, with two principal forms. Type 1 presents abruptly in the first two decades of life, is usually found in patients who are lean, and is often caused by autoimmune destruction of pancreatic β-cells. Type 2 Diabetes mellitus usually becomes manifest in adulthood, is associated with obesity and does not require insulin treatment for survival.

Family history is an important risk factor for the development of both type 1 and type 2 diabetes mellitus. The sibling of a patient with type 1 diabetes has a 15-fold higher risk of developing the disease (6%) than does an unrelated individual (0.4%).[1] In Type 2 diabetes the absolute risk of siblings is 30%~40%, as compared to a population prevalence of 7%. In both type 1 and type 2 diabetes, the rates of concordance are much higher for monozygotic as compared to dizygotic twins.[2,3]

GENETICS OF TYPE 1 DIABETES

Type 1 diabetes mellitus results from selective destruction of the insulin-producing β cells in the pancreatic islets of Langerhans, a process that is immunologically mediated and occurs in genetically susceptible individuals. The current concept is that the islet β cells are destroyed by an autoimmune response mediated by T-lymphocytes (T cells) that react specifically to one or more β cell proteins (autoantigens). Thus genetic factors play a significant role in the autoimmune pathogenesis of type 1 diabetes. However, there seems to exist a delicate balance between genetic factors, environmental factors, in addition to immune regulation and chemical mediators. Thus the appearance of diabetes is influenced by the net effects of genetic and environmental factors on immuno regulatory responses.

Nearly 20 different regions of the human genome have been shown to be linked with type 1 diabetes.

Table 1. Genetics of Type 1 Diabetes

1.	HLA REGION
	DP
	DQ
	DR --- DR3 Allele – Significant risk
	DR4 Allele – Significant risk
2.	NON HLA RELATED GENES
	T Cell receptor genes
	Immunoglobulin genes
	CD 4 genes
	Vitamin D receptor genes

Table 2. Loci in the Human Genome Associated with Type 1 Diabetes with Associated Chromosome Location and Candidate Genes or Microsatellite Markers

Name	Chromosome location	Candidate genes or microsatellites
IDDM1	6p21	HLA-DQ/DR
IDDM2	11p15	Insulin VNTR
IDDM3	15q26	D15s107
IDDM4	11q13	MDU1, ZFM1, RT6, FADD/MORT1, LRP5
IDDM5	6q25	ESR, MnSOD
IDDM6	18q21	D18s487, D18s64,JK(kidd locus)
IDDM7	2q31	D2s152, IL-1, NEUROD, GALNT3
IDDM8	6q27	D6s264, D6s446, D6s281
IDDM9	3q21-q25	D3s1303
IDDM10	10p13- q11	D10s193, D10s208, D102588
IDDM11	14q24-q31	D14s67
IDDM12	2q33	CTLA-4, CD28
IDDM13	2q34	D2s137, D2s164, IGFBP2, IGFBP5
IDDM14	2q34-35	NCBI # 3413
IDDM15	6q21	D6s283, D6s434, D6s1580
IDDM16	14q32	NCBI # 3415
IDDM17	10q25	D10s1750 - D10s1773
IDDM18	5q33- 34	ILI2B

These can be broadly classified as HLA region related and non HLA related genes as shown in Table 1. The details of some of these subtypes now called as IDDM 1, IDDM 2, etc. are given in Table 2.

Most interest has focused on genes encoded within the HLA region (whose contribution to disease risk is now designated as IDDM 1),and this still appears to be the most powerful determinant of genetic susceptibility to the disease accounting for around 40% of familial inheritance.[4] The contribution of several other genes are minor, accounting for only a small part of the total genetic predisposition.

The role of the Human Leukocyte Antigen (HLA) gene region in immune regulation, and ready availability of serological markers, led investigators to discover the association between certain HLA alleles and type 1 DM in the early 1970s. The major genetic susceptibility locus for type 1 DM is localized within the HLA region on the short arm of chromosome 6.[5-7] Figure 1 shows a map of the HLA region. The global importance of HLA on type 1 has since been confirmed in genome-wide scans for linkage.[8,9]

The complexity of the HLA genes has made their contribution to typel diabetes difficult to elucidate. This is compounded by the occurrence of linkage disequilibrium (LD) across the HLA region. LD is a phenomenon where recombination during meiosis is relatively infrequent, and leads to combinations of alleles at different loci (haplotypes) being inherited *en bloc*. HLA antigens are glycoproteins found on the cell surface. They comprise class I and class II, which are encoded by different genes within the HLA region and thus show difference in the structure. Specific regions of both class I and class II molecules are highly polymorphic.

