

Genetics of Diabetes

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3/6/2013

Classificações da Diabetes

- **Type 1 diabetes**
- **Type 2 diabetes** or "non-insulin-dependent diabetes mellitus" (**NIDDM**).
- **Type 2 "MODY"** -- MODY is the diagnosis given to **youngsters** who, were they adults, would be diagnosed with typical type 2 diabetes. MODY stands for "maturity onset diabetes of youth." This type of diabetes can run in families, too. Several relevant genes have been identified.
- **Secondary** -- The word "secondary" implies that diabetes is not the only feature of the disorder. For example, **physical trauma to the pancreas, including alcohol toxicity**, can lead to diabetes. Diabetes is also a part of some genetic syndromes, which we will mention later.

Type 1 diabetes

- **selective autoimmune destruction** of islet b-cells. Too little insulin is produced
- **pathogenetic sequence**
 - genetic factors
 - environmental factors
 - immune regulation
 - chemical mediators
- Most, but not all, cases of type 1 diabetes occur in **children**.
- This type of diabetes **can run in families**.
- **Several relevant genes** have been identified.

Type 2 diabetes

a polygenic disorder

multiple genes

located on different chromosomes

environmental factors

55% to 75% of all diabetes mellitus

also known as "non-insulin-dependent diabetes mellitus" (**NIDDM**).

A minority of cases of type 2 diabetes are caused by **single gene defects**

maturity onset diabetes of the young (MODY),

syndrome of insulin resistance (insulin receptor defect)

maternally inherited diabetes and deafness (mitochondrial gene defect).

Secondary: physical trauma to the pancreas, including alcohol toxicity, can lead to diabetes. Diabetes is also a part of some genetic syndromes

Type 2 diabetes mellitus appears in almost epidemic proportions Of diabetes mellitus

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Received May 28, 2003

- **type 2 diabetes can run in families**

The brothers and sisters of a type 2 diabetic have almost a 40% risk of developing type 2 diabetes or near-diabetes (glucose intolerance).

- The children of a type 2 diabetic have a 33% chance of developing type 2 diabetes or near-diabetes.
- The identical twin of a type 2 diabetic has a 70% to 80% chance of developing type 2 diabetes.

- **When type 2 diabetes runs in families, is the reason genes or environment?**

- As in most human disease, type 2 diabetes has genetic components and environmental components. So, it's a matter of nature and nurture, not nature versus nurture.

Genes cujo efeito varia com variação ambiental drástica. Gene útil ou pernicioso?

- The high frequencies for **Nauruans and Pimas** are new, and resulted from a change in their **pattern of food intake**. Until recently, food was scarce in these populations. Obesity and, therefore, type 2 diabetes were rare. **When food became abundant, both abnormalities became common.**
- Food is abundant in the United States, yet the frequency of type 2 diabetes is much lower than on Nauru or for the Pimas. Why the difference in frequencies? Most likely, **the Nauruans and the Pimas have gene variants that give them a tendency toward obesity and type 2 diabetes when food is plentiful.**
- Presumably, these gene variants may help the Nauruans and the Pimas function when food is scarce, or help them survive starvation.
- This is typical of the relationship between genes and environment -- **the environment determines whether a gene is helpful or harmful.**

Taxas de concordância

- Studies of twins provide the clearest evidence for **genes and environment both having a role**. For example, in one study researchers looked at 56 pairs of twins in which at least one twin had type 2 diabetes .
- | Type of twin pair | Number of twin pairs | Twin pairs in which both twins had type 2 diabetes ("concordance rate") |
|---------------------|----------------------|---|
| Identical twins | 46 | (37 of 46 pairs) 80% |
| Non-identical twins | 10 | (4 of 10 pairs) 40% |
- If type 2 diabetes were governed only by genes, then every time one identical twin had it, the other should have it, too. (Because identical twins have the same genes.) In other words, the "concordance rate" should be 100%. The table shows, however, that instead of a 100% concordance, there is an 80% concordance between identical twins. This shows **that type 2 diabetes has a small environmental component**. If type 2 diabetes were purely an environmental condition, then genes should make no difference at all. The concordance rate would be the same for identical twins and non-identical twins. The table shows, however, that the concordance rate is twice as high in identical twins (80%) as in non-identical twins (40%). **This shows that type 2 diabetes has a strong genetic component.**
- In summary, **type 2 diabetes has a genetic component that is subject to a major influence from the environment** .

What genes are involved in type 2 diabetes?

- The genetic component is the result of multiple genes acting together.

Scientists have identified some gene variants that contribute to type 2 diabetes, but have not yet found the variants that contribute to most cases.

Gene Name	Chromosome	Comments
Insulin	11	Insulin, of course, is a critical part of diabetes. Yet, only a few variants of the insulin gene have been discovered, and they are not common.
Insulin receptor	19	In order to send its signal to the body's tissues, insulin must chemically react with another protein -- the insulin receptor. (It's like putting a key into a lock.) In contrast to the insulin gene, more than 40 variants of the insulin receptor gene have been found. Most of these variants reduce the efficiency of the insulin "signal." Thus, people who have variants of the insulin receptor gene are partially resistant to the effects of insulin -- a key step on the road to developing type 2 diabetes.
NIDDM1	2	This gene was found after analyzing the DNA of 330 pairs of Mexican-American siblings near the Rio Grande in Texas. In this group, the gene is a major contributor to the development of type 2 diabetes. There is some evidence that a second gene must work in combination with this one in order for diabetes to develop.
NIDDM2	12	This gene has not been precisely identified. It was "discovered" in a group of 26 families from an isolated area in western Finland. The NIDDM2 gene is near a gene that is responsible for some cases of type 2 MODY. Thus, some scientists suspect that NIDDM2 may be a different variant of the MODY gene.

What genes are involved in type 2 diabetes? (2)

Gene Name	Chromosome	Comments
NIDDM3	20	This gene was found by analyzing 477 Finnish families. It has not been precisely identified.
HNF4A	20	At least five variants of this gene are associated with diabetes. Four are related to type 2 MODY, and one is related to typical type 2 diabetes. None of the gene variants have been found in more than one or two families.
GLUT4	17	In a study of 6 patients with type 2 diabetes, one proved to have a unique variant of this gene. The gene is a blueprint for a protein that is involved in sugar processing.
NEUROD pancreas	12	Unique variants of this gene have been found in two families. In one of the families, there were some people with the variant, but without diabetes. It appears that this gene affects the way the pancreas develops as an organ.

MAPK8IP111 A variant of this gene was found in a single family in which type 2 diabetes was present in 4 generations. Some people in the family who carried the variant gene did not have diabetes. This gene is the blueprint for a protein that has an effect on the movement of sugar in the pancreas and other organs. tRNA-LEUmito. Different variants of this gene produce different diseases. For example, one variant causes the MELAS syndrome and another causes the MERRF syndrome. Type 2 diabetes is a part of the MERRF syndrome, which also includes a type of [epilepsy](#) and eye disease.

What environmental factors are involved in type 2 diabetes?

- **Body weight** would seem to be the most obvious environmental factor involved in type 2 diabetes. However, as we discuss at length in the article on [obesity](#), body weight is largely under genetic control.
- As we mentioned earlier, **damage to the pancreas can bring on or hasten the appearance of diabetes. Alcohol, trauma, pancreatitis, and perhaps some toxins are capable of damaging the pancreas.**
- Learning more about the genetics of type 2 diabetes will make it easier to identify and understand environmental contributions to the disease.
- **When type 2 diabetes runs in families, why don't all family members have it?**
- It helps to frame this question a little differently.... All members of a family do not have the same height, weight, and face. So, it makes sense that they don't all have the same conditions and diseases -- or the same susceptibility to various diseases.
- Here again, it's genetic and environmental differences that explain differences in our appearance and health. Some family members will inherit genes that predispose to diabetes, and others will not. Some family members will be exposed to environmental agents that trigger disease, and others will not.
- **There is no type 2 diabetes in my family. Does this mean it will never occur in my family?**
- No. Anyone can develop diabetes. Most people with diabetes do not have a parent, brother, sister, or child with diabetes. But if someone in your family does have diabetes, you are at greater risk.

Nephron Clin Pract. 2009 Jun 16;112(4):c213-c221. [Epub ahead of print]

Genetics of Diabetic Nephropathy: Are There Clues to the Understanding of Common Kidney Diseases?

[Conway BR](#), [Maxwell AP](#).

Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK.

- How will discoveries about DNA help people and families with type 2 diabetes? [\[Top\]](#)
- Further discoveries about diabetes genes will lead to more individualized medicine. Prevention, diagnosis, treatment, and prognosis will be personalized, based largely on the strengths and weaknesses found in a person's genes.
- Treatment -- better use of existing treatments
- Several medicines have been approved to treat diabetes. How does your physician know which is best for you? Part of the answer may be in your genes.
- In this article, we've seen how specific genes influence the development and progression of a complex condition -- diabetes. Similarly, specific genes may influence the responses to different treatments. Better genetic information could explain why some drugs work better in some people than others. This will make choosing treatments less hit-and-miss than in the past.
- Treatment -- discovery of new treatments
- Whenever scientists discover a gene involved in diabetes, it's a doorway to designing new treatments. If the gene is over-active, then scientists can look for ways to turn it off or interfere with its activity. If the gene is under-active or broken, then scientists can look for ways to turn it on or increase its activity.
- Prevention, Diagnosis, Prognosis
- Prevention, diagnosis, and prognosis all improve when our ability to calculate risk improves. Scientists believe genes will tell us a lot about the risk of developing diabetes and the progression of diabetes.

Diabetes - Factores de risco associados

- **Risco aumentado de doenças autoimunes**
 - tiroidite autoimune, anemia perniciosa, doença de Addison's, Acs contra as células dos ilhéus do pâncreas

- **Associação com Ags HLA classe II**

HLA -DR3 e / ou HLA DR4 em 95 %

- Irmãos com IDDM têm **os mesmos haplótipos mais frequentemente do que o esperado** pelo acaso.
- O **risco** de desenvolver diabetes é **maior** quando os dois Ags **DR3 e DR4** estão presentes simultâneamente nos familiares directos do doente IDDM.
- O início da diabetes é mais frequente no **outono e inverno** e supõe-se ter na sua origem uma **etiologia viral** em indivíduos geneticamente susceptíveis.
- **Vários genes** têm sido sugeridos como candidatos genes de susceptibilidade em ambas as formas de diabetes, mas ainda não se demonstrou que nenhum deles tenha um efeito major nessa predisposição.

web sites that deal with type 2 diabetes

- Diabetes web site at the National Institute of Diabetes and Digestive and Kidney Diseases:
<http://www.niddk.nih.gov/health/diabetes/diabetes.htm>
- The MedlinePlus web site for diabetes:
<http://www.nlm.nih.gov/medlineplus/diabetes.html>
- The Centers for Disease Control's frequently asked questions about diabetes:
<http://www.cdc.gov/diabetes/faqs.htm>
- The Joslin Diabetes Center:
<http://www.joslin.harvard.edu/>

Scans do genoma

- There is evidence for a genetic susceptibility to diabetic kidney disease, but despite intensive research efforts it has proved difficult to identify the causative genes.
- Improvements in genotyping technologies have made genome-wide association studies (GWAS), employing hundreds of thousands of single nucleotide polymorphisms, affordable.
- Recently, such scans have advanced understanding of the genetics of common complex diseases, finding more than 100 novel susceptibility variants for diverse disorders including type 1 and 2 diabetes, coronary heart disease, Crohn's disease and rheumatoid arthritis.
- In this review, type 2 diabetes is highlighted to illustrate how genome-wide association studies have been used to study the genetics of complex multifactorial conditions;

Polimorfismos no DNA mitocondrial associados à Diabetes

- mtDNA genetic variants will be differentially associated with T2DM depending on the diabetes status of the parents?
- **“Parental diabetes status reveals association of mitochondrial DNA haplogroup J1 with type 2 diabetes”**

BMC Med Genet. 2009 Jun 18;10(1):60.

Susceptibilidade à Obesidade e Diabetes

Diabetologia. 2009 Jun 13.

Is the thrifty genotype hypothesis supported by evidence based on confirmed type 2 diabetes- and obesity-susceptibility variants?

[Southam L](#), [Soranzo N](#), [Montgomery SB](#), [Frayling TM](#), [McCarthy MI](#), [Barroso I](#), [Zeggini E](#).

Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.

HYPOTHESIS: According to the thrifty genotype hypothesis, the high prevalence of type 2 diabetes and obesity is a consequence of genetic variants that have undergone positive selection during historical periods of erratic food supply.

We find a high F (ST) for rs7901695 at TCF7L2, the largest type 2 diabetes effect size found to date.

CONCLUSIONS/INTERPRETATION: Our results provide some evidence for selection at specific loci, but there are no consistent patterns of selection that provide conclusive confirmation of the thrifty genotype hypothesis. Discovery of more signals and more causal variants for type 2 diabetes and obesity is likely to allow more detailed examination of these issues.

Diabetes e doença vascular

- Eur J Vasc Endovasc Surg. 2009 Jun 8.
- Prevalence of Symptomatic and Asymptomatic Peripheral Arterial Disease and the Value of the Ankle-brachial Index to Stratify Cardiovascular Risk.
Ramos R, Quesada M, Solanas P, Subirana I, Sala J, Vila J, Masiá R, Cerezo C, Elosua R, Grau M, Cerdón F, Juvinyà D, Fitó M, Isabel Covas M, Clarà A, Angel Muñoz M, Marrugat J; on behalf of the REGICOR Investigators.
- Association with symptomatic peripheral arterial disease (PAD), association with cardiovascular risk factors (CVRF), and impact of adding ABI measurement to coronary heart disease (CHD) risk screening.
- DESIGN: Population-based cross-sectional survey of 6262 participants aged 35-79 in Girona, Spain.
- METHODS: Standardized measurements (CVRF, ABI, 10-year CHD risk) and history of intermittent claudication (IC), CHD, and stroke were recorded. ABI<0.9 was considered equivalent to moderate-to-high CHD risk (> /=10%).

do genoma

- Nippon Rinsho. 2009 Jun;67(6):1090-4.
[Diabetes susceptibility genes]

Kasuga M.

- Type 2 diabetes mellitus is a complex polygenic disorder in which common genetics variants interact with environmental factors.
- Genome-wide association study(GWAS) revealed **more than 10 diabetes susceptibility loci** for type 2 diabetes mellitus including SNPs in KCNQ1, which was first identified in Japanese by two independent Japanese groups.
- However, these variants identified by GWAS showed low O.R. (odds ratio) such as 1.1-1.5 suggesting **low penetrance of these variants.**
- Diabetes mellitus is also caused by a mutation in one gene such as glucokinase and HNF-1 alpha, which showed **high penetrance.**
- Therefore, **next challenge will be to identify low-frequency variants with intermediate penetrance**, which may be associated with diabetes mellitus.

[Association study on the mitochondrial genome region np16181-16193 variation with type 2 diabetes mellitus.]

- Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2009 Jun;26(3):340-4.
- **METHODS:** Blood samples of 199 unrelated T2DM patients and 205 normal controls were collected to detect the mitochondrial DNA region np16181-16193 variations by PCR and sequencing, and to analyze the association of the variations with the major clinical symptoms.
- **RESULTS:** The mitochondrial DNA np16181-16193 region is a hypervariable area, with several polymorphisms. Four types of np16181-16193 region variations were found only in T2DM.
- **The 1-hour postprandial blood glucose (P1BG) in the T2DM individuals with np16181-16193 region variations was significantly higher than those without variations ($P < 0.05$), while there was no significant difference in other biochemical parameters ($P > 0.05$).**
- **CONCLUSION:** The mitochondrial DNA np16181-16193 variations could not be regarded as a risk factor for T2DM.

Expressão de genes

- Methods Mol Biol. 2009;560:239-61.
- Gene expression analysis in diabetes research.

White P, Kaestner KH.

Department of Genetics and Institute for Diabetes, Obesity and Metabolism, University of Pennsylvania School of Medicine, 752 Clinical Research Building, 415 Curie Boulevard, Philadelphia, PA, 19104-6145, USA.

Global gene expression profiling through the use of microarray technology is among the most powerful molecular biological techniques available to diabetes researchers today.

- In this chapter, we outline how to appropriately perform a microarray experiment using pancreatic islets or total pancreas, based upon over a decade of experience in our laboratory. Through the utilization of careful experimental designs, large numbers of biological replicates, production of high-quality starting material, optimized protocols for hybridization, and sophisticated tools for data processing and statistical analysis, the full potential of high-quality expression profiling can be realized.

Haplótipos HLA e peso ao nascer

- HLA haplotypes and birth weight variation: is your future going to be light or heavy?

[Capittini C](#), [Pasi A](#), [Bergamaschi P](#), [Tinelli C](#), [De Silvestri A](#), [Mercati MP](#), [Badulli C](#), [Garlaschelli F](#), [Sbarsi I](#), [Guarene M](#), [Martinetti M](#), [Salvaneschi L](#), [Cuccia M](#).

Immunogenetics Laboratory, Department of Genetics and Microbiology, University of Pavia, Pavia, Italy.

Abstract Birth weight is known to be a direct indicator of perinatal mortality and a clear predictor of adult pathologies too. It has been correlated with several causes of mortality in adulthood: low birth weight with diabetes, nephropathy and cardiovascular diseases and high birth weight with autoimmune diseases and cancer.

- In genome-wide studies, an extended human leucocyte antigen (HLA) region has been linked to birth weight variation. We focused our attention on the HLA haplotypes marked by HLA-A, HLA-B and HLA-DRB1 polymorphisms in 1206 healthy Caucasian newborns belonging to the Cord Blood Bank of Pavia (Italy) and their mothers, aiming to investigate the association between this restricted HLA region and birth weight variation.
- In our study, the HLA-B*38;DRB1*13 haplotype showed an ascending trend among centiles addressing to the high foetal weight.
- The HLA-A*02;B*15 haplotype showed a descending trend among centiles addressing to the low foetal weight. Besides the acknowledged correlation between the HLA-A*02 and HLA-B*15 alleles (as well as low birth weight) and type I diabetes and between the HLA-B*38 and HLA-DRB1*13 alleles (as well as high birth weight) and several autoimmune diseases, we cannot predict if our babies, healthy at birth, will suffer from these pathologies during life.
- Nevertheless, our data point to the HLA telomeric end for markers linked to the low birth weight and to the HLA centromeric end for markers linked to the high birth weight, thus limiting the region involved in birth weight variation, which still represents a useful predictor of disease risk in adulthood.

Genes que influenciam a secreção da insulina

- J Hum Genet. 2009 Jun 5.
- The E23K variation in the KCNJ11 gene is associated with type 2 diabetes in Chinese and East Asian population. [Zhou D](#), [Zhang D](#), [Liu Y](#), [Zhao T](#), [Chen Z](#), [Liu Z](#), [Yu L](#), [Zhang Z](#), [Xu H](#), [He L](#).
- The genes (ABCC8 and KCNJ11) have a key role in glucose-stimulated insulin secretion and thus have always been considered as excellent susceptibility candidates for involvement in type 2 diabetes.
- Common polymorphisms (KCNJ11 E23K and ABCC8 exon16-3t/c) in these genes have been reported to be associated with type 2 diabetes in various European-descent populations. However, there were inconsistent results in previous studies in East Asian populations and no large case-control studies have been carried out in the Chinese Han population.
- In this study, these two variants were genotyped in about 4000 Chinese by using TaqMan technology on an ABI7900 system. A meta-analysis was also used to assess the results of association between the two variants and type 2 diabetes in East Asian populations.
- **Our investigation confirmed the association between the KCNJ11 E23K variant and type 2 diabetes under a recessive model (KK vs EK+EE) in the Chinese Han population (odds ratio (OR)=1.25, 95% confidence interval (95% CI) 1.04-1.50, P=0.017).**
- The meta-analysis of East Asian populations also showed a **strong significant association of the K allele with diabetes (OR=1.15, P=3 x 10⁻⁹)**, whereas the exon16-3t/c variant (rs1799854) in ABCC8 showed no significant association. Thus, the common E23K variant is considered as a strong candidate for type 2 diabetes susceptibility across different ethnicities. Journal of Human Genetics advance online publication, 5 June 2009; doi:10.1038/jhg.2009.54.

Genes do metabolismo da glicose

- Diabetes. 2009 Jun 2.

- **Endoplasmic Reticulum Stress Regulates Adipocyte Resistin Expression.**

[Lefterova MI](#), [Mullican SE](#), [Tomaru T](#), [Qatanani M](#), [Schupp M](#), [Lazar MA](#).

Objective: Resistin is a secreted polypeptide that impairs glucose metabolism and, in rodents, is derived exclusively from adipocytes. In murine obesity, resistin circulates at elevated levels but its gene expression in adipose tissue is paradoxically reduced.

- The mechanism behind the downregulation of resistin mRNA is poorly understood. Here we investigated whether endoplasmic reticulum (ER) stress, which is characteristic of obese adipose tissue, regulates resistin expression in cultured mouse adipocytes.
- Research Design and Methods: The effects of ER stress inducers on resistin mRNA and secreted protein levels were examined in differentiated 3T3-L1 adipocytes, focusing on the expression and genomic binding of transcriptional regulators of resistin.
- The association between downregulated resistin mRNA and induction of ER stress was also investigated in the adipose tissue of mice fed a high-fat diet.
- Results: ER stress reduced resistin mRNA in 3T3-L1 adipocytes in a time- and dose-dependent manner. The effects of ER stress were transcriptional, due to downregulation of C/EBPalpha and PPARgamma transcriptional activators and upregulation of the transcriptional repressor CHOP10. Resistin protein was also substantially downregulated, showing a close correspondence with mRNA levels in 3T3-L1 adipocytes as well as in the fat pads of obese mice.
- Conclusions: ER stress is a potent regulator of resistin, suggesting that ER stress may underlie the local downregulation of resistin mRNA and protein in fat in murine obesity. The paradoxical increase in plasma may be due to various systemic abnormalities associated with obesity and insulin resistance.

Inflamação crônica e resistência à insulina

- Circ Res. 2009 May 28.
MIF Deficiency Reduces Chronic Inflammation in White Adipose Tissue and Impairs the Development of Insulin Resistance, Glucose Intolerance, and Associated Atherosclerotic Disease.
[Verschuren L](#), [Kooistra T](#), [Bernhagen J](#), [Voshol PJ](#), [Ouwens DM](#), [van Erk M](#), [de Vries-van der Weij J](#), [Leng L](#), [van Bockel JH](#), [van Dijk KW](#), [Fingerle-Rowson G](#), [Bucala R](#), [Kleemann R](#).

Chronic inflammation in white adipose tissue (WAT) is positively associated with obesity, insulin resistance (IR) and the development of type 2 diabetes.

- The proinflammatory cytokine MIF (macrophage migration inhibitory factor) is an essential, upstream component of the inflammatory cascade. This study examines whether MIF is required for the development of obesity, IR, glucose intolerance, and atherosclerosis in the LDL receptor-deficient (Ldlr(-/-)) mouse model of disease. Ldlr(-/-) mice develop IR and glucose intolerance within 15 weeks, whereas Mif(-/-)Ldlr(-/-) littermates are protected. MIF deficiency does not affect obesity and lipid risk factors but specifically reduces inflammation in WAT and liver, as reflected by lower plasma serum amyloid A and fibrinogen levels at baseline and under inflammatory conditions.
- Conversely, MIF stimulates the in vivo expression of human C-reactive protein, an inflammation marker and risk factor of IR and cardiovascular disease. In WAT, MIF deficiency reduces nuclear c-Jun levels and improves insulin sensitivity;
- MIF deficiency also reduces macrophage accumulation in WAT and blunts the expression of two proteins that regulate macrophage infiltration (intercellular adhesion molecule-1, CD44). Mechanistic parallels to WAT were observed in aorta, where the absence of MIF reduces monocyte adhesion, macrophage lesion content, and atherosclerotic lesion size.
- These data highlight the physiological importance of chronic inflammation in development of IR and atherosclerosis and suggest that MIF is a potential therapeutic target for reducing the inflammatory component of metabolic and cardiovascular disorders.

Mutações de genes dos canais do potássio

- Clin Genet. 2009 May;75(5):440-8.
- **The spectrum of ABCC8 mutations in Norwegian patients with congenital hyperinsulinism of infancy.**
[Sandal T](#), [Laborie LB](#), [Brusgaard K](#), [Eide SA](#), [Christesen HB](#), [Søvik O](#), [Njølstad PR](#), [Molven A](#).
aSection for Pathology, The Gade Institute, and bSection for Pediatrics, Department of Clinical Medicine, University of Bergen, Norway.
Potassium channels in the plasma membrane of the pancreatic beta cells are critical in maintaining glucose homeostasis by responding to ATP and coupling metabolic changes to insulin secretion. These channels consist of subunits denoted the sulfonylurea receptor SUR1 and the inwardly rectifying ion channel KIR6.2, which are encoded by the genes ABCC8 and KCNJ11, respectively.
- Activating mutations in the subunit genes can result in monogenic diabetes, whereas inactivating mutations are the most common cause of congenital hyperinsulinism of infancy (CHI). Twenty-six Norwegian probands with CHI were analyzed for alterations in ABCC8 and KCNJ11.
- Fifteen probands (58%) had mutations in the ABCC8 gene. Nine patients were homozygous or compound heterozygous for the mutations, indicating diffuse pancreatic disease. In five patients, heterozygous and paternally inherited mutations were found, suggesting focal disease. One patient had a de novo mutation likely to cause a milder, dominant form of CHI. Altogether, 16 different ABCC8 mutations (including the novel alterations W231R, C267X, IVS6-3C>G, I462V, Q917X and T1531A) were identified. The mutations IVS10+1G>T, R1493W and V21D occurred in five, three and two families, respectively. KCNJ11 mutations were not found in any patients.
- Based on our mutation screening, we estimate the minimum birth prevalence of ABCC8-CHI in Norway to 1:70,000 during the past decade. Our results considerably extend the knowledge of the molecular genetics behind CHI in Scandinavia.

Farmacogenética

Efeitos adversos de fármacos

- **ABCB1 genotypes predict cyclosporine-related adverse events and kidney allograft outcome.**
[Cattaneo D, Ruggenenti P, Baldelli S, Motterlini N, Gotti E, Sandrini S, Salvadori M, Segoloni G, Rigotti P, Donati D, Perico N, Remuzzi G; Mycophenolate Steroids Sparing \(MYSS\) Genetics Study Group.](#) Collaborators (27)
- [Remuzzi G, Cattaneo D, Gotti E, Ruggenenti P, Perico N, Sandrini S, Setti G, Maiorca R, Piperno R, Bertoni E, Salvadori M, Segoloni G, Messina M, Rocchietti M, Piccoli G, Rigotti P, Baldan N, Liberati L, Rigoni L, Ancona E, Donati D, