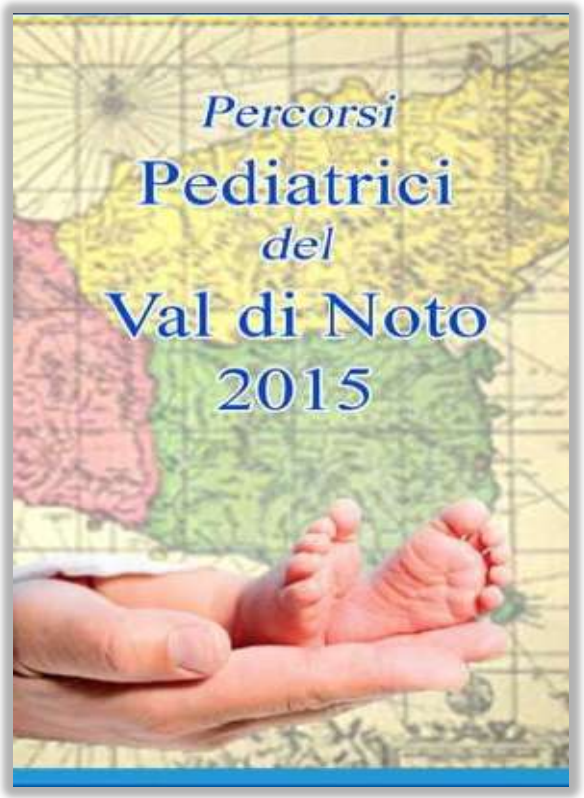
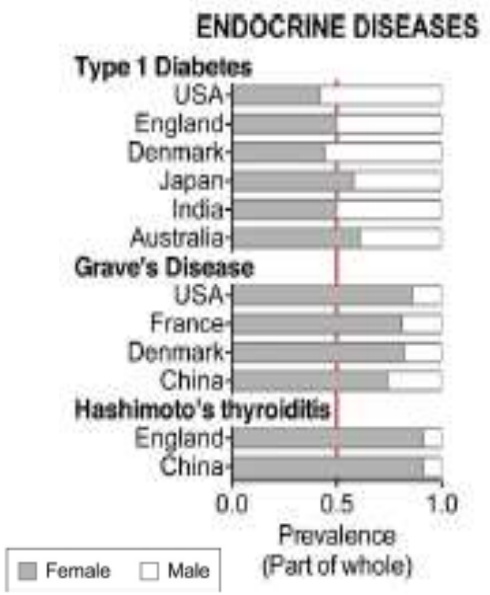
Università degli Studi di Messina
Dipartimento di Scienze Pediatriche, Ginecologiche, Microbiologiche e Biomediche

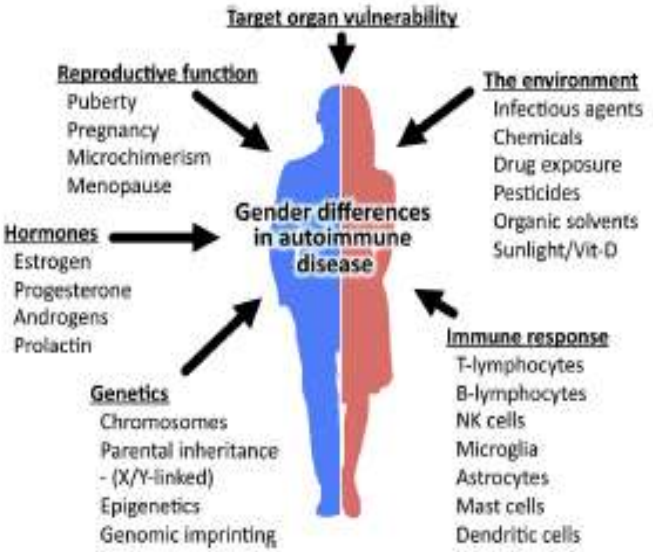


Genetica ed Endocrinopatie

Teresa Arrigo

Gender differences in autoimmune disease





Frontiers in Neuroendocrinology 35 (2014) 347–369

Generation of immune repertoires in thymus or bone marrow

CENTRAL TOLERANCE

Anti-self lymphocytes deleted by apoptosis

WRONG GENES

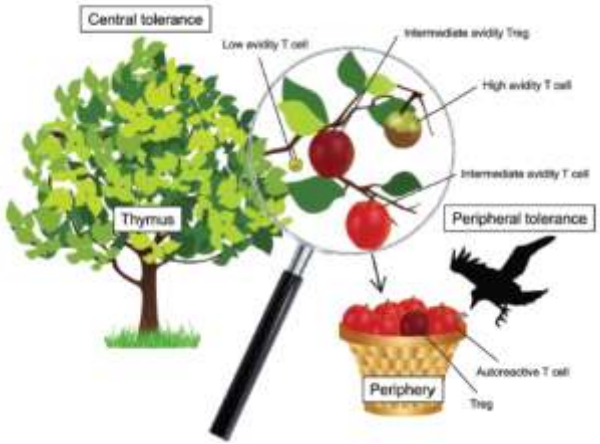
WRONG ENVIRONMENT

Some anti-self lymphocytes escape central tolerance

PERIPHERAL TOLERANCE

- Ignorance
- Anergy
- Homeostasis - CTLA-4
- Regulation

FAILURE OF TOLERANCE
RESULTING IN AUTOIMMUNITY

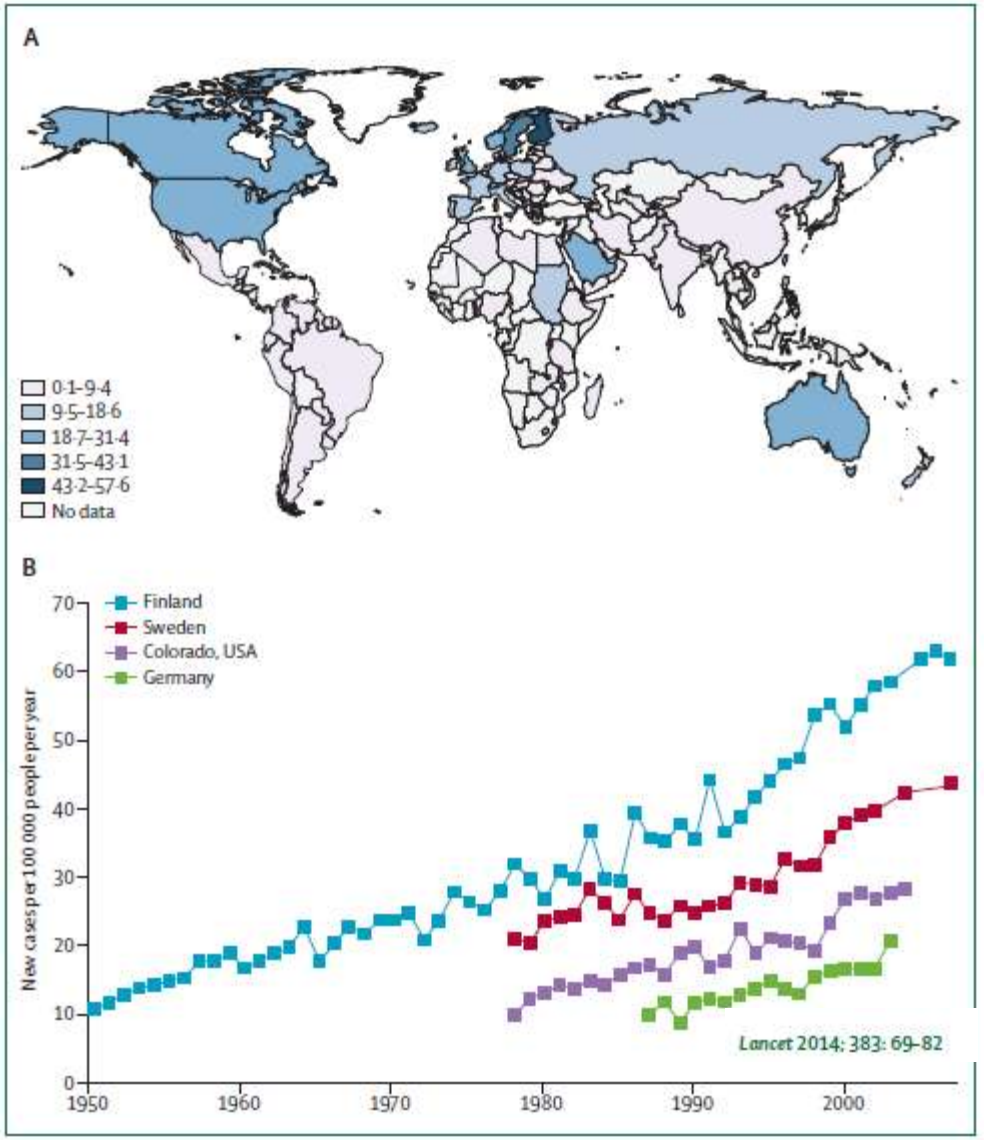


Diabete tipo I

- *E' la malattia metabolica piu' frequente in eta' pediatrica.*
- *E' determinata da distruzione autoimmune delle cellule beta.*
- *L'incidenza e' piu' alta nei paesi sviluppati (Italia 7-36/ 100.000).*
- *Predisposizione preesistente (HLA DR3, DR4, DQ2)*
- *Fattori ambientali (enterovirus, rosolia, alimenti, etc..).*
- *Associazioni con altre malattie autoimmuni (celiachia, tiroidite…)*
- *Esordio classico nel 70-80% dei casi (poliuria-polidipsia).*
- *Esordio subdolo piu' frequente a 10-20 anni (LADA).*

Type 1 diabetes

- *E' la malattia metabolica piu' frequente in eta' pediatrica.*
- *L'incidenza e' piu' alta nei paesi sviluppati (Italia 7-36/100.000).*



: Incidence of type 1 diabetes in children aged 0–14 years, by geographical region and over time
(A) Estimated global incidence of type 1 diabetes, by region, in 2011.[11] (B) Time-based trends for the incidence of type 1 diabetes in children ages 0–14 years in areas with high or high-intermediate rates of disease.[12–16]

Definizione

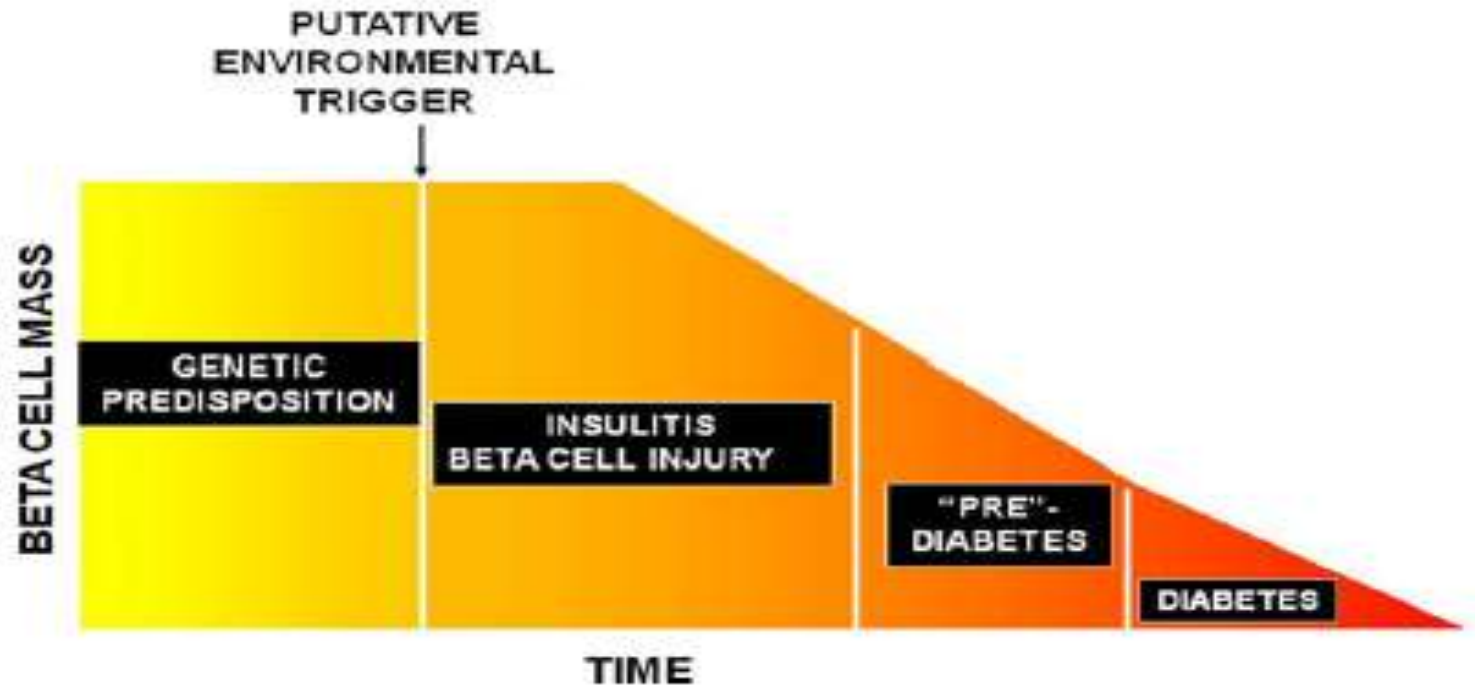
Il diabete mellito di tipo 1 è la malattia cronica più frequente in età pediatrica.
E' dovuto ad uno stato di deficit assoluto o relativo di insulina con conseguente elevazione cronica delle concentrazioni di glucosio nel sangue (iperglicemia).