Class I genes encode an α peptide chain, which combines with β_2 microglobulin, encoded by a gene on chromosome 15. Class I molecules are found on the surface of all nucleated cells and are crucially involved in the restriction of cytotoxic- T lymphocytes

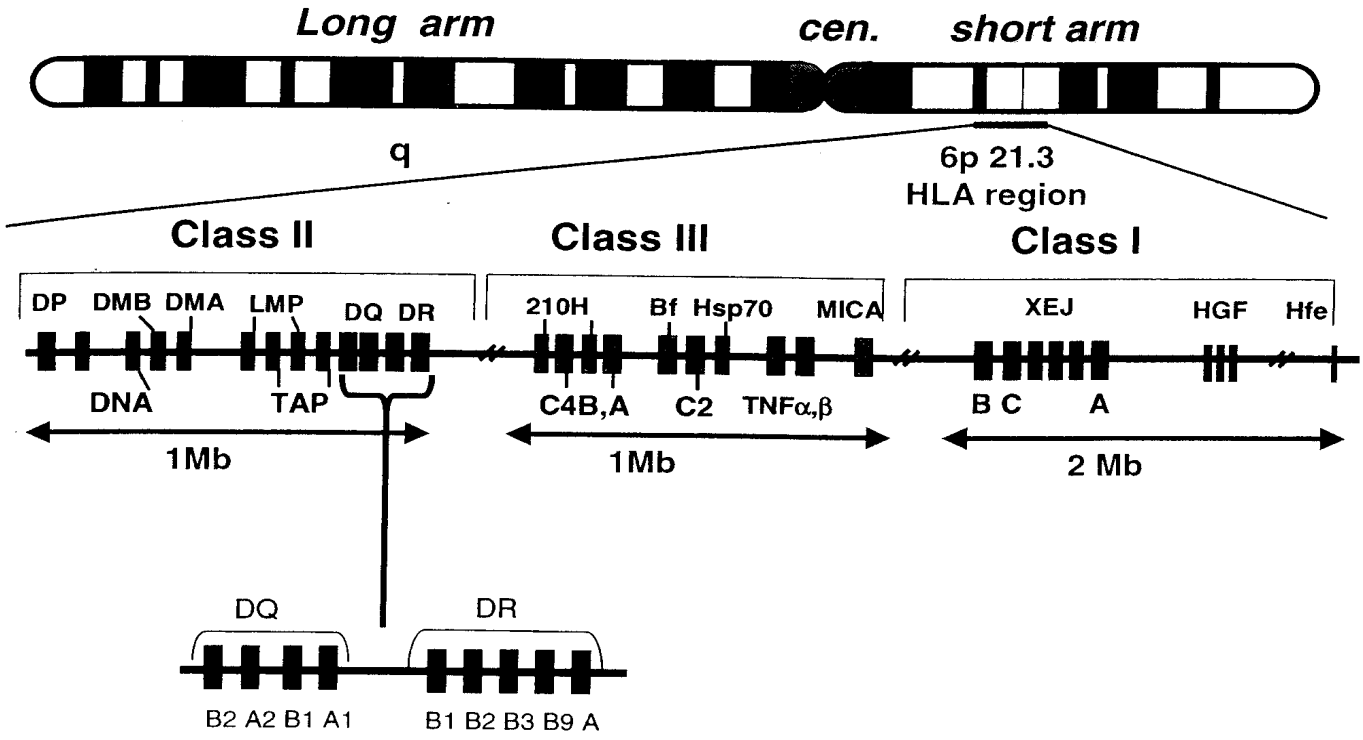

Fig. 1. A map of major histocompatibility complex (MHC) showing the HLA region

activity, i.e the recognition by CD 8-positive T lymphocytes of antigen peptides only when these are presented together with the HLA molecules.

