The Genetics of Diabetes

Helen C. Looker MBBS

Aims of the Session

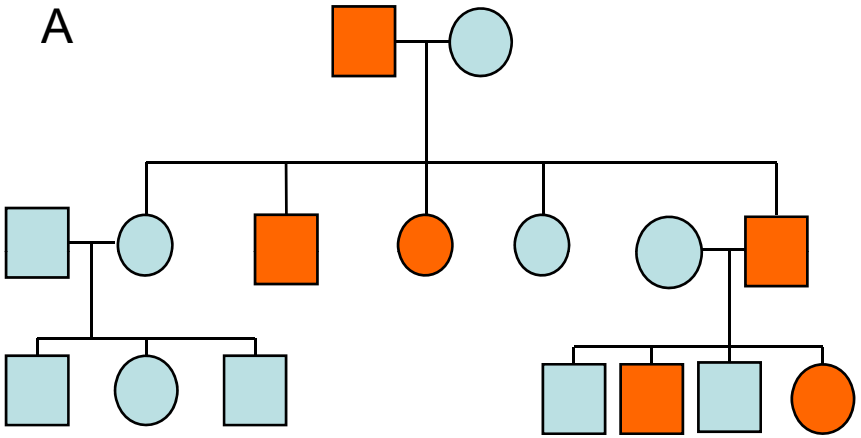
- To provide a framework for understanding genetic studies.
- To explain the various strategies currently available for genetic research including linkage and association studies.
- To summarize the current research on the genetics of diabetes.

What is the evidence that diabetes has a genetic element?

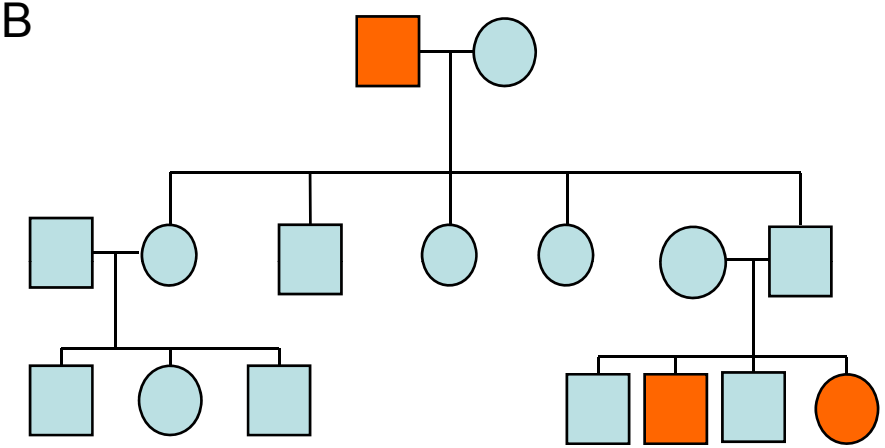
- Risk varies by ethnicity
- Risk increases with family history of diabetes
- Twin studies