Esordio classico nel 70-80% dei casi (poliuria-polidipsia).

Diabete	*mmol/l*	*mg/dl*
glicemia a digiuno	*> 7.0*	*> 126*
glicemia random o 2 ore dopo carico di glucosio	*> 11.1*	*> 200*
Intolleranza al glucosio		
glicemia a digiuno	*6.1-7.0*	*118-126*

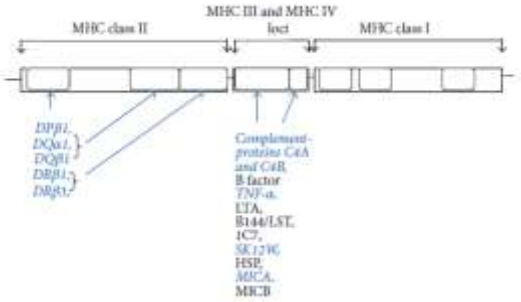
DM1 all'esordio : segni e sintomi

- *PPPD (Poliuria, Polidipsia, Polifagia, Dimagrimento)*
- *Dolori addominali*
- *Alito acetonico*
- *Dispnea, respiro di Kussmaul*
- *Vomito incoercibile*
- *Vulvovaginiti, balanopostiti*
- *Enuresi secondaria*
- *Convulsioni - "stato settico"*
- *Letargia, irritabilità, stato stuporoso, coma*



Natural history of type 1 diabetes. Adapted from Haller et al, Pediatr Clin North Am 2005;52:1553-78,[8] and Winter, Pediatric Endocrinology. New York, NY: Informa Healthcare USA, Inc; 2007:83-99.

Fattori genetici



- *Predisposizione genetica pre - esistente :*

- *HLA DR3,*
- *DR4,*
- *DQ -DRB1*0401-DQB1*0302- DRB1 0301 -DQB1*0201.*

- *Possibili geni candidati*

	cromosoma
INS[b]	11
PTPN22	1
CTLA4	2
IL2RA/CD25	10
SUMO4	6
IL12B	5
IL4R	16
IL4 (for IL4R replication study)[d]	5
IL13 (for IL4R replication study)[d]	5

	cromosoma
OAS1	12
VDR	12
CXCL12	10
PAX4	7
FOXP3[e]	X
IRS1	2
TCF7[f]	5
IFIH1	2
IFIH1 region (intergenic)	

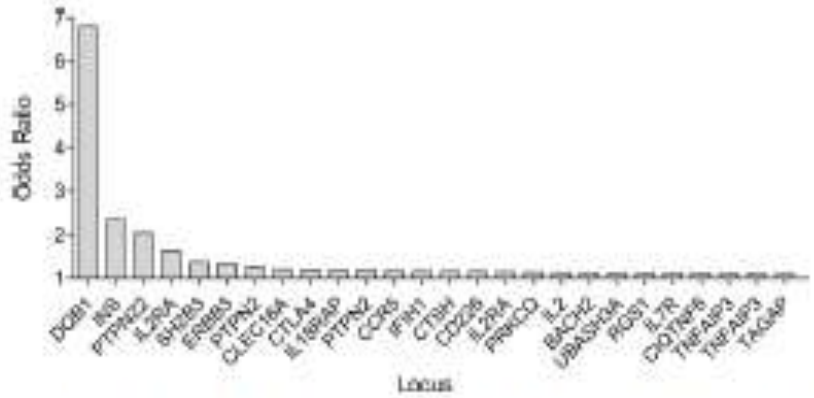
	cromosoma
IFIH1 region (intergenic)	
IFIH1 region (IFIH1)	
IFIH1 region (GCA)	
IFIH1 region (intergenic)	
IFIH1 region (KCNH7)	
CAPSL	5
CEACAM21	19
EFHB	3
Q7Z4C4	5

Genes Immun. 2009

T1D susceptibility genetic loci with their corresponding gene products and function

Locus	Gene product	Function
DQB1	HLA-DQ β chain	HLA class II Ag presentation
INS	Insulin	β-cell key hormone and Ag
PTPN22	Protein tyrosine phosphatase, nonreceptor type 22	TCR signaling
IL2RA	CD25	IL-2 receptor α-chain
SH2B3	SH2B3 adaptor protein	Negative regulation of cytokine signaling
ERBB3	ErbB-3 tyrosine protein kinase receptor	Member of the epidermal growth factor (EGF) receptor family
PTPN2	Protein tyrosine phosphatase, nonreceptor type 2	Signaling
CLEC16A	C-type lectin domain family 16, member A	Unknown
CTLA4	Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)	Negative costimulation molecule
IL18RAP	Accessory protein of the IL-18 receptor	Enhances IL-18 binding to its receptor
CCR5	Chemokine (C-C motif) receptor 5	Immune cell homing
IFIH1	IFN induced with helicase C domain 1	Apoptosis of virus-infected cells
CTSH	Cathepsin H	Lysosomal degradation of proteins, Ag processing
CD226	CD226	Adhesion, cytotoxicity, lymphokine secretion
PRKCQ	Protein kinase C theta	T-cell activation and IL-2 secretion
IL2	IL-2	Key T-cell growth factor
BACH2	BTB and CNC homology 1, basic leucine zipper transcription factor 2	Transcription factor
UBASH3A	Ubiquitin associated and SH3 domain containing A	Inhibits tyrosine kinase receptor down-regulation after activation
RGS1	Regulator of G-protein signaling 1	Regulation of B-cell activation
IL7R	IL-7 receptor	T-cell differentiation
C1QTNF6	Unknown	Unknown
TNFAIP3	TNFα-induced protein 3	Ubiquitin-processing enzyme, inhibition of inflammatory signaling
TAGAP	T-cell activation rho GTPase activating protein	T-cell activation

Beyond the Hormone: Insulin as an Autoimmune Target in Type 1 Diabetes



Odds ratios for the T1D susceptibility alleles identified at each of the indicated loci. See Table 1 for details about gene products and proposed functions corresponding to each locus.

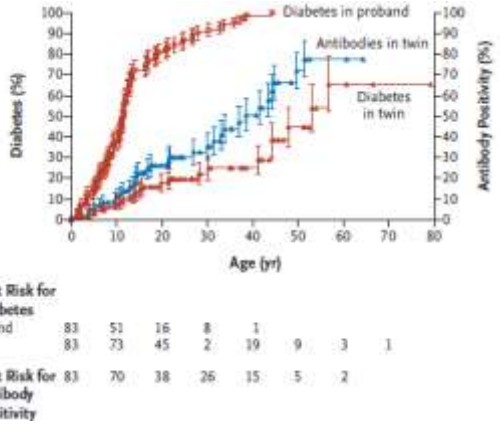
(*Endocrine Reviews* 32: 623–669, 2011)

Type 1 Diabetes: Current Concepts in Epidemiology, Pathophysiology, Clinical Care, and Research

. Risk of Type 1 Diabetes

General population	1 in 300-400
First degree relative with T1D	1 in 20
Offspring of affected mother	1 in 50
Offspring of affected father	1 in 14
Concordance rates	
In monozygotic twins	1 in 2-3 (30%-50%)
In dizygotic twins	1 in 10-16 (6%-10%)
DR3/DR4 (+) in the general population	1 in 40
Random sibling risk	1 in 20
Sibling HLA identical to affected sibling	1 in 7
Sibling shares DR3/DR4 with affected sibling	1 in 4

T1D, type 1 diabetes; HLA, human leukocyte antigen.



Because the incidence of T1D continues to increase worldwide at a rate of nearly 3% per year, we must be ever vigilant to ensure early and accurate diagnosis.

Curr Probl Pediatr Adolesc Health Care 2012;42:269-291

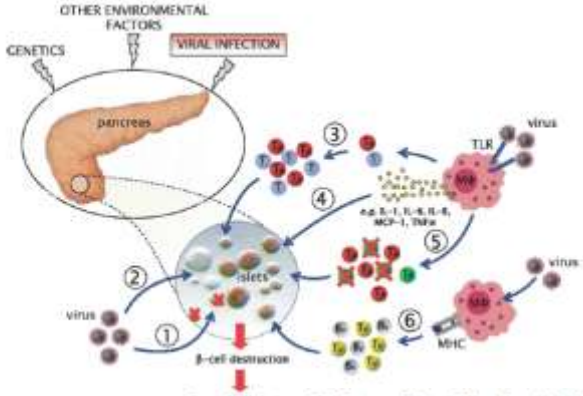
Fattori ambientali

Fattori ambientali (aumento di incidenza in popolazioni migranti, studi su gemelli, epidemie in alcune regioni, etc.):

- ***Infezioni virali** :*

Enterovirus, Coxsackie A e B, Echovirus,

Rosolia, Morbillo, Rotavirus, CMV

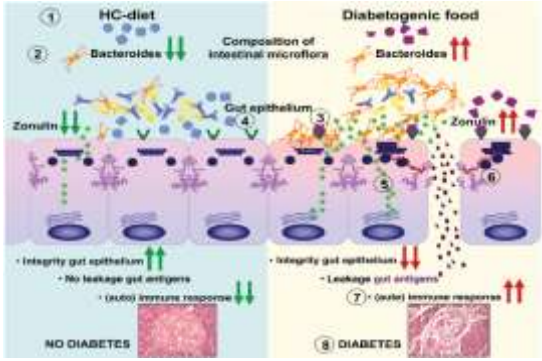


Diabetes Metab Res Rev 2007; **23**: 169–183.