Class II region contains genes which encode HLA molecules involved in antigen processing and those with non-immune functions. The HLA-DR,-DQ, -DP genes are each subdivided into A and B loci. The DQA1 and DQB1 genes encode α and β chains respectively. The expression of Class II molecules are confined to antigen presenting cells such as macrophages, B lymphocytes and activated T lymphocytes. Structural variations in the α-and β-chains can affect the binding of autoantigen peptide and its presentation to the helper T lymphocyte, providing a mechanism by which specific polymorphisms in the class II genes could increase or decrease susceptibility to autoimmune diseases such as type 1 diabetes.[10]

The strongest initial associations were found with class II genes in the D region of the *HLA* locus, encoding DRB, DQA, and DQB genes.[11,12] Having either the DR3 or DR4 alleles increases the risk of developing type 1 diabetes. Conversely, the DR2 allele is protective.[13] These serologic denominations have now been refined at the DNA sequence level: DR4 includes the alleles DRB1*0401, DRB1*0402, and DRB1*0405; DR3 denotes the allele DRB1*0301; and DR2 denotes the allele DRB1*1501.

Because certain alleles in the HLA region show strong allelic association [linkage disequilibrium (LD)], it has been difficult to identify the causal mutation(s) in the HLA. Alleles in the DRB1 gene are often tightly associated with alleles in the DQB1 gene, meaning that the variation associated with increased risk of diabetes at the population level can be a haplotype extending across the entire set of HLA-D genes. In addition, the higher risk of DR3/DR4 heterozygotes compared with either homozygote also suggests multiple susceptibility alleles at this locus. Further progress identifying the causal mutation(s) in the *HLA* will require a combination of identifying individuals in whom LD has broken down and functional assays of particular molecular changes.

The second genetic risk factor for T 1 DM is a variable repeat locus (VNTR) at the 5' region of insulin gene (INS). Based on the number of repeat units, VNTR alleles are divided into three classes: the shorter class I (26-63 repeats), intermediate size class II (80 repeats), and the longer class III (140-200 repeats).

Homozygosity for class I VNTR is associated with a 2 to 5 fold increase in diabetes risk, while most class III VNTRs confer dominant protection from the development of type 1 diabetes.[14] Significant progress has been made in understanding the functional role of the VNTR locus in type 1 diabetes. Several studies have shown that the VNTR stimulates insulin steady-state transcription and that VNTR length correlates with steady-state insulin m RNA level. Insulin transcription also correlates with proinsulin production in the thymus[15] where proinsulin appears to be the main product of the insulin gene.[16]

This probably influences immune responsiveness to insulin, a key autoantigen in type 1 diabetes. Since the immunogenetic mechanisms underlying susceptibility/protection at both the above mentioned loci appear to involve basic immunological functions such as thymic selection and immunoregulation, these loci may essentially influence the ability of immune system to control its reactivity against insulin and other islet cell autoantigens. Thus the two best defined susceptibility loci for type 1 diabetes may influence the specificity of the autoimmune response rather than a genetic predisposition to autoimmunity.

A large number of genes have been implicated in susceptibility to type 1 diabetes. These include the T-cell receptor(TCR) genes, immunoglobulin genes, CD 4 gene and vitamin D receptor gene. Association studies of these genes have produced conflicting results, and hence their contribution to disease risk is currently unclear, but probably minimal.

Genome-scans and family-based association studies have identified a number of chromosomal intervals that may contain susceptibility genes for type 1 diabetes. To date however, no susceptibility genes within these regions have been unequivocally identified.