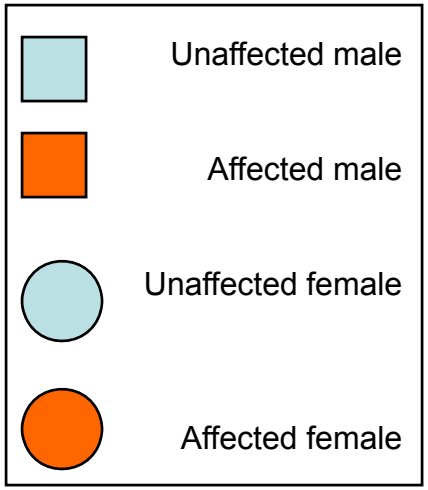
Mode of Inheritance

A

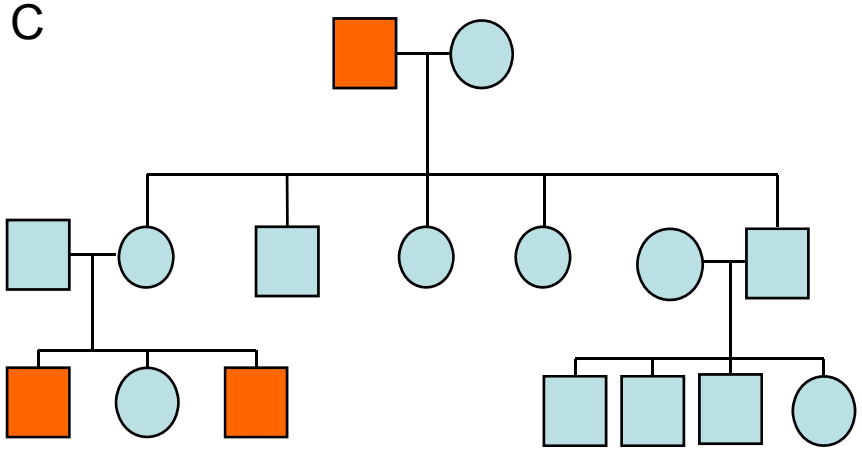


B

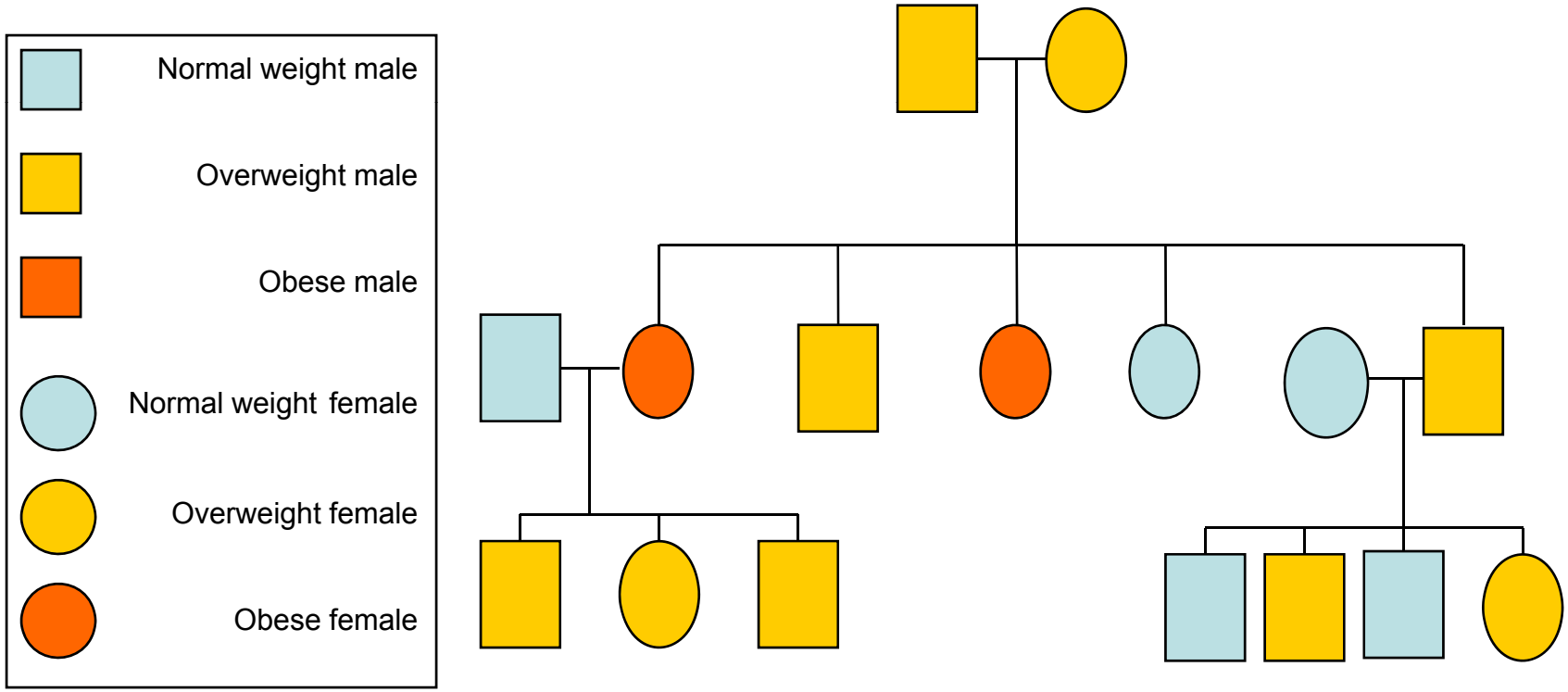




C



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