- ***Alimenti***

proteine del latte vaccino, glutine,

vitamina D



Ann N Y Acad Sci. 2009

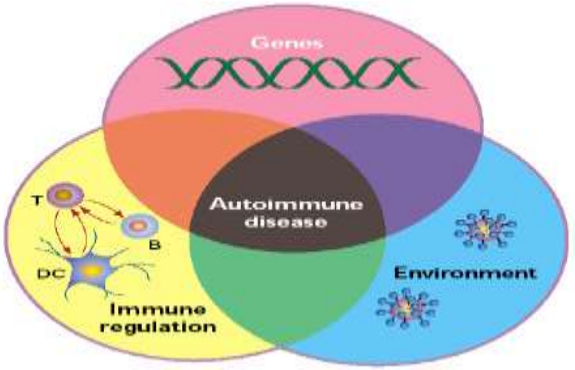
I fattori ambientali favoriscono l'instaurarsi dei meccanismi autoimmunitari che conducono alla distruzione

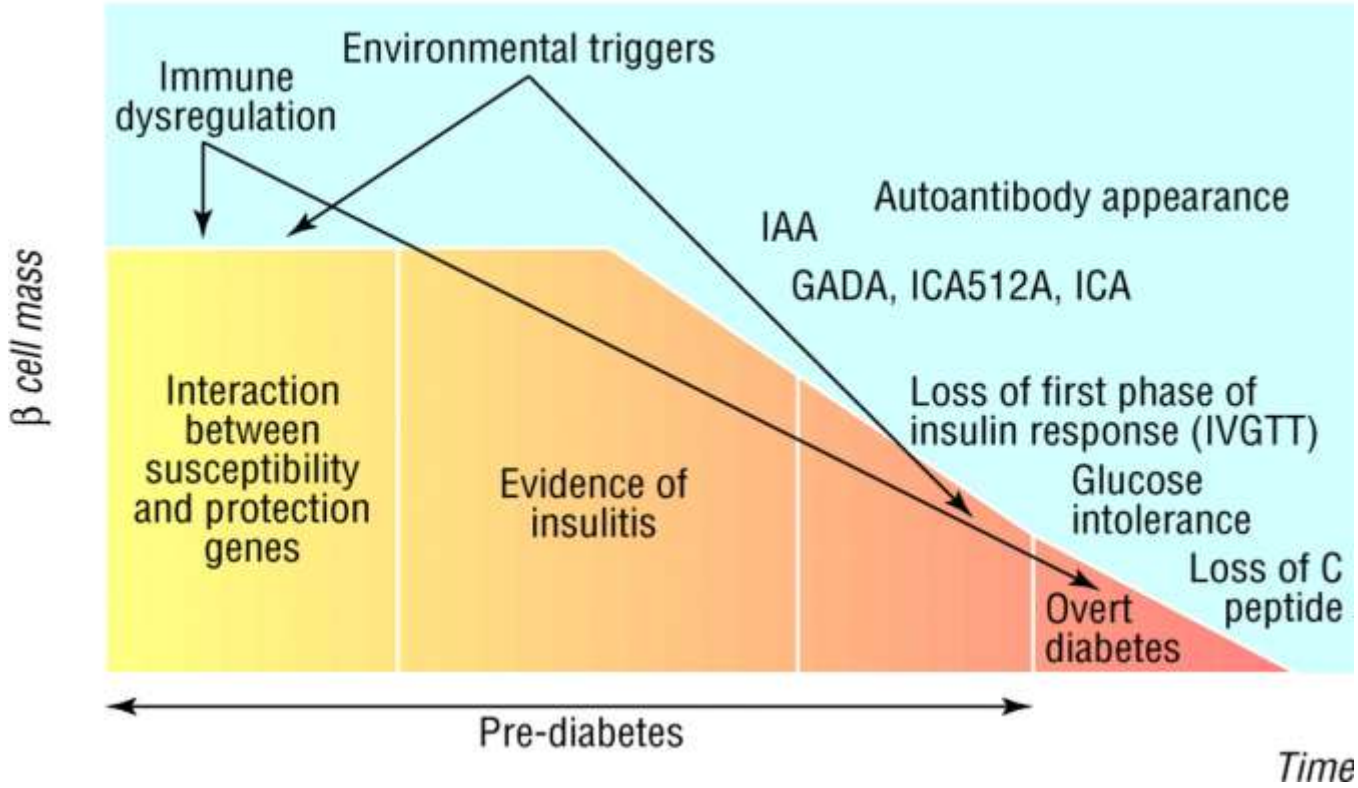
Fattori immunologici

*Autoanticorpi circolanti diretti contro le cellule insulari (**ICA**) si ritrovano nella maggior parte dei soggetti con T1DM di recente diagnosi*

- ✓ *Autoanticorpi circolanti diretti contro le cellule insulari (ICA) si ritrovano nella maggior parte dei soggetti con T1DM di recente diagnosi*
- ✓ *Gli ICA ad alto titolo (> 20 unità JDF) predicono un rischio del 40-60% nei successivi 5-7 anni*
- ✓ *Gli ICA e gli altri auto-anticorpi* **(GAD,IAA, IA2A /ICA512,ZnT8)** *sono presenti nel periodo di "prediabete"*
- ✓ *Quando sono presenti anticorpi multipli (2 o più) , la capacità predittiva aumenta fino al 70% in 10 anni*

Storia naturale del T1DM





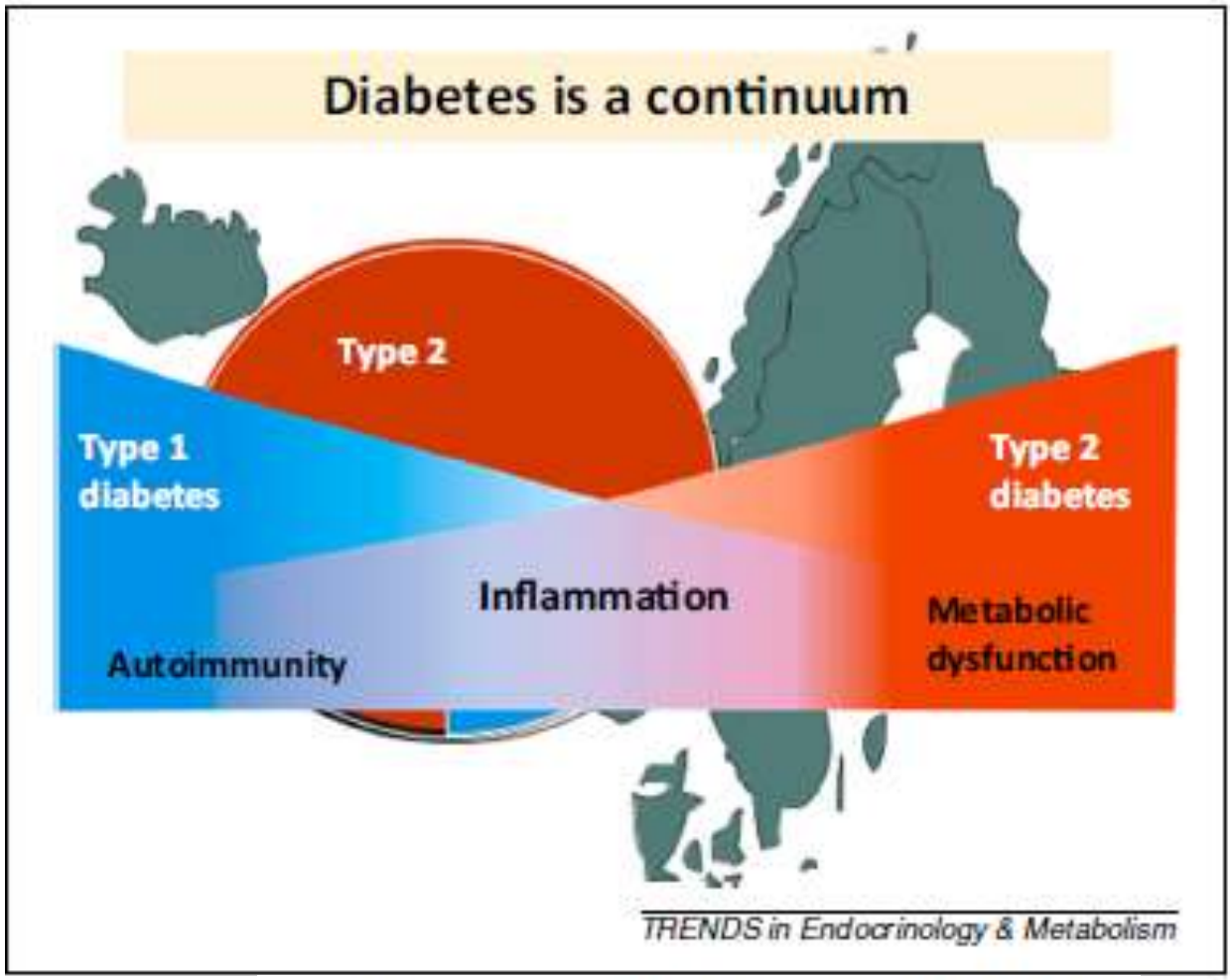
Diagnosis and classification of autoimmune diabetes mellitus

Classification and clinical characteristics of diabetes mellitus.

Characteristics	T1A	T1B	Fulminant T1	Double diabetes	LADA	Type 2 diabetes
Genetics	Polygenic	?	Polygenic	Polygenic?	Polygenic?	Polygenic
Age at onset	Mostly 6 months to youth, but can appear at any age	Any age	Mostly young adults, but can appear at any age and during pregnancy or just after delivery	Children and adolescents	Adults	Mostly adults but can appear at any age
Clinical presentation	Most often acute	?	Severely acute	Variable: from slow, mild to severe	Variable: from slow, mild to severe	Variable: from slow, mild to severe
Autoimmunity	Present (ICA, GADA, IA-2, IAA, ZnT8A)	Absent	Usually absent, GADA can be detectable in some cases	Present (GADA, IA-2 and IAA)	Present (GADA or ICA positive)	Absent, but some reports described IgG antibodies associated with insulin resistance and auto-antibodies against pancreatic islet antigens
Ketosis	Common	Common	Common	Uncommon	Uncommon	Uncommon
Obesity	Population frequency	Population frequency	Population frequency	Increased frequency	Increased frequency	Increased frequency
Acanthosis nigricans	No	No	No	Maybe	Maybe	Yes
Family history of diabetes	Maybe (2–4%)	?	Maybe	Maybe	Yes	Yes (80%)
Insulin requirement	Yes	Yes	Yes	Maybe	Usually not	Maybe

Autoimmunity Reviews 13 (2014) 403–407

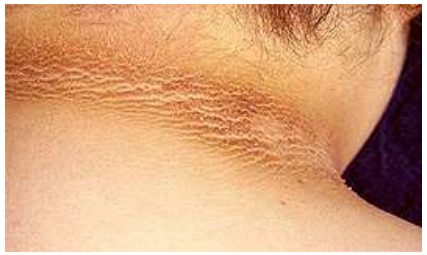
Can genetics improve precision of therapy in diabetes?