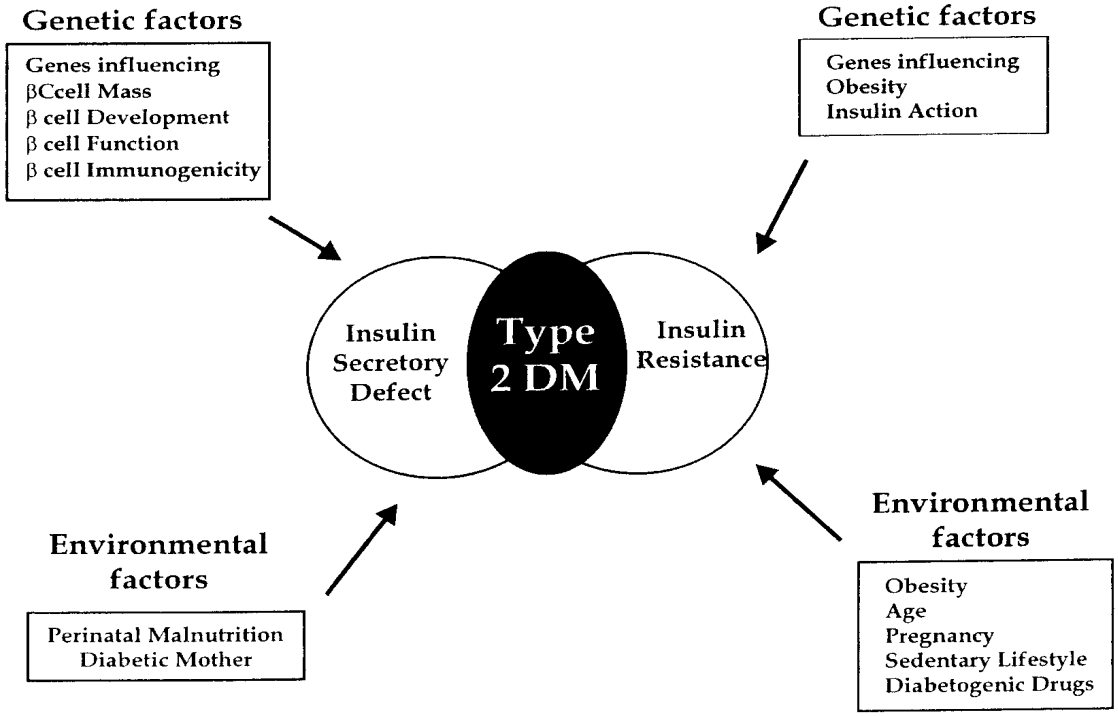

Fig. 2. Genes-environment interactions in Type 2 diabetes

Table 3. Genetics of Type 2 Diabetes

1. Genetics of Monogenic form of Diabetes (Rarer forms) eg. MODY and its subtypes, MIDD, etc.
2. Genetics of Polygenic forms of Diabetes (more common forms of type 2 diabetes).

GENETICS OF TYPE 2 DIABETES

Type 2 diabetes mellitus is a heterogeneous syndrome resulting from defects of both insulin secretion and action.[17] The precise molecular mechanisms leading to chronic hyperglycaemia are largely unknown.[18] It is generally accepted that type 2 diabetes results from a complex interplay of genetic and environmental factors influencing a number of intermediate traits of relevance to diabetic phenotype (β-cell mass, insulin secretion, insulin action, fat distribution and obesity) (Figure 2).

The genetics of type 2 diabetes can be broadly considered under genetics of monogenic forms of diabetes and genetics of polygene forms (Table 3).

In the majority of cases, type 2 diabetes is polygenic in nature although monogenic forms such as maturity onset diabetes of the young (MODY) and maternally inherited diabetes and deafness (MIDD)[19] have been frequently identified and these are discussed in detail in Chapter 23 (Sec. IV) Despite the evidence of a strong genetic background in type 2 diabetes, very little is yet known about the genetic risk factors for type 2 diabetes. Most of the results have been obtained by studying the highly familial and monogenic forms of diabetes with a young age of onset.

In contrast to MODY which is monogenic, type 2 diabetes is polygenic and its inheritance is complex in nature. Again, in contrast to the genes involved in monogenic forms are causal in nature, the genes involved in polygenic forms *predispose* to the disease rather than cause it. The polygenic nature of type 2 diabetes implies that a number of genes are involved with each one contributing to a varied extent in the causation of diabetes. This is further complicated by the fact that environmental factors also play a major role in precipitating the disease. Despite numerous studies, no clear-cut causation has been proved with respect to any gene. However, a number of genes have been associated with the disease status and validation of such studies are underway (Table 4).

An important motivation for studying rare, monogenic forms of diabetes was the hope that mutations in these genes would explain a sizeable proportion of diabetes in the population. The hypothesis was that the same genes might harbor severe mutations (causing rare Mendelian forms, leading to gene discovery), as well as less deleterious (and perhaps more common) changes that would contribute significantly to the population burden of disease. Initial studies of coding changes in these genes have not demonstrated reproducible associations with type 2 diabetes. Whether this is because there are no such effects, or because genetic variation in each of these genes has not yet been adequately assessed with appropriate study design and sufficient power of the study is not clear.