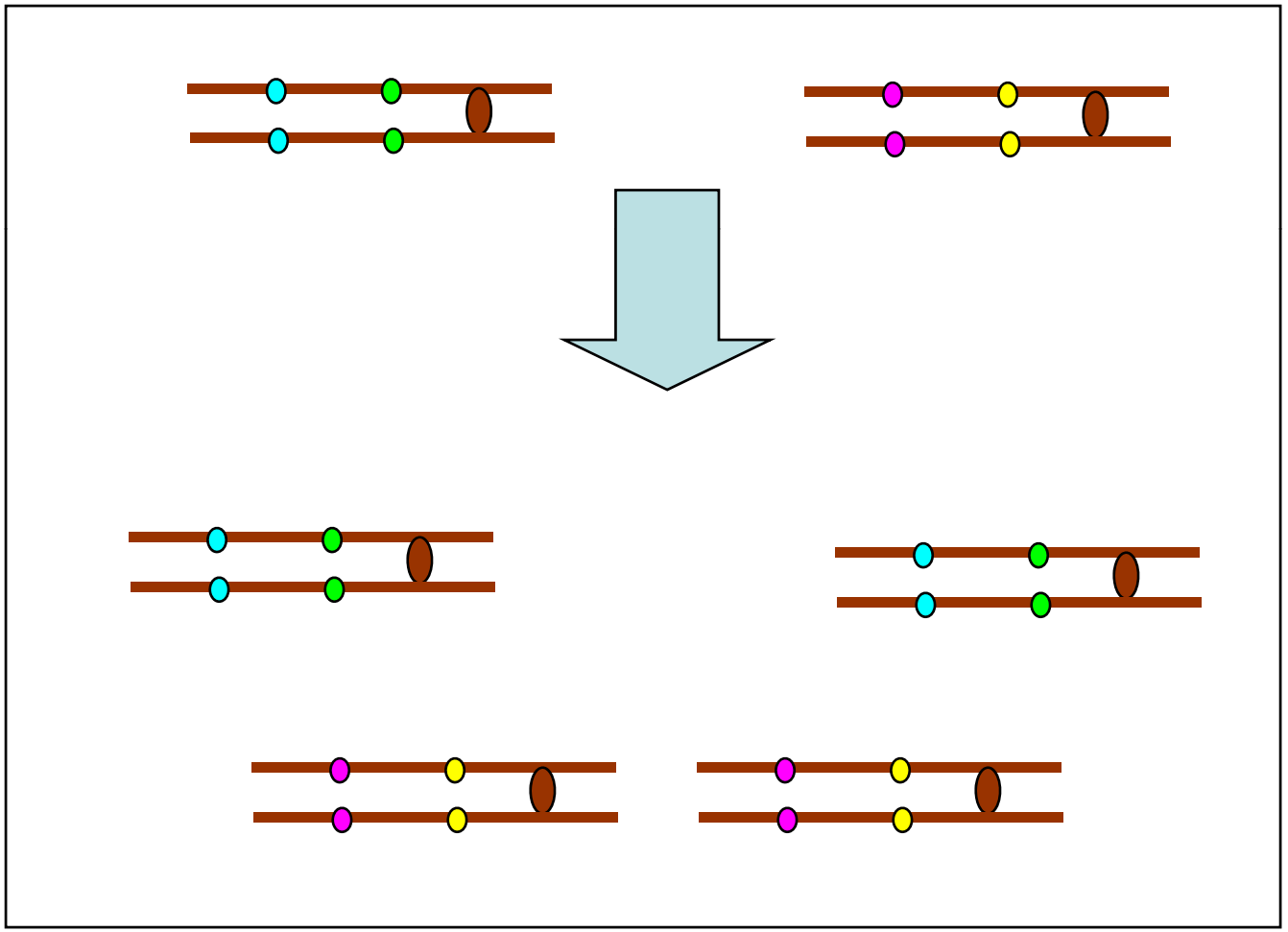
Linkage Disequilibrium

- Genetic markers are considered to be inherited independently of each other
- When two genetic markers are inherited together ≥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

