

The Genetics of Diabetes

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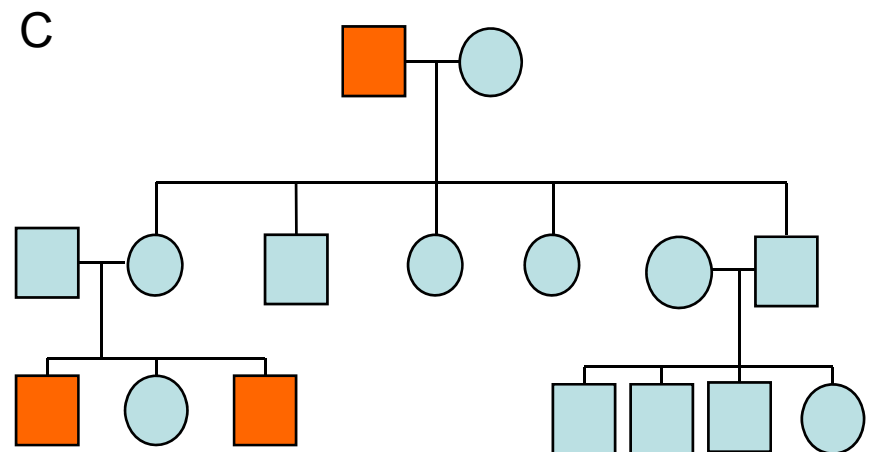
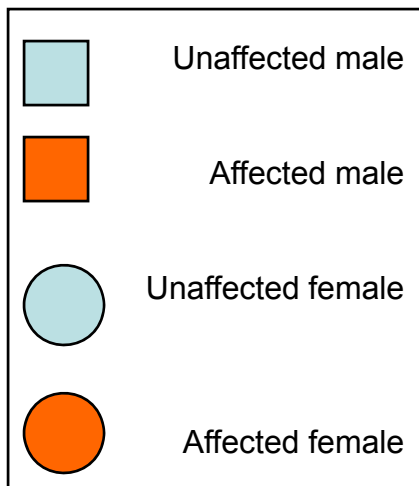
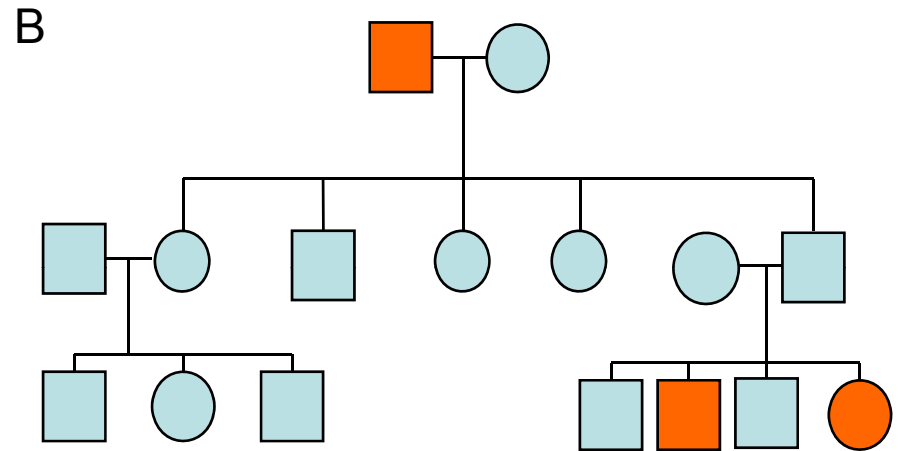
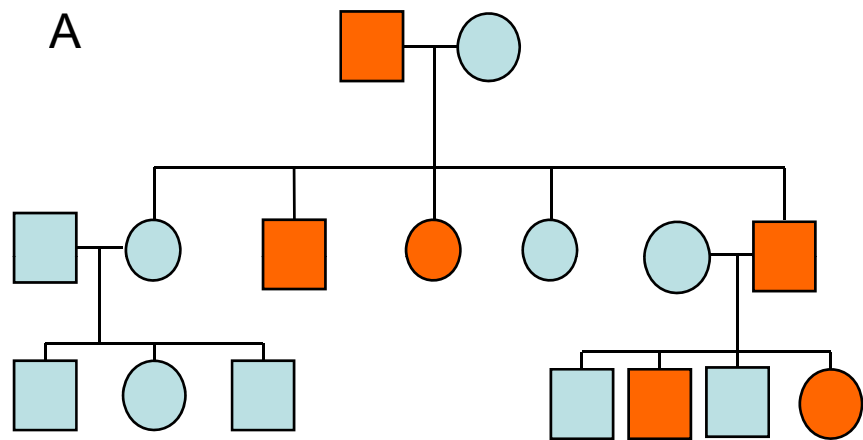
Aims of the Session

- To provide a framework for understanding genetic studies.
- To explain the various strategies currently available for genetic research including linkage and association studies.
- To summarize the current research on the genetics of diabetes.