Advances in genome mapping produced genome wide collections of markers and technologies for typing them in hundreds of individuals. Thus, whole-genome linkage scans are performed with the aim of localizing genes responsible for common forms of

Table 4. A List of Candidate Genes for Type 2 Diabetes

Genes	Implications
Peroxisome Proliferator activated receptor -γ (PPAR-γ) PPAR-γ Coactivator-1 (PGC-I) GLUT 4 (Glucose Transporter 4) Adiponectin Resistin Leptin Uncoupling protein-2 (UCP2)	Obesity & Insulin Resistance leading to Type 2 diabetes
Insulin Receptor Substrate (IRS) Calpain 10 GLUT 1	Insulin signalling and glucose transport
IRS-1 Insulin GLUT2 GCK (Glucokinase) ABCC8 [SUR (Sulphonyl Urea Receptor), Kir 6.2 (Potassium Channel, Inwardly Rectifying)] TCF7L2 (Transcription factor-7 like 2)	Genes involved in insulin secretion

Table 5. Location of Potential Type 2 Diabetes Genes

Chromosome no. & Gene location	Gene name
1p	Leptin receptor
2q	Calpain 10
2q	IRS-1
3q27	PPAR-gamma
3q	IGF2BP2
4q	FABP
5q	p85α
6q	PC-1
7p	GCK
7q	Leptin
8p	Beta 3 adrenergic receptor
8q	SLC30A8
9p	CDKN2A/CDKN2B
9q	Frataxin
10q	TCF7L2
10q	HHEX/IDE
11q	EXT2
6p	Insulin
6p	Kir 6.2 Sulphonyl
6p	Urea Receptor
6p	CDKAL1
12q	HNF-1α
13q	IRS-2
13q	IPF
16q	Rad
17p	SERCA
17q	HNF-1β
17q	Glucagon Receptor
19p	Insulin receptor
19q	Glycogen synthase
20q	HNF-4α
Xq	IRS-4

diabetes without assumptions about biochemical pathways or relationship to monogenic forms of disease. Though this technique proved immensely successful in Mendelian disorders it has met with mixed results in the more common forms of type 2 diabetes.

Several genome-wide linkage analyses have been done to look for regions conferring risk of type 2 diabetes. In contrast to the HLA region in type 1 diabetes, no single region has been widely replicated in type 2 diabetes. Only a few regions have shown significant evidence for linkage in a single scan or consistent replication across scans.

Regions that have shown evidence for linkage in more than one study include chromosomes 1q25.3, 2q37.3, 3p24.1, 3q28, 10q25, 10q26.13, 12q24.31,and 18p11.22.[20-24] Several other regions have shown suggestive evidence of linkage, with one (20q13.12) replicated in multiple other studies.[25-28] Table 5 summarizes the multiple locations of potential type 2 diabetes genes on the human genome.

One of the earliest significant linkage peaks was at chromosome 2q37.3, which led to the identification of *CAPN10*, encoding calpain 10. In 1999, Bell and colleagues reported significant linkage of T2D in Mexican-Americans to a 12-centimorgan (cM) region in chromosome 2q.[29] Horikawa and colleagues[30] took on the challenge of the positional cloning of this region. Guided by examination of other single nucleotide polymorphisms(SNPs) in this region the A→G polymorphism in intron 3 of this gene was implicated with risk of T2D. Only heterozygotes were found to be at increased risk; homozygotes for the at-risk variant (G/G) showed no evidence for increased risk. In further analysis by them, a combination of two different three marker haplotypes carrying the highest risk was identified. Trends consistent with these data were seen in a second group of Mexican-Americans and in two populations reported from Europe.[31,32]

Subsequent to this initial report, many groups have published large studies examining the correlation of sequence variation in *CAPN10* and T2D. However, the specific model proposed by Horikawa and colleagues has not been widely reproduced even in other populations.[33-36] Some studies suggested that other sequence variants or haplotype combinations[37] at the *CAPN10* locus might be associated with disease. Thus, a consistent picture of genotype-phenotype correlation at *CAPN10* is yet to emerge. This could be due to a number of reasons producing inconsistency in association studies[38,39] including population-specific environmental triggers, gene-gene interactions, or population-specific patterns of LD.