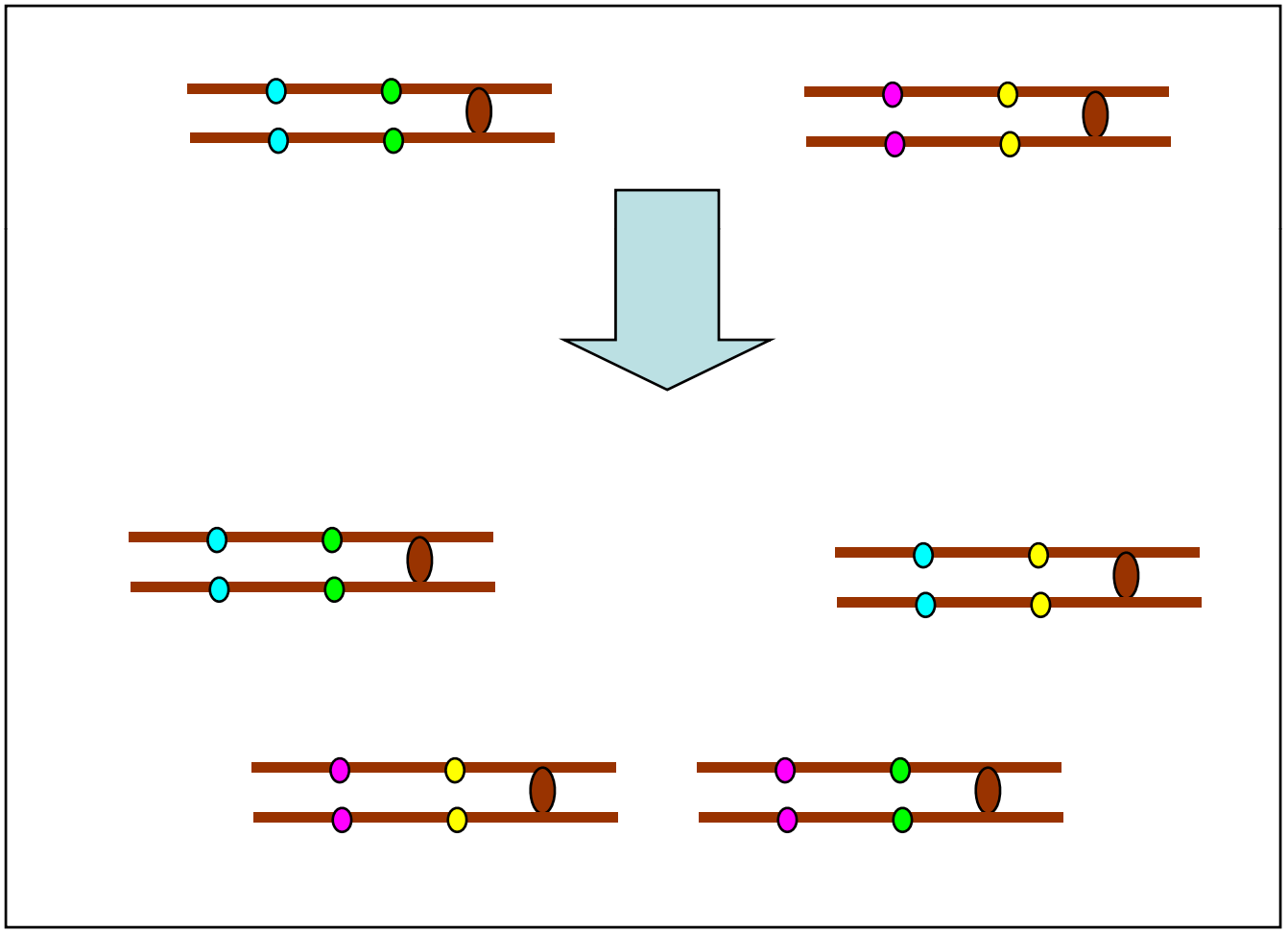
Gamete Genotypes



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

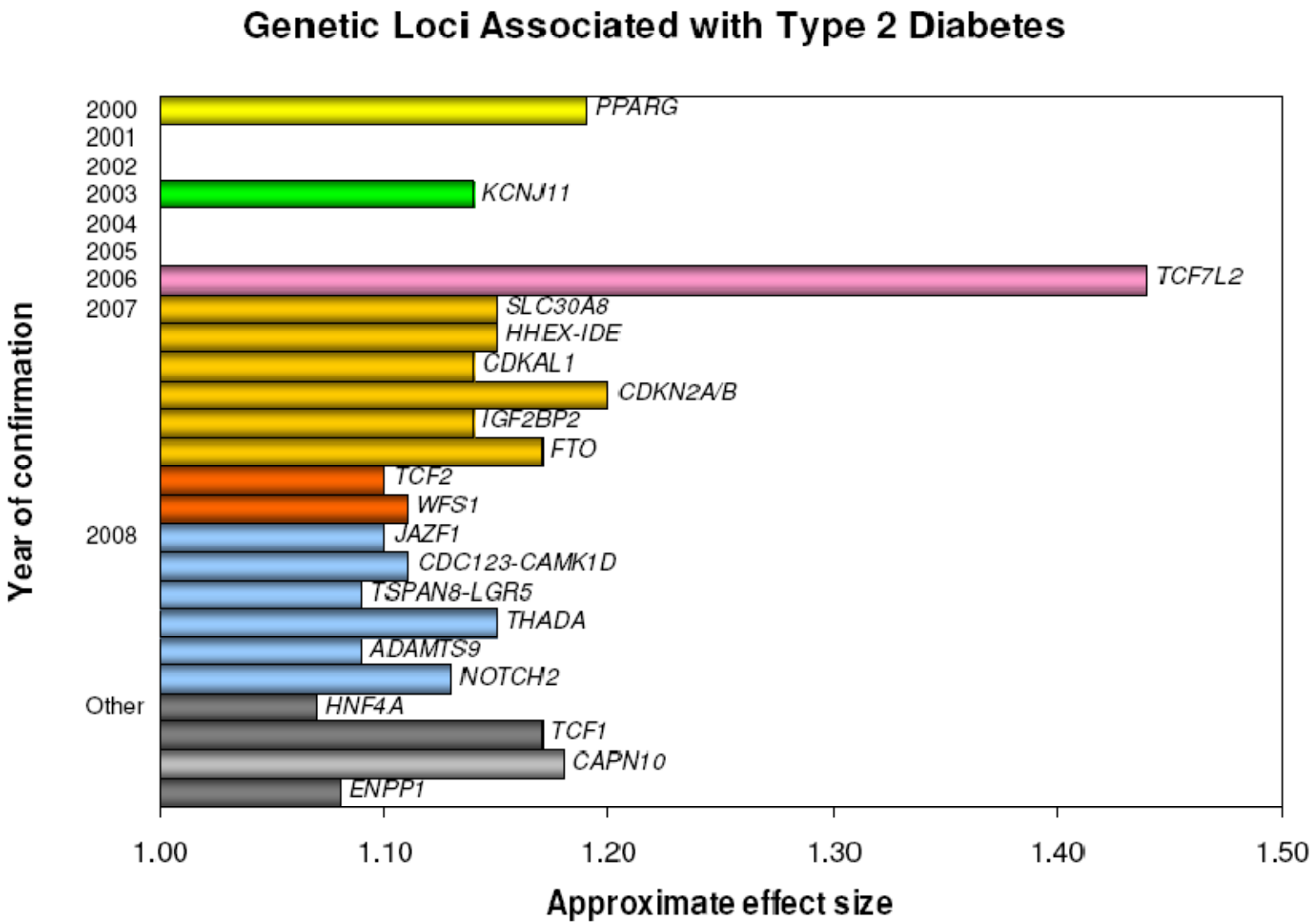
Other Type 2 Diabetes Genes

- 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 allelle 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
Year of confirmation
2000
2001
2002
2003
2004
2005
2006
2007
2008
Other
PPARG
KCNJ11
TCF7L2
SLC30A8
HHEX-IDE
CDKAL1
CDKN2A/B
IGF2BP2
FTO
TCF2
WFS1
JAZF1
CDC123-CAMK1D
TSPAN8-LGR5
THADA
ADAMTS9
NOTCH2
HNF4A
TCF1
CAPN10
ENPP1
1.00
1.10
1.20
1.30
1.40
1.50
Approximate effect size

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	*NOTCH2*	Transmembrane receptor implicated in pancreatic organogenesis	T	1.13	4.1×10^{-8}	(103)
rs7578597	2	Missense: T1187A	*THADA*	Thyroid adenoma; associates with PPARγ	T	1.15	1.1×10^{-9}	(103)
rs4607103	3	38 kb upstream	*ADAMTS9*	Secreted metalloprotease expressed in musle and pancreas	C	1.09	1.2×10^{-8}	(103)
rs4402960	3	Intronic	*IGF2BP2*	Growth factor binding protein; pancreatic development	T	1.14	8.9×10^{-16}	(109)