Trends in Endocrinology and Metabolism September 2014, Vol. 25, No. 9

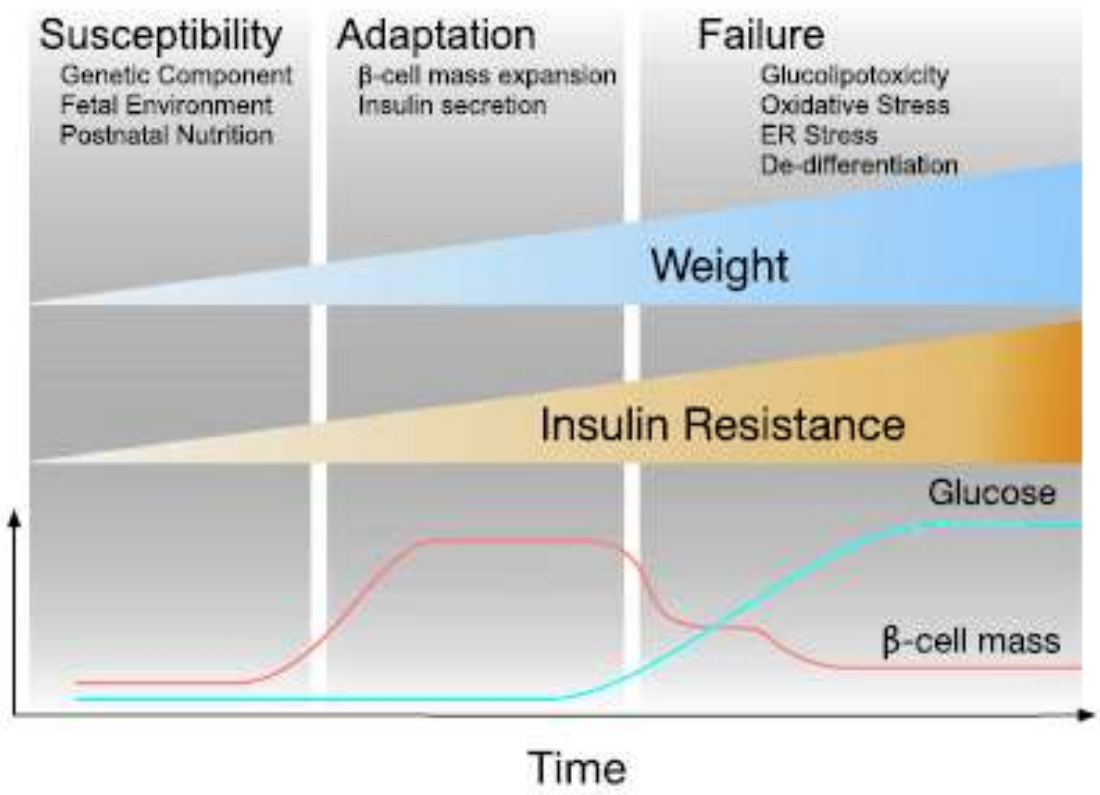
EPIDEMIOLOGIA ATTUALE DEL DIABETE DI TIPO 2 IN ETA' EVOLUTIVA

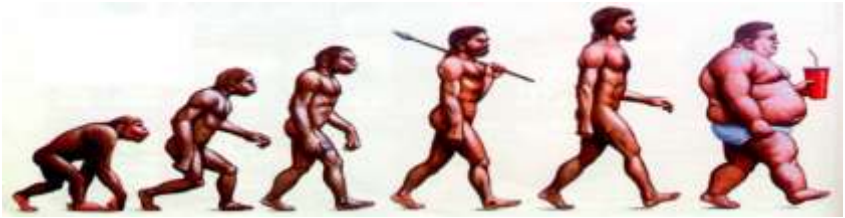
- *Costituisce il 20-30 % circa delle forme di diabete nell'adolescente*
- *L'età di esordio è mediamente fra 12 e 14 anni (in coincidenza con l'aumento dell'insulino-resistenza tipico della pubertà)*
- *Il sesso più colpito è quello femminile (1.6:1)*
- *Il 96 % dei giovani colpiti hanno un BMI > 85° percentile*
- *L'86 % hanno un' acanthosis nigricans*
- *Il 30 % hanno un'ipertensione arteriosa*
- *Tutti questi dati sottolineano la stretta correlazione fra diabete di tipo 2 ed obesità (considerato che acanthosis nigricans ed ipertensione sono spesso una conseguenza dell'obesità)*



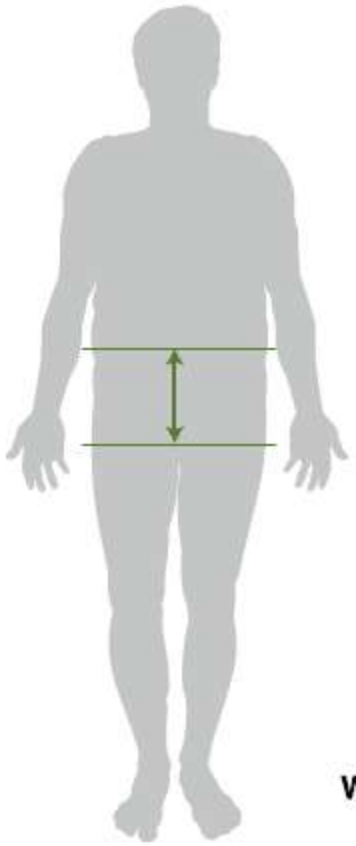
Natural history of β-cell adaptation and failure in type 2 diabetes

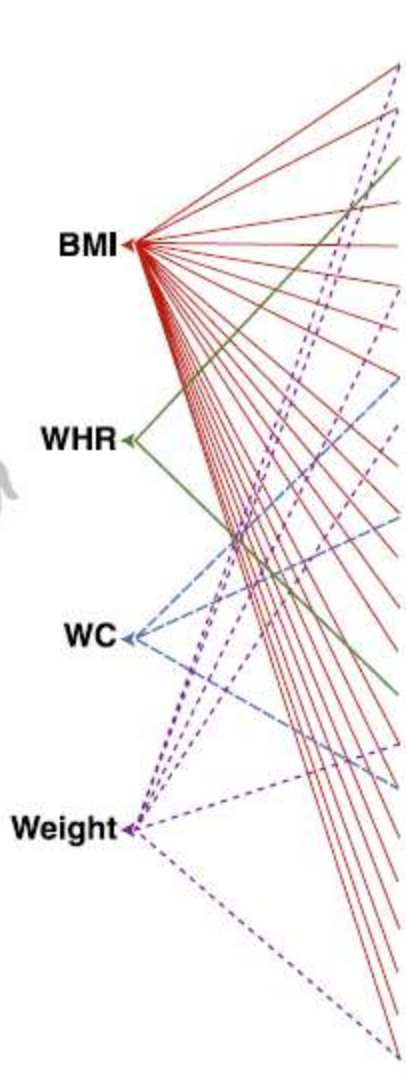
E.U. Alejandro et al./Molecular Aspects of Medicine ■■ (2014) ■■–■■





The Genetics of Obesity

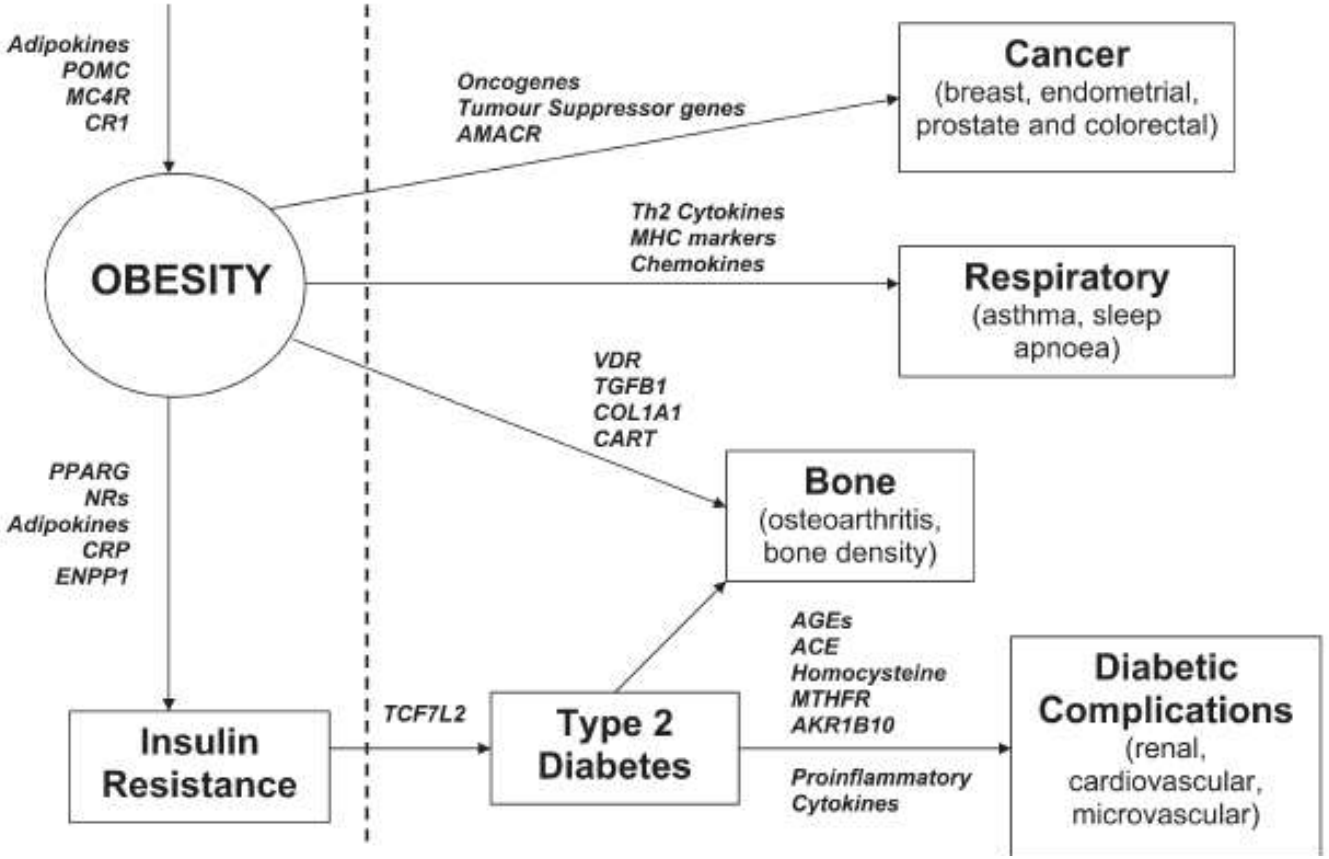




Gene name	Position
NEGR1	1p31
SEC16B, RASAL2	1q25
LYPLAL1, ZC3H11B	1q41
SDCCAG8	1q43–q44
TMEM18	2p25
Near ETV5	3q27
Near GNPDA2	4p13
TFAP2B	6p12
NCR3, AIF1, and BAT2	6p21
PRL	6p22.2–p21.3
MSRA	8p23.1
PTER	10p12
MTCH2	11p11.2
BDNF region	11p14
C12orf51/PTPN11	12q24
FAIM2, BCDIN3D	12q13
NRXN3	14q31
SH2B1 region	16p11.2
MAF	16q22–q23
FTO[a]	16q22.2
NPC1	18q11.2
MC4R[b]	18q22
KCTD15	19q13.11

Curr Diab Rep (2010) 10:498–505

Genetics of obesity and the prediction of risk for health



Examples of clinically relevant biomarkers for assessing the development of obesity and its sequelae. The dotted line represents the division between clinical health and disease. Key (in alphabetical order): ACE, angiotensin I-converting enzyme (peptidyl-dipeptidase A) 1; AGEs, advanced glycation end-products; AKR1B10, aldo-keto reductase family 1, member B10 (aldose reductase); AMACR, alpha-methylacyl-CoA racemase; CART, cocaine- and amphetamine-regulated transcript; COL1A1, collagen, type I, alpha 1; CR1, cannabinoid receptor 1; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; MC4*R*, melanocortin-4 receptor; MTHFR, 5,10-methylenetetrahydrofolate reductase (NADPH); NRs, nuclear receptors; POMC, pro-opiomelanocortin; PPARG, peroxisome proliferative activated receptor, gamma; TCF7L2, transcription factor 7-like 2 (T-cell specific, HMG-box); TGFB1, transforming growth factor, beta 1; VDR, vitamin D (1,25-dihydroxyvitamin D3) receptor.

Human Molecular Genetics, 2006, Vol. 15, No. 2

Genes and the hypothalamic control of metabolism in humans

Obesity monogenes identified in Caucasians and their expression in the hypothalamus.

Gene	Gene name
LEP	Leptin
LEPR	Leptin receptor
MC4R	Melanocortin-4 receptor
BDNF	Brain-derived neurotrophic factor
NTRK2	Neurotrophin receptor TrkB
SH2B1	SH2B adaptor protein 2 isoform 1
POMC	Pro-opiomelanocortin
PCSK1	Prohormone convertase 1 gene
TUB	Tubby gene

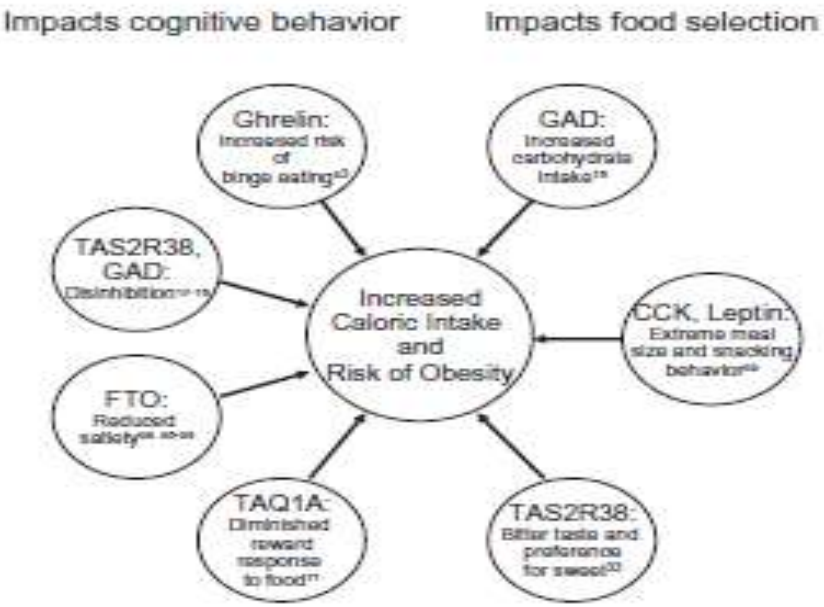
Best Practice & Research Clinical Endocrinology & Metabolism 28 (2014) 635–647

GWAS derived BMI associated loci identified in Caucasians and their expression in the hypothalamus.

Lead SNP	Regional gene(s)	Gene name
rs6602024	*PFKP*	Phosphofructokinase, platelet
rs1558902	*FTO*	Fat mass and obesity associated gene
rs2867125	*TMEM18*	Transmembrane protein 18
rs571312	*MC4R*	Melanocortin-4 receptor
rs543874	*SEC16B*	Leucine zipper transcription regulator 2
rs13107325	*SLC39A8*	Solute carrier family 39 (zinc transporter) member 8
rs10767664	*BDNF*	Brain-derived neurotrophic factor
rs10938397	*GNPDA2*	Glucosamine-6-phosphate deaminase 2
rs12444979	*GPRC5B*	G protein-coupled receptor, family C, group 5
	IQCK	IQ motif containing K
rs11847697	*PRKD1*	Protein kinase D1
rs7359397	*SH2B1*	SH2B adaptor protein 2 isoform 1
	APOB48R	Apolipoprotein B48 receptor
	SULT1A2	Sulfotransferase family, cytosolic, 1A, member 2
	ATXN2L	Ataxin 2 related protein
	TUFM	Tu translation elongation factor, mitochondrial
rs2287019	*GIPR*	Gastric inhibitory polypeptide receptor
	QPCTL	Glutaminyl-peptide cyclotransferase-like
rs9816226	*ETV5*	ets variant gene 5
rs713586	*POMC*	Pro-opiomelanocortin
	DNAJC27	DnaJ (Hsp40) homologue, subfamily C, member 27
	ADCY3	Adenylate cyclase 3
rs2815752	*NEGR1*	Neuronal growth regulator 1
rs987237	*TFAP2B*	Transcription factor AP-2 beta
rs2241423	*MAP2K5*	Mitogen-activated protein kinase kinase 5
	SKOR1	SKI family transcriptional corepressor 1
rs10150332	*NRXN3*	Neurexin 3
rs7138803	*FAIM*	Fas apoptotic inhibitory molecule
rs6013029	*CTNNBL1*	Catenin β-like 1
rs10968576	*LRRN6C*	Leucine rich repeat and Ig domain containing 2
rs2112347	*HMGCR*	3-hydroxy-3-methylglutary Coenzyme A reductase
	POC5	POC5 Centriolar Protein
rs887912	*FANCL*	Fanconi anaemia, complementation group L
rs13078807	*CADM2*	Immunoglobulin superfamily, member 4D
rs3810291	*TMEM160*	Transmembrane protein 160
	ZC3H4	Zinc finger CCCH-type containing 4
rs2890652	*LRP1B*	Low density lipoprotein-related protein 1B
rs4771122	*MTIF3*	Mitochondrial translational initiation factor 3
	GTF3A	Transcription factor IIIA
rs4712652	*PRL*	Prolactin
rs1514175	*TNNI3K*	TNNI3 interacting kinase
rs4836133	*ZNF608*	Zinc finger protein 608
rs3817334	*MTCH2*	Mitochondrial carrier 2
	NDUFS3	NADH dehydrogenase (ubiquinone) Fe-S protein 3
	CUGBP1	CUG triplet repeat, RNA-binding protein 1
rs29941	*KCTD15*	Potassium channel tetramerisation domain
rs1555543	*PTBP2*	Polypyrimidine tract binding protein 2
rs4929949	*TUB*	Tubby gene
	RPL27A	Ribosomal protein L27a
rs206936	*NUDT3*	Nudix-type motif 3
	HMGA1	High mobility group AT-hook 1
rs1805081	*NPC1*	Niemann–Pick disease, type C1 precursor
rs1424233	*MAF*	v-maf musculoaponeurotic fibrosarcoma oncogene
rs10508503	*PTER*	Phosphotriesterase related

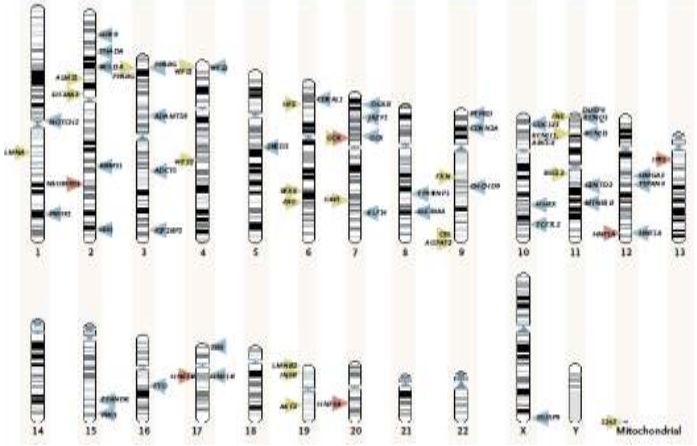
Common variants associated with meal selection and size.

Hormone	Gene variants	Physiologic effect of gene product	Contribution to eating behavior
CCK	rs6809785, rs7611677, rs6801844	Rapid post-prandial satiety	Extreme meal size
Leptin	rs4577902, rs2060736, rs4731413	Promotes satiety	Extreme snacking behavior
Ghrelin	Leu72Met, 51GLN	Promotes meal intake and hunger Metabolic syndrome Obesity	Binge eating
FTO	rs9939609	Downregulates leptin, suppresses satiety	Reduced post-prandial satiety, increased caloric intake
GAD	rs7908975, rs992990	Promotes GABA, regulates food intake	Increased carbohydrate intake

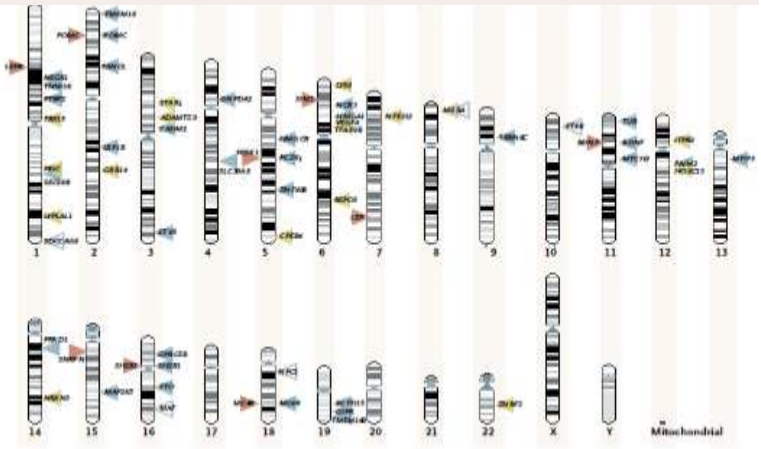


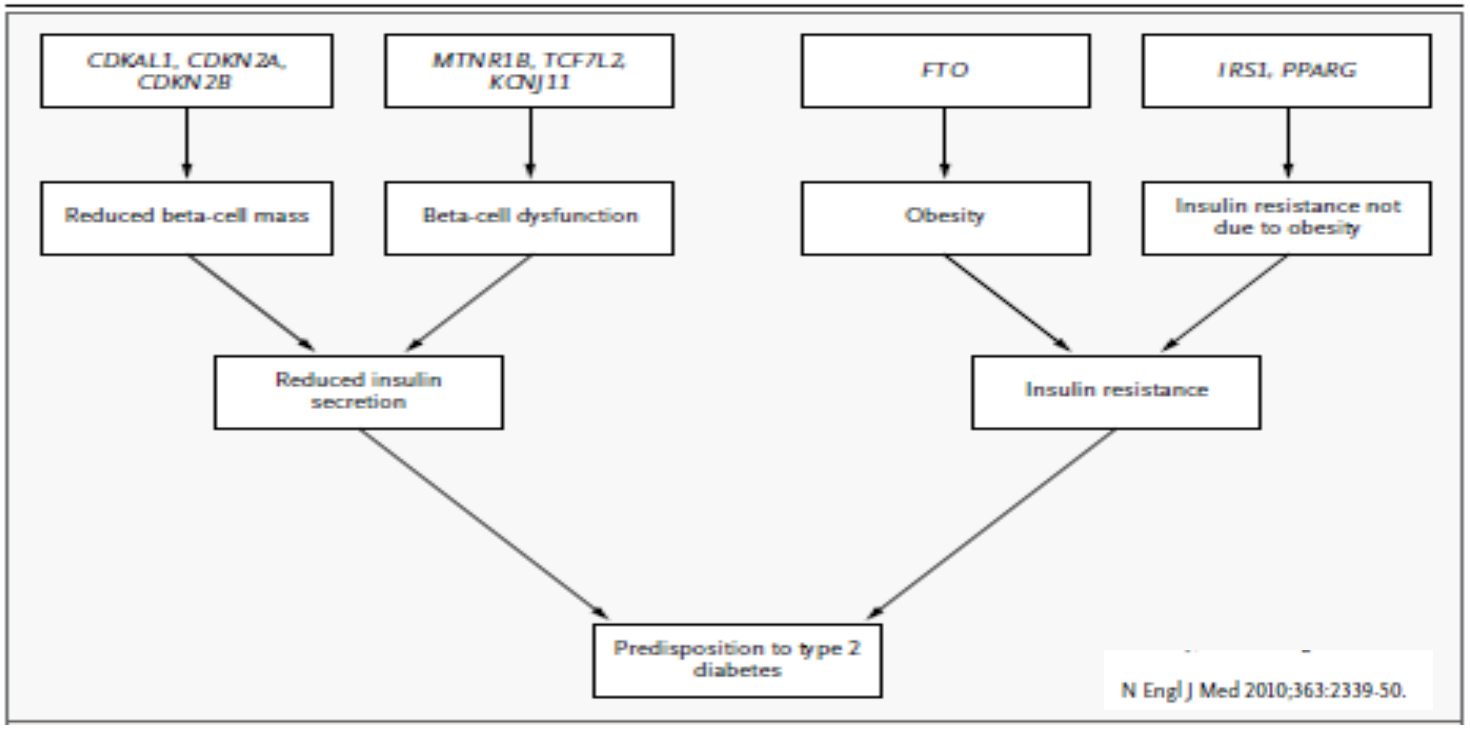
Genomics, Type 2 Diabetes, and Obesity

Genomic Locations of Proven Signals of Nonautoimmune Forms of Diabetes.



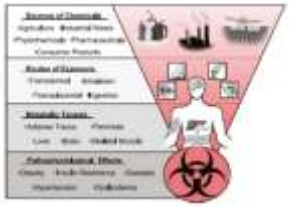
Genomic Locations of Proven Signals of Body-Mass Index (BMI), Obesity, and Related Phenotypes.





N Engl J Med 2010;363:2339-50.

Early determinants of type-2 diabetes



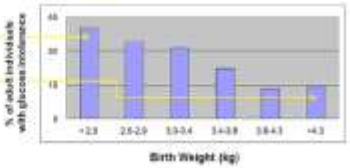
Obesity
Gestational weight gain

Maternal insulin resistance/T2D/GDM
Hyperglycaemia

Placental insufficiency

Maternal over- or under-nutrition

Mother's early life exposures



Paternal health status

Genetic factors

Epigenetics

PROGRAMMING – *in utero*
Morphological, physiological and metabolic adaptations

Catch up growth/Failure to thrive

Poor quality diet

Lack of physical activity

Age

Pancreatic β cell dysfunction
↓ insulin secretion

↑ fat mass
Central adiposity

Disruption of central neurocircuits
Hyperphagia

Hormone imbalances
Glucose intolerance

Altered insulin sensitivity of muscle, liver and adipose tissue

Inflammation, cellular/ER stress, oxidative stress

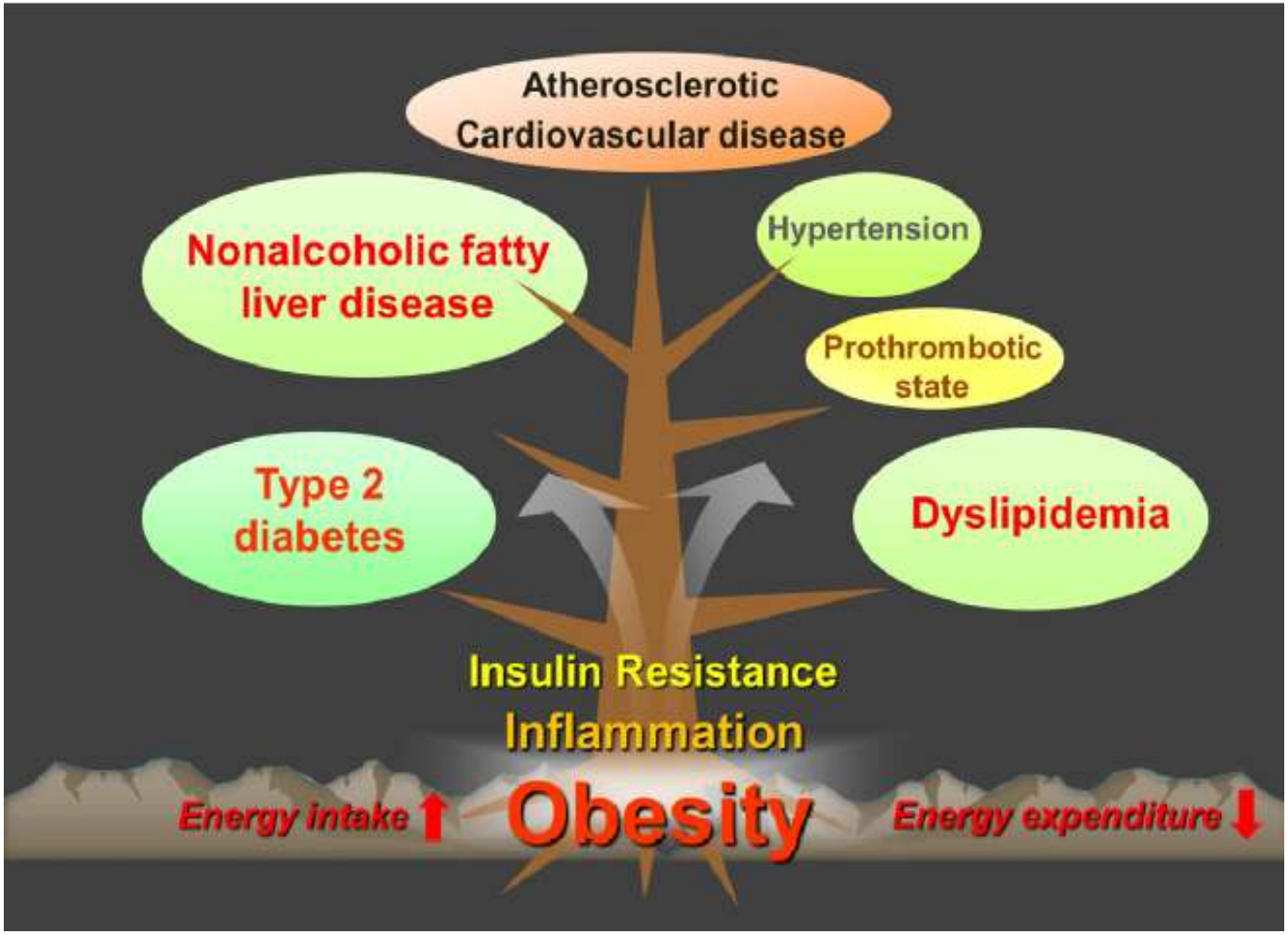
Type-2 diabetes

Insulin resistance

↑ T2D risk for future generations

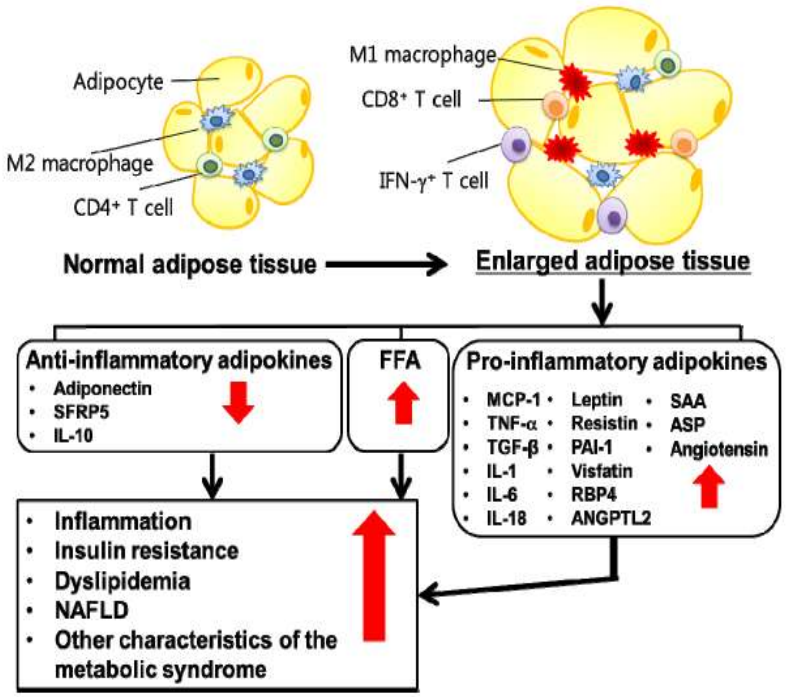
/ Best Practice & Research Clinical Endocrinology & Metabolism 26 (2012) 569–580

Obesity and Its Metabolic Complications:
The Role of Adipokines and the Relationship between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease



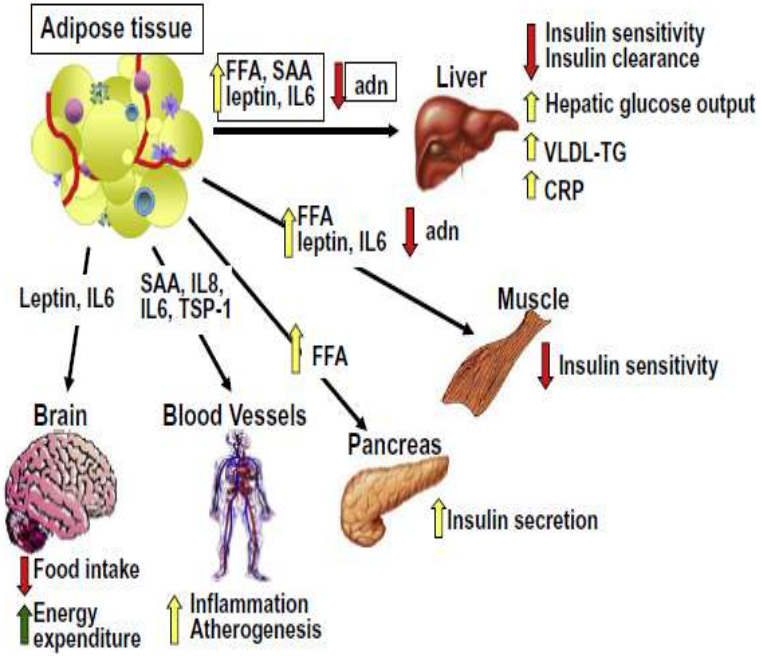
Int. J. Mol. Sci. **2014**, *15*, 6184-6223

Obesity and Its Metabolic Complications:
The Role of Adipokines and the Relationship between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease



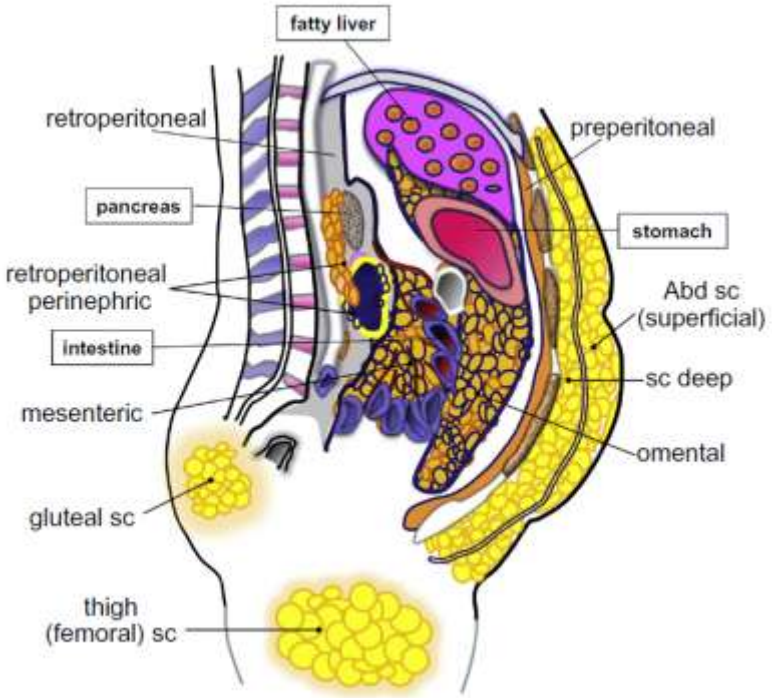
Int. J. Mol. Sci. **2014**, *15*, 6184-6223

Adipose tissue heterogeneity: Implication of depot differences in adipose tissue for obesity complications



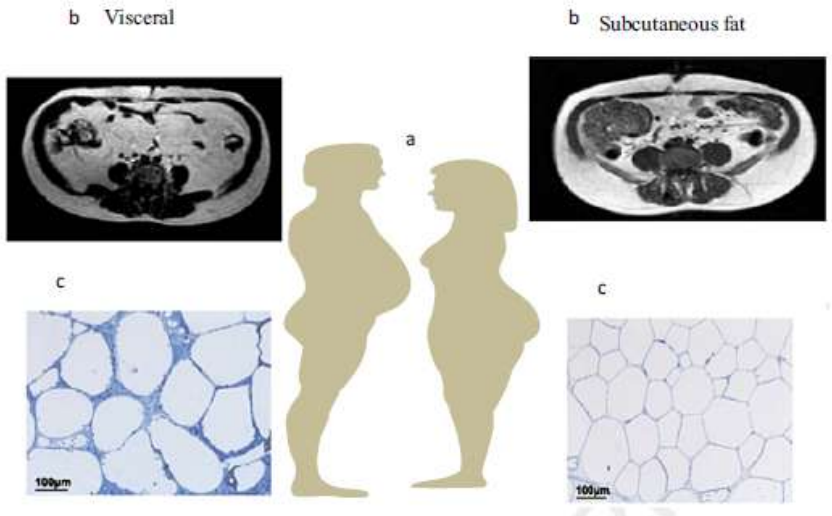
M.-J. Lee et al. / Molecular Aspects of Medicine 34 (2013) 1–11

Adipose tissue heterogeneity: Implication of depot differences in adipose tissue for obesity complications



M.-J. Lee et al. / Molecular Aspects of Medicine 34 (2013) 1–11

The sexual dimorphism of obesity



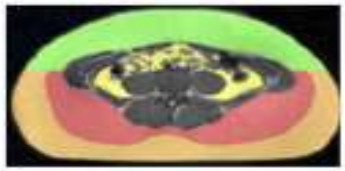
B.F. Palmer, D.J. Clegg/Molecular and Cellular Endocrinology ■■ (2015)

High Visceral and Low Abdominal Subcutaneous Fat Stores in the Obese Adolescent

A

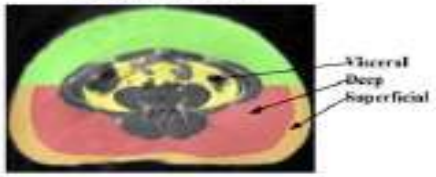
Males

Tertile 1
Age: 14
BMI: 35.3
Percent Fat: 41.7%



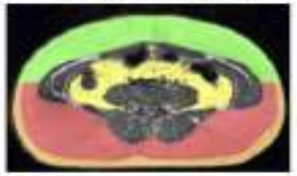
Proportion of Visceral Fat: 0.08
Visceral Fat: 56 cm^2
Subcutaneous Fat: 628 cm^2
Deep-to-Superficial Ratio: 0.84
Matsuda Index: 2.60
Fasting Insulin: 23 μU/ml
2-hr Glucose: 80 mg/dl
TG: 100 mg/dl
HDL: 39 mg/dl

Tertile 2
Age: 14
BMI: 34.0
Percent Fat: 39.3%



Proportion of Visceral Fat: 0.10
Visceral Fat: 68 cm^2
Subcutaneous Fat: 616 cm^2
Deep-to-Superficial Ratio: 2.08
Matsuda Index: 1.17
Fasting Insulin: 33 μU/ml
2-hr Glucose: 118 mg/dl
TG: 109 mg/dl
HDL: 34 mg/dl

Tertile 3
Age: 14
BMI: 33.1
Percent Fat: 38.4%

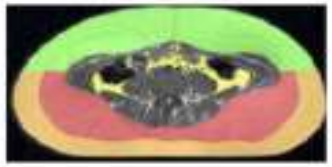


Proportion of Visceral Fat: 0.15
Visceral Fat: 89 cm^2
Subcutaneous Fat: 519 cm^2
Deep-to-Superficial Ratio: 2.84
Matsuda Index: 0.82
Fasting Insulin: 43 μU/ml
2-hr Glucose: 124 mg/dl
TG: 140 mg/dl
HDL: 40 mg/dl

B

Females

Tertile 1
Age: 12
BMI: 33.3
Percent Fat: 40.4%

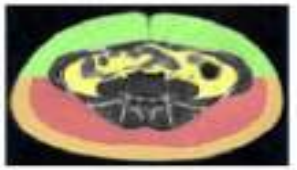


Proportion of Visceral Fat: 0.05
Visceral Fat: 28 cm^2
Subcutaneous Fat: 518 cm^2
Deep-to-Superficial Ratio: 1.15
Matsuda Index: 1.90
Fasting Insulin: 33 μU/ml
2-hr Glucose: 95 mg/dl
TG: 15 mg/dl
HDL: 44 mg/dl

Tertile 2
Age: 13
BMI: 27.7
Percent Fat: 38.2%

Proportion of Visceral Fat: 0.11
Visceral Fat: 50 cm^2
Subcutaneous Fat: 409 cm^2
Deep-to-Superficial Ratio: 1.26
Matsuda Index: 1.15
Fasting Insulin: 32 μU/ml
2-hr Glucose: 165 mg/dl
TG: 82 mg/dl
HDL: 61 mg/dl

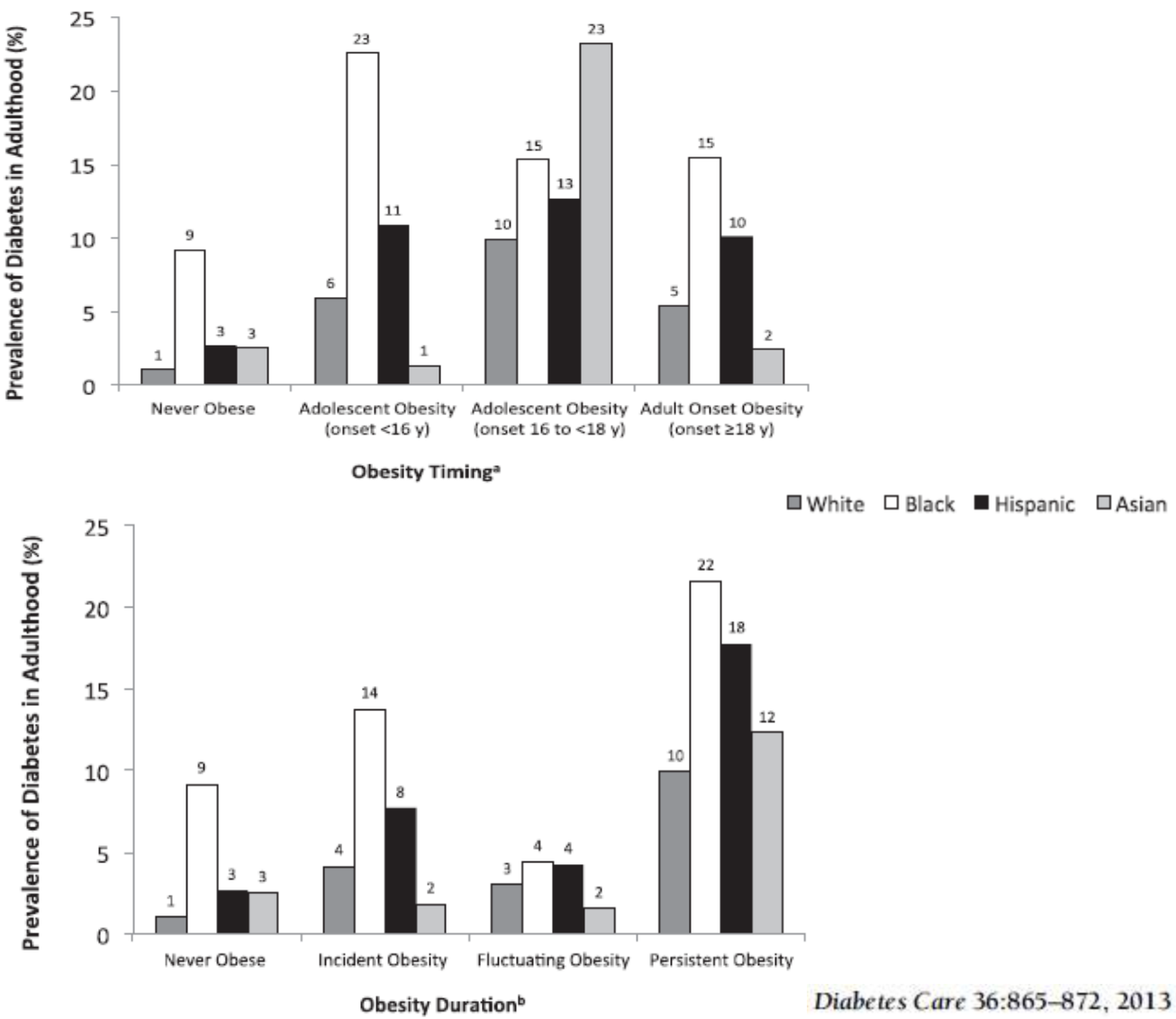
Tertile 3
Age: 11
BMI: 27.6
Percent Fat: 37.7%



Proportion of Visceral Fat: 0.15
Visceral Fat: 58 cm^2
Subcutaneous Fat: 338 cm^2
Deep-to-Superficial Ratio: 1.39
Matsuda Index: 0.27
Fasting Insulin: 77 μU/ml
2-hr Glucose: 185 mg/dl
TG: 143 mg/dl
HDL: 33 mg/dl

FIG. 2. Representative MRI images of Caucasian male (*A*) and female (*B*) subjects from each of the three visceral tertiles. Note the increase in visceral fat, decrease in subcutaneous fat, and increase in deep-to-superficial subcutaneous fat ratio across tertiles. In addition, there is a decrease in insulin sensitivity (Matsuda index) and an increase in fasting insulin, 2-h glucose, and triglycerides.

Timing and Duration of Obesity in Relation to Diabetes



Diabetes Care 36:865–872, 2013

Diabete mellito : nell'ambulatorio pediatrico….

- ***Tipo 1:*** *L'esordio è spesso imprevedibile, tranne che per alcune categorie a rischio, al momento attuale non è prevenibile (TRIALS : interventi dietetici, farmacologici, trapianto).*

Fare una rapida diagnosi in base ai sintomi per avviare un trattamento tempestivo

- ***Tipo 2:*** *L'esordio è prevedibile , e in molti casi prevenibile (alimentazione corretta, attività fisica, interventi psico-comportamentali).*

Identificare i bambini a rischio

Malattie autoimmuni della tiroide (AITD)

- *La causa più comune di malattie della tiroide nei bambini e negli adolescenti;*
- *Rappresentano la causa più comune di ipotiroidismo acquisito, con o senza gozzo;*
- *L'incidenza è circa 1-3% nella popolazione scolare (F:M 7:1);*
- *Può comparire nei primi 3 anni di vita, più frequente dopo i 6 anni ; il picco di incidenza è durante l'adolescenza.*
- *AITD può far parte di una sindrome polighiandolare autoimmune (10%);*
- *I bambini con sindrome di Down (7%), di Turner (15%) e di Klinefelter , malattia celiaca, T1DM (4%) sono a più alto rischio per avere associata una AITD.*

AITD

- *AITD sono disordini poligenici multifattoriali con l'importante contributo dell'ambiente sul fenotipo della malattia*

- *Lo spettro delle AITD includono: la malattia di Graves(GD), la tiroidite di Hashimoto (HT), e la Hashitossicosi (Htx).*

- *Lo spettro delle AITD differisce in termini di funzione tiroidea, durata della malattia e comparsa di altre localizzazioni anatomiche.*

- *AITD rappresentano un processo dinamico: la funzione della tiroide può subire variazioni durante il follow-up.*

Presentazione clinica

La AITD si può presentare come :

- ***Eutiroidismo** e nessun sintomo (52.1%)*
- ***Ipotiroidismo** subclinico (19.2%)*
- *" " " ipotiroidismo conclamato (22.2%)*
- ***Ipertiroidismo** subclinico (3%)*
- ***Ipertiroidismo** conclamato (3.5%).*

*Sintomi e segni di **ipotiroidismo** conclamato sono:*

gozzo, scarso accrescimento staturale, ritardo maturazione ossea, ritardo dello sviluppo puberale, aumento di peso, irregolarità mestruali, ridotto rendimento scolastico, ipotermia, intolleranza al freddo, cute secca, perdita dei capelli,

*Segni clinici di **ipertiroidismo** conclamato sono:*

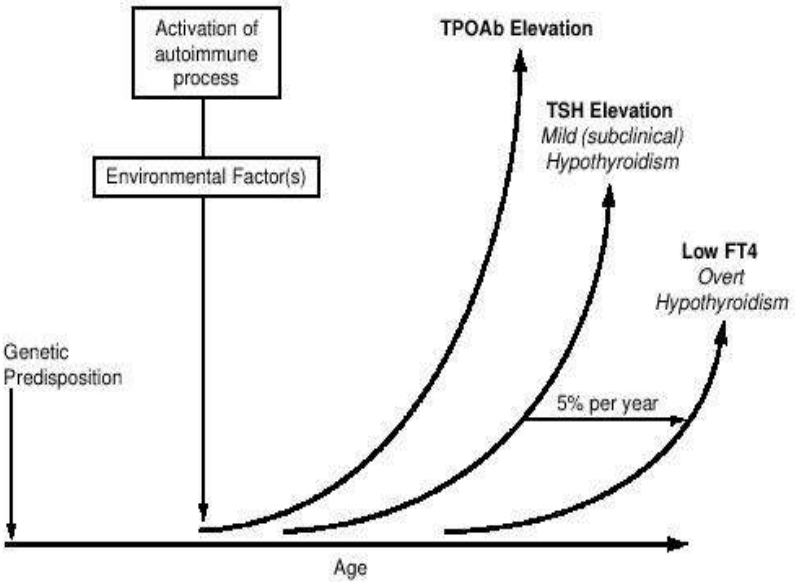
gozzo, nervosismo, irritabilità, iperattività, sudorazione, esoftalmo, difficoltà di concentratione, mal di testa, tachicardia, ipertensione , diarrea, perdita di peso, intolleranza al caldo, tremori.

Horm Res Paediatr 2012; 78:232-36

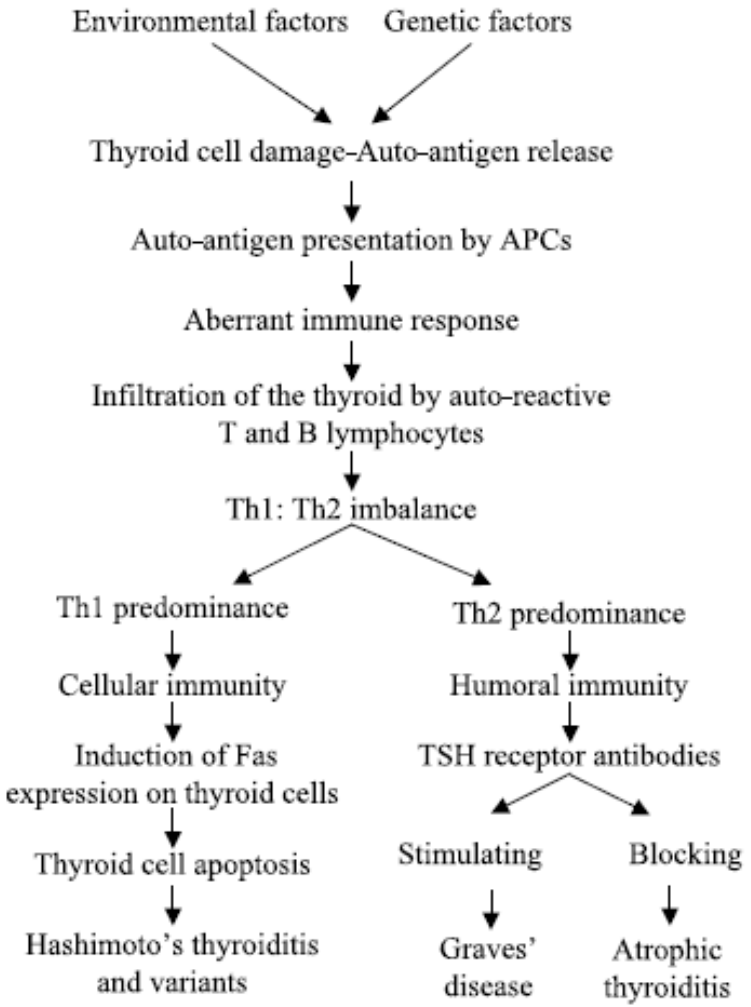
Rapporti fra Hashimoto (HT) e Graves (GD)

- *In coppie di gemelli monozigoti uno può sviluppare l'HT e l'altro la GD*
- *Possono aggregare nelle stesse famiglie*
- *Possono coesistere nella stessa ghiandola*
- *Possono succedersi nella storia clinica degli stessi pazienti*
- *L'aplotipo HLA predispondente è lo stesso (DR3)*

Patogenesi



Thyroid 2003 Mary Ann Liebert, Inc

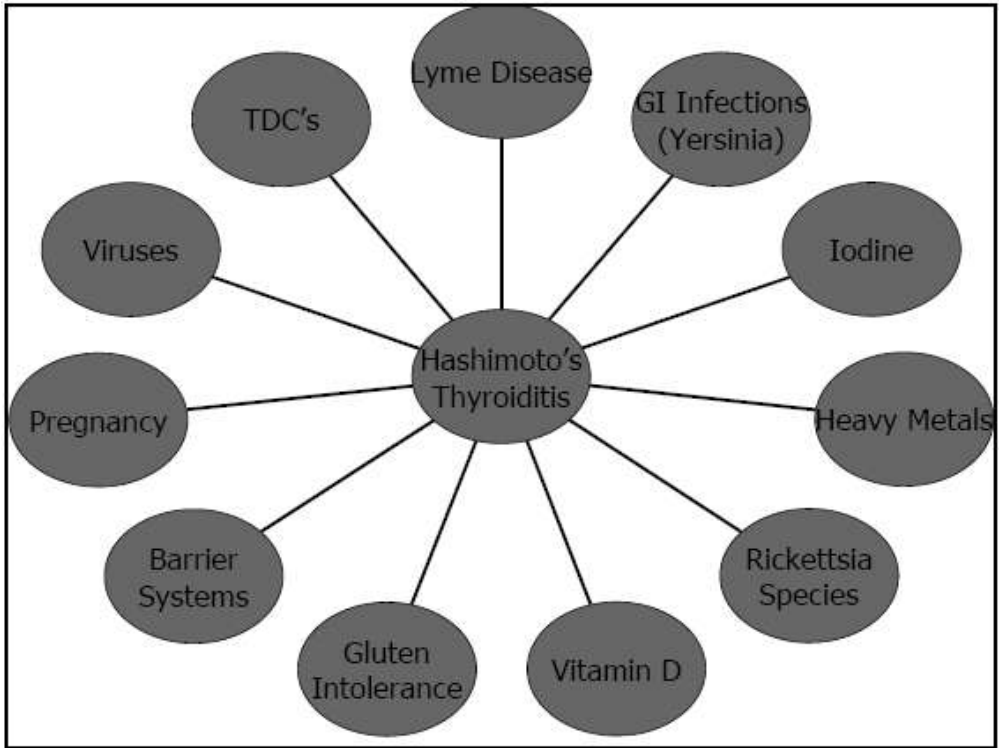


Clinical Endocrinology (2004) **60**, 397–409

Geni di Immunosusceptibilità

Risposta immunità cellulare

Immunità Umorale



Fattori ambientali

Infezioni,
Farmaci (litio, amiodarone, interferon - alpha),
ormoni (estrogeni),
Alimenti (iodio, selenio),
Stress,
Fumo,
Tossine ambientali.

Susceptibility genes in thyroid autoimmunity

Some HLA association studies in GD performed in Caucasians.

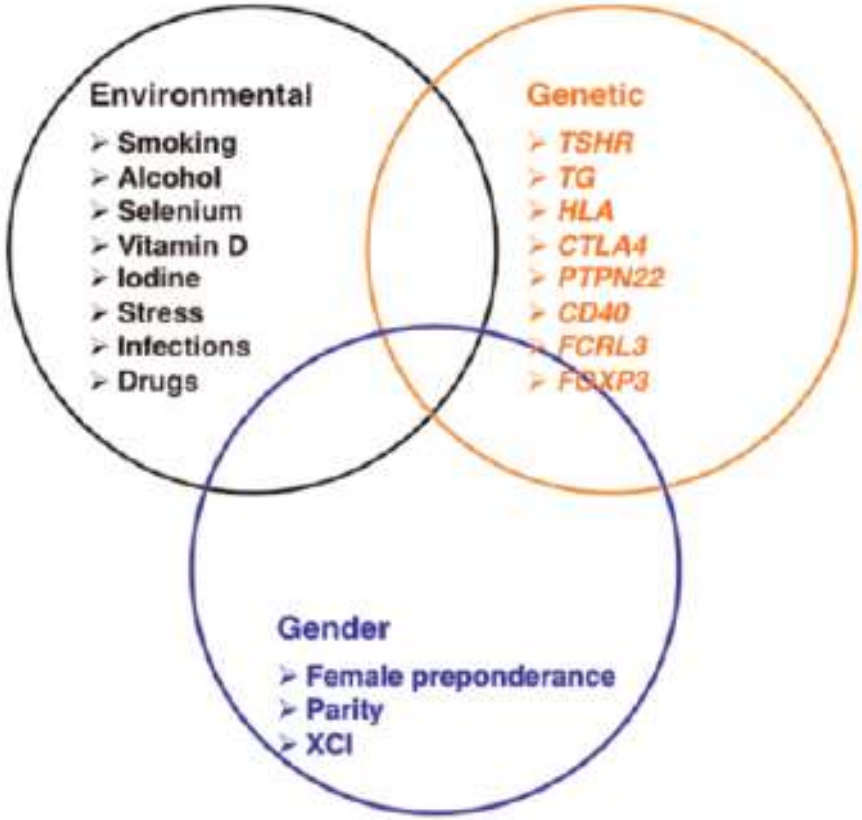
Country	No. of patients	HLA allele	Relative risk/*p*-value	Reference
Belgium	194	DRB1*0301	2.53	Zamani et al. (2000)
Canada	175	B8	3.1	Farid et al. (1980)
		DR3	5.7	
Denmark	86	B8	2.80	Bech et al. (1977)
		Dw3	3.94	
Germany	253	DR3	2.52	Schleusener et al. (1989)
Hungary	256	B8	3.48	Stenszky et al. (1985)
		DR3	4.8	
Sweden	78	B8	4.4	Dahlberg et al. (1981)
		DR3	3.9	
UK	127	B8	2.77	Kendall-Taylor et al. (1988)
		DR3	2.13	
UK	101	DR3	1.10	Weetman et al. (1988)
USA	65	DR3	3.38	Mangklabruks et al. (1991)
USA	92	DRB1*03	2.6	Chen et al. (1999)
		DRB1*08	3.2	
UK	120	DQA1*0501	3.8	Barlow et al. (1996)
UK	228	DRB1*0304	2.7	Heward et al. (1998a)
		DQB1*0301	1.9	
		DQA1*0501	3.2	
USA	94	DQA1*0501	3.71	Yanagawa et al. (1993)

Susceptibility genes in thyroid autoimmunity

Some CTLA-4 association studies in autoimmune thyroid diseases in Caucasians and non-Caucasian population.

CTLA-4 polymorphism	Country	Ethnic group	Dis.	No.	RR*/*P* value	Reference
CTLA-4(AT)	USA	Caucasians	GD	133	2.82	Yanagawa et al. (1995)
CTLA-4(AT)	UK	Caucasians	GD	112	2.1	Kotsa et al. (1997a)
			HT	44	2.2	
CTLA-4(AT)	Hong-Kong	Chinese	GD	94	$p = 0.037$	Nistico et al. (1996)
CTLA-4(AT)	Japan	Japanese	GD + HT	349	1.8	Volpe (1990)
Thr/Ala $(A/G)_{49}$	Germany	Caucasians	GD	305	2.0	Donner et al. (1997a)
Thr/Ala $(A/G)_{49}$	UK	Caucasians	GD	94	$p = 0.003$	Vaidya et al. (1999b)
Thr/Ala $(A/G)_{49}$	UK	Caucasians	GD	379	1.6	Heward et al. (1999a)
Thr/Ala $(A/G)_{49}$	UK	Caucasians	GD	484	$p < 0.0001$	Allahabadia et al. (2001)
Thr/Ala $(A/G)_{49}$	USA	Caucasians	GD	85	1.6	Villanueva et al. (2000)
Thr/Ala $(A/G)_{49}$	Germany	Caucasians	HT	73	$p < 0.04$	Donner et al. (1997b)
Thr/Ala $(A/G)_{49}$	Italy	Caucasians	HT	126	NS*	Petrone et al. (2001)
Thr/Ala $(A/G)_{49}$	UK	Caucasians	HT	158	1.57	Nithiyananthan et al. (2002)
Thr/Ala $(A/G)_{49}$	Slovenia	Caucasians	TAb's	67	$p < 0.005$	Zaletel et al. (2002)
Thr/Ala $(A/G)_{49}$	Japan	Japanese	GD	153	2.64	Yanagawa et al. (1997)
Thr/Ala $(A/G)_{49}$	Korea	Korean	GD	97	1.6	Park et al. (2000)
			HT	110	NS	

Autoimmune thyroid disease: mechanism, genetics and current knowledge



European Review for Medical and Pharmacological Sciences 2014; 18: 3611-3618

Tiroidite di Hashimoto

- *E' la malattia autoimmune più frequente in età pediatrica .*
- *Di solito asintomatica colpisce maggiormente le femmine , nel periodo dell'adolescenza.*
- *Si può associare frequentemente ad altre malattie autoimmuni ed in particolare la celiachia.*
- *Non esiste una netta distinzione fra HT e GD: nei soggetto con s. di Down e s. di Turner è frequente una trasformazione da HT a GD e viceversa.*
- *Sono sufficienti pochi esami per la diagnosi.*
- *Non sempre è indicata terapia.*
- *Necessario un attento e prolungato follow-up.*

Percorsi Pediatrici del Val di Noto

Vittoria 31 gennaio 2015