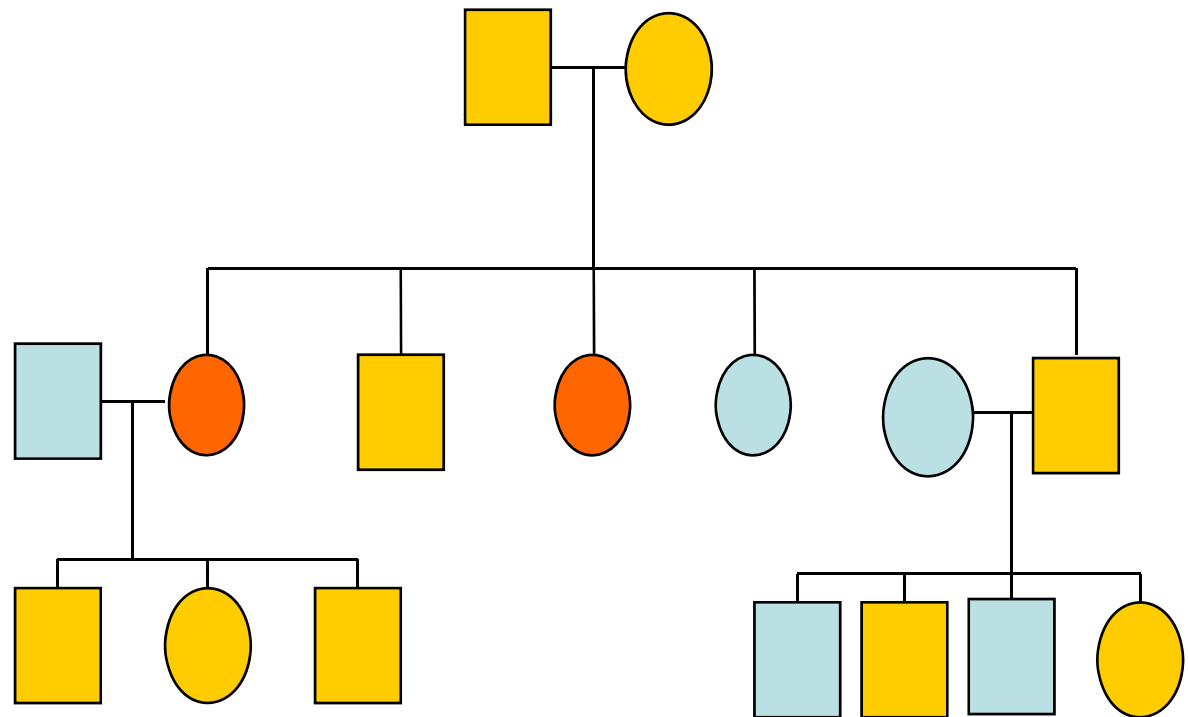
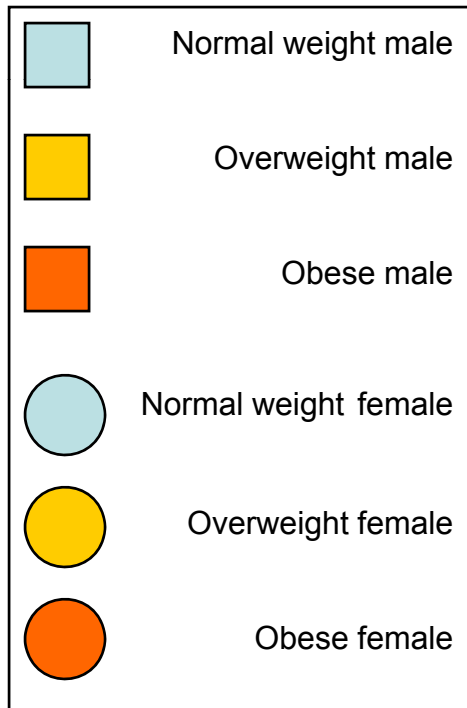
What is the evidence that diabetes has a genetic element?