rs1801282	3	Missense: P12A	*PPARG*	Transcription factor involved in adipocyte development	C	1.19	1.5×10^{-7}	(110)
rs10010131	4	Intron-exon junction	*WFS1*	Endoplasmic reticulum transmembrane protein	G	1.15	4.5×10^{-5}	(109)
rs7754840	6	Intronic	*CDKAL1*	Homologous to CDK5RAP1, CDK5 inhibitor; islet glucotoxicity sensor	C	1.12	4.1×10^{-11}	(109)
rs864745	7	Intronic	*JAZF1*	Transcriptional repressor; associated with prostate cancer	T	1.10	5.0×10^{-14}	(103)
rs13266634	8	Missense: R325W	*SLC30A8*	β-cell zinc transporter ZnT8; insulin storage and secretion	C	1.12	5.3×10^{-8}	(109)
rs10811661	9	125 kb upstream	*CDKN2A/B*	Cyclin-dependent kinase inhibitor and p15 tumor suppressor; islet development	T	1.20	7.8×10^{-15}	(109)
rs12779790	10	Intergenic region	*CDC123-CAMK1D*	Cell cycle/protein kinase	G	1.11	1.2×10^{-10}	(103)
rs7903146	10	Intronic	*TCF7L2*	Transcription factor; transactivates proglucagon and insulin genes	T	1.37	1.0×10^{-48}	(67)