Recently, Grant *et al*[40] reported that within a region in linkage to type 2 diabetes on chromosome 10q, a set of single nucleotide polymorphisms (SNPs) and a microsatellite marker in a well-defined linkage disequilibrium block (LD) in the transcription factor 7 -like 2 (TCF7L2) gene were strongly associated with

type 2 diabetes in Icelandic subjects. Florez et al,[41] reported that the polymorphisms rs12255372 (G/T) and rs7903146 (C/T) in the TCF7L2 gene were associated with an increased risk of type 2 diabetes in persons with impaired glucose tolerance. By far, this gene has shown greatest promise as a strong candidate for type 2 diabetes risk since positive replication has been reported by virtually all the studies conducted so far[42-48] including our own study in South Indian population[49] where the intronic SNP has been shown to be associated with type 2 diabetes. Although the exact role of *TCF7L2* is unknown, it appears to act through the Wnt pathway. The search for diabetes susceptibility genes on most other chromosomes is ongoing.

On of the widely reproduced associations between a genetic variation and population risk of T2D is that of the Pro12Ala polymorphism in the peroxisome proliferator-activated receptor γ (PPARγ). PPAR plays a central role in adipocyte development, and is a drug target for the thiazolidinedione medications used clinically to treat T2D.[40] Deeb et al[41] initially reported that the less common alanine allele led to increased insulin sensitivity and was protective against T2D in Finnish and second-generation Japanese populations. Shortly after, however, four additional studies of this variant in T2D were published, none of which reached statistical significance .The picture of association to T2D became clearer as larger and more numerous studies were published. Although subsequent studies have examined this association,[42-45] only some of these published reports reach statistical significance when considered individually. All the large studies (which examined>1,000 individuals) show similar and statistically convincing associations.[46-48] The large sample size required to prove association of Pro12Ala with T2D is due to the modest effect of the risk allele: Individuals who are homozygous for the higher-risk proline allele have only a 25% increase in diabetes risk. Although it has a small effect on the individual, this variant has a substantial effect on the population because the frequency of the proline allele is very common.

Another strong candidate gene for T2D is *ABCC8*, which encodes the sulfonylurea receptor (SUR1). This protein is the drug target for a widely used class of hypoglycemic medications, and the *ABCC8* gene is also mutated in the monogenic disorder familial hyperinsulinism.[49] *ABCC8* carries a silent C→T polymorphism in exon 18 (T759T; also reported as "exon 22" or T761T), which has been associated with T2D in several populations[50-53], though not in others.[54]

A third, promising candidate gene is closely related to *ABCC8*, both functionally and chromosomally: the sulfonylurea receptor is physically associated at the cell membrane with Kir6.2, an ATP-dependent potassium channel whose gene (*KCNJ11*) is directly adjacent to *ABCC8* on chromosome 6.[55]

A recent meta-analysis[56] identified some early reproducibility of an association between variation in *GLUT1* and T2D, originally reported in 1988[57] Complete evaluation of this association would require comprehensive testing of variation in this gene in large samples.

Whole genome association study is a new approach to gene discovery unbiased with regard to presumed functions or locations of causal variants. Recently, genome wide association studies have provided convincing evidence for new gene regions,TCF7L2[40], HHEX–IDE[68], SLC30A8[68], CDKAL1[69], CDKN2A–2B[70], IGF2BP2[70] and FTO[71] associated with type 2 diabetes. Together with candidate approaches, these studies have identified 11 confirmed genomic regions that alter the risk of type 2 diabetes in the European population.

CONCLUSION

The various epidemiological and genetic studies performed demonstrate that diabetes mellitus comprises a variety of entities with different pathophysiological and genetic basis and natural history. Clearly, substantial progress has been made in genetics of T1D and MODY, whereas knowledge of T2D seems to be slowly unfolding. However, studies of diabetes have played a major role in shaping the thinking about the genetic analysis of complex diseases. Based on trends in genomic information and technology, combined with the growing public health importance of diabetes, this will likely continue to be an important arena in which methods will be pioneered and many lessons learned.

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