- Risk varies by ethnicity
- Risk increases with family history of diabetes
- Twin studies

Mode of Inheritance



Mode of Inheritance



Concordance Rates in Identical Twins

- Type 1 Diabetes
 - 30-50%
- Type 2 Diabetes
 - Approaching 100%

How to find the gene(s)?

- Candidate genes
- Linkage analysis
- Association studies
- Expression studies

Phenotype

- All genetic studies depend on having well characterized subjects for the phenotype of interest
- Problems associated with diabetes as the phenotype of interest
 - Variable age of onset
 - Environmental factors

Beware...

- Population stratification
- Confounders
- Vaguely defined phenotypes

How to find the gene(s)?

- Candidate Gene
- Linkage Studies
- Association Studies

All use the presence of variation within the genome to act as markers for unknown functional variants that give rise to disease.

Genetic Markers

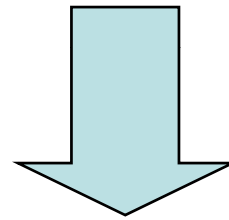
- Single nucleotide polymorphisms (SNPs)
- Microsatellites

Linkage Disequilibrium

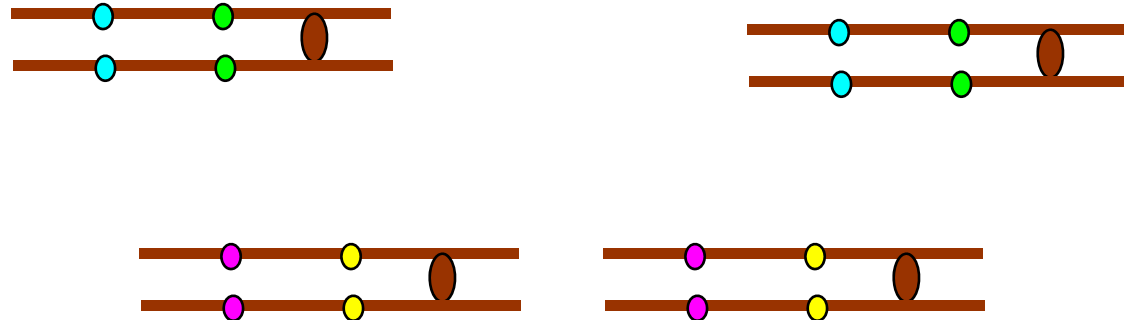
- Genetic markers are considered to be inherited independently of each other
- When two genetic markers are inherited together $\geq 50\%$ of the time they are said to be in linkage disequilibrium with each other
- If they are always inherited together they are in perfect linkage disequilibrium

No Recombination

Parental
Genotype

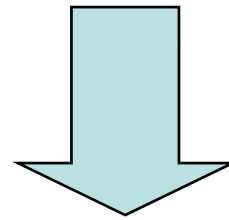


Gamete
Genotypes

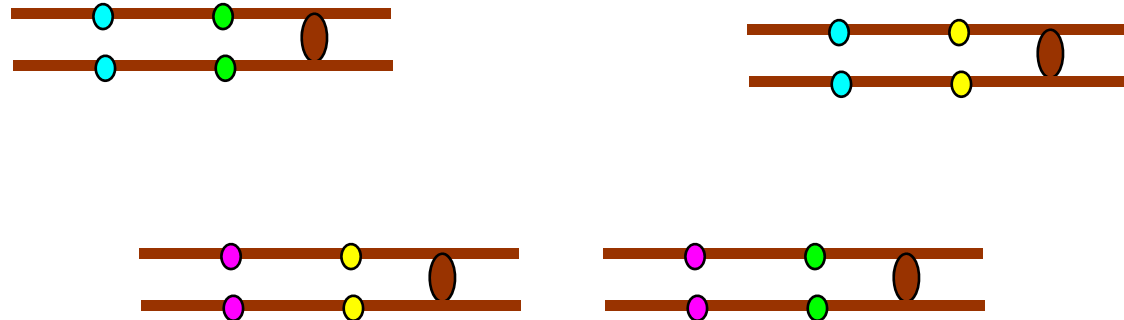


No Recombination

Parental
Genotype



Gamete
Genotypes



How to find the gene(s)?

- Candidate genes
- Linkage analysis
- Association studies
- Expression studies

How to find the gene(s)?

- Candidate genes
 - Genotype specific genes involved in pathways involved in maintaining glycemia to identify variations that are associated with a phenotype.
 - If variants are associated can test for variant being functional to confirm gene variant is cause of disorder
- Linkage analysis
- Association studies
- Expression studies

Candidate Genes

- Strengths
 - Hypothesis driven
 - Limited need for genotyping
- Weaknesses
 - Based on limited knowledge of gene functions
 - Non systematic

How to find the gene(s)?

- Candidate genes
- Linkage analysis
 - Using DNA from family members to identify areas of the genome that are inherited along with the unknown disease related gene variant
 - Identifies an area of the genome associated with the disease
- Association studies
- Expression studies

Linkage Studies

- Strengths
 - Does not presume knowledge of gene
- Weaknesses
 - Requires extensive genotyping
 - Will not identify marker gene allele
 - Requires replication in multiple populations
 - False positives

How to find the gene(s)?

- Candidate genes
- Linkage analysis
- Association studies
 - Using DNA from cases and controls to identify marker alleles associated with the phenotype of interest
- Expression studies

Association Studies

- Strengths
 - Does not require family data
 - Does not presume knowledge of gene
- Weaknesses
 - Requires extensive genotyping
 - Multiple testing
 - False positives

How to find the gene(s)?

- Candidate genes
- Linkage analysis
- Association studies
- Expression studies
 - Takes mRNA from tissues from cases and controls and then using RNA chips identifies which genes are over-expressed or under-expressed in the cases compared to the controls.

Expression Studies

- Strengths
 - Does not presume knowledge of gene
 - Tissue specific
- Weaknesses
 - Tissue specific
 - Multiple testing

Genome Wide Significance

- Takes into account multiple testing
- Levels required vary depending on whether this is a confirmational study or not

Genes and Type 1 Diabetes

Human Leukocyte Antigen Complex

- aka HLA complex is associated with risk for many autoimmune diseases including Type 1 diabetes
- On short arm of chromosome 6
- Most highly polymorphic part of the human genome with some genes in the region having 400 known alleles

HLA alleles and type 1 diabetes

95% of people with type 1 diabetes carry the DR3, DR4 or both alleles

- Presence of the DR3 allele increases risk for type 1 diabetes by ~7 times
- Presence of the DR4 allele increases risk for type 1 diabetes by ~9 times
- Presence of the DR3 and DR4 allele increases risk for type 1 diabetes by ~14 times

Insulin Gene (IDDM2)

- Contained in a 4.1kb region on chromosome 11 identified by linkage analysis
- May be due to variation in gene transcription
- Accounts for 10% of genetic element of type 1 diabetes

Other Type 1 Diabetes Genes

PTPN22 gene

- encodes LYP a protein tyrosine phosphatase involved in modulating T cell activation
- also associated with other autoimmune diseases

Cytotoxic T Lymphocyte Antigen 4 (CTLA-4)

- CTLA4 antigen expressed on activated T cells
- in the “IDDM12” region on chromosome 2

Genes and Type 2 Diabetes

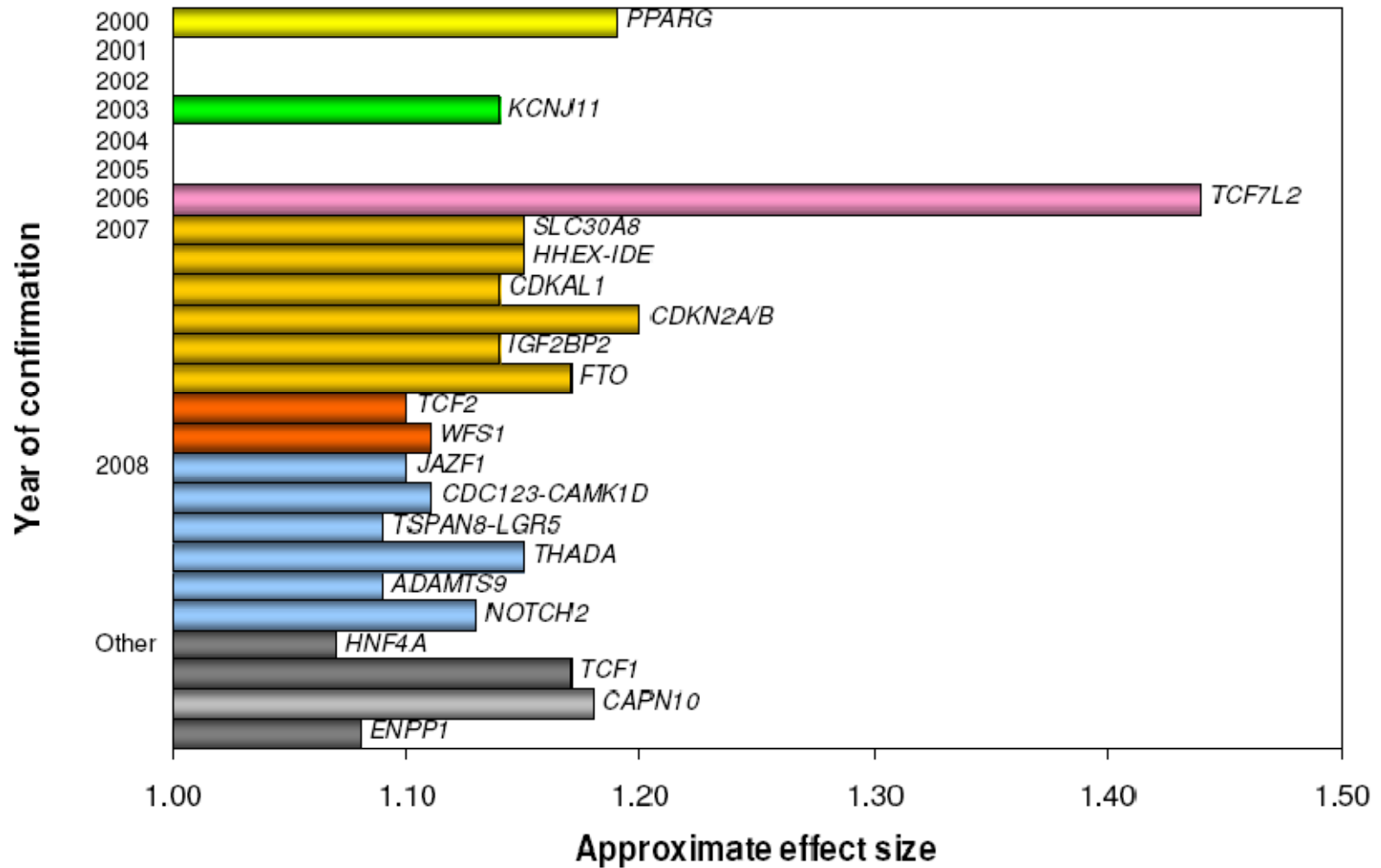
Transcription Factor 7-Like 2 (TCF7L-2)

- Chromosome 10
- Encodes for a transcription factor involved in Wnt signaling
- *TCF7L2* expression in human islets increased in T2D, particularly in carriers of the TT genotype
- Over-expression of *TCF7L2* in human islets reduced glucose-stimulated insulin secretion
- T allele associated with
 - impaired insulin secretion
 - impaired incretin effects
 - enhanced rate of hepatic glucose production

Other Type 2 Diabetes Genes

- PPARG Gene
 - Codes for peroxisomal proliferator-activated receptor gamma which is the target for the thiazolidinedione drugs.
 - Mutation at position 12 causes a coding change in the receptor
 - Proline allele associated with 1.20 greater risk for type 2 diabetes than the alanine allele
- KCNJ11
 - Codes for the K_{ATP} channel in the B cell
 - E23K variant (glutamate instead of lysine) associated with 1.14 greater risk for diabetes
 - Glutamate allele associated with impaired insulin secretion
- CAPN10 Gene
 - Codes for calpain 10 a ubiquitously expressed protease believed to have a role in insulin secretion
 - Only susceptibility gene identified purely via positional cloning
- CDKN2A/2B
 - Codes for cyclin-dependent kinase inhibitors
 - Inhibit CDK4 and CDK6
 - In mice CDK4 activity is associated with beta-cell mass
 - Also tumour suppressor genes

Genetic Loci Associated with Type 2 Diabetes



TABLES

Table 1: Genetic variants associated with type 2 diabetes at or near genome-wide levels of statistical significance, ordered by chromosome (Chr)

Marker	Chr	Description	Gene region	Function	Risk allele	Odds ratio	P value	Reference
rs10923931	1	Intronic	<i>NOTCH2</i>	Transmembrane receptor implicated in pancreatic organogenesis	T	1.13	4.1×10^{-8}	(103)
rs7578597	2	Missense: T1187A	<i>THADA</i>	Thyroid adenoma; associates with PPAR γ	T	1.15	1.1×10^{-9}	(103)
rs4607103	3	38 kb upstream	<i>ADAMTS9</i>	Secreted metalloprotease expressed in muscle and pancreas	C	1.09	1.2×10^{-8}	(103)
rs4402960	3	Intronic	<i>IGF2BP2</i>	Growth factor binding protein; pancreatic development	T	1.14	8.9×10^{-16}	(109)
rs1801282	3	Missense: P12A	<i>PPARG</i>	Transcription factor involved in adipocyte development	C	1.19	1.5×10^{-7}	(110)
rs10010131	4	Intron-exon junction	<i>WFS1</i>	Endoplasmic reticulum transmembrane protein	G	1.15	4.5×10^{-5}	(109)
rs7754840	6	Intronic	<i>CDKAL1</i>	Homologous to CDK5RAP1, CDK5 inhibitor; islet glucotoxicity sensor	C	1.12	4.1×10^{-11}	(109)
rs864745	7	Intronic	<i>JAZF1</i>	Transcriptional repressor; associated with prostate cancer	T	1.10	5.0×10^{-14}	(103)
rs13266634	8	Missense: R325W	<i>SLC30A8</i>	β -cell zinc transporter ZnT8; insulin storage and secretion	C	1.12	5.3×10^{-8}	(109)
rs10811661	9	125 kb upstream	<i>CDKN2A/B</i>	Cyclin-dependent kinase inhibitor and p15 tumor suppressor; islet development	T	1.20	7.8×10^{-15}	(109)
rs12779790	10	Intergenic region	<i>CDC123-CAMK1D</i>	Cell cycle/protein kinase	G	1.11	1.2×10^{-10}	(103)
rs7903146	10	Intronic	<i>TCF7L2</i>	Transcription factor; transactivates proglucagon and insulin genes	T	1.37	1.0×10^{-48}	(67)
rs1111875	10	7.7 kb downstream	<i>HHEX</i>	Transcription factor involved in pancreatic development	C	1.13	5.7×10^{-10}	(109)
rs5219	11	Missense: E23K	<i>KCNJ11</i>	Kir6.2 potassium channel; risk allele impairs insulin secretion	T	1.14	6.7×10^{-11}	(16)
rs7961581	12	Intronic	<i>TSPAN8-LGR5</i>	Cell surface glycoprotein implicated in GI cancers	C	1.09	1.1×10^{-9}	(103)
rs8050136	16	Intronic	<i>FTO</i>	Alters BMI in general population	A	1.17	1×10^{-12}	(109)
rs757210	17	Intronic	<i>HNF1B</i>	Transcription factor involved in pancreatic development	A	1.12	5×10^{-6}	(109)

Monogenic Diabetes

Maturity Onset Diabetes of the Young (MODY)

- Young onset of type 2 diabetes inherited in an autosomal dominant fashion
- Linkage studies identified several areas on the genome and currently 6 mutations have been identified which each produce a distinct form of MODY

MODY Genes

Table 1
Subtypes of maturity-onset diabetes of the young and genes involved

MODY type	Gene locus	Gene name	Year of discovery [reference]	Distribution	Onset of diabetes	Primary defect	Severity of diabetes	Complications
MODY1	20q	<i>HNF4α</i>	1996 [12]	Rare	Adolescence Early adulthood	Pancreas/other	Severe	Frequent
MODY2	7p	<i>GCK</i>	1992 [11]	10%–65% ^a	Early childhood	Pancreas/liver	Mild	Rare
MODY3	12q	<i>TCF1/HNF1α</i>	1996 [13]	20%–75% ^a	Adolescence Early adulthood	Pancreas/kidney /other	Severe	Frequent
MODY4	13q	<i>IPF1</i>	1997 [15]	Rare	Early adulthood	Pancreas	Severe	Unknown
MODY5	17q	<i>TCF2/HNF1β</i>	1997 [16]	Rare	—	Kidney/pancreas	Severe	Kidney disease
MODY6	2q32	<i>NEUROD1</i>	1999 [17]	Rare	Early adulthood	Pancreas	Severe	Unknown

^a Different distributions in different populations.

Summary

- Evidence for genetic element of diabetes initially came from family studies
- Type 2 diabetes has greater genetic component than type 1 diabetes
- Various types of studies used to identify potential genes
 - Candidate gene studies
 - Linkage studies
 - Association studies
 - Gene expression studies

Summary

- Handful of identified genes do not explain all genetic risk
 - HLA complex and INS gene main genetic factors identified for Type 1 Diabetes
 - TCF7L2, PPARG, CDNK2A/B, KCNJ11 main genes identified so far for Type 2 Diabetes
- Monogenic forms of diabetes