rs1111875	10	7.7 kb downstream	*HHEX*	Transcription factor involved in pancreatic development	C	1.13	5.7×10^{-10}	(109)
rs5219	11	Missense: E23K	*KCNJ11*	Kir6.2 potassium channel; risk allele impairs insulin secretion	T	1.14	6.7×10^{-11}	(16)
rs7961581	12	Intronic	*TSPAN8-LGR5*	Cell surface glycoprotein implicated in GI cancers	C	1.09	1.1×10^{-9}	(103)
rs8050136	16	Intronic	*FTO*	Alters BMI in general population	A	1.17	1×10^{-12}	(109)
rs757210	17	Intronic	*HNF1B*	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	*HNF4α*	1996 [12]	Rare	Adolescence Early adulthood	Pancreas/other	Severe	Frequent
MODY2	7p	*GCK*	1992 [11]	10%–65%[a]	Early childhood	Pancreas/liver	Mild	Rare
MODY3	12q	*TCF1/HNF1α*	1996 [13]	20%–75%[a]	Adolescence Early adulthood	Pancreas/kidney /other	Severe	Frequent
MODY4	13q	*IPF1*	1997 [15]	Rare	Early adulthood	Pancreas	Severe	Unknown
MODY5	17q	*TCF2/HNF1β*	1997 [16]	Rare	—	Kidney/pancreas	Severe	Kidney disease
MODY6	2q32	*NEUROD1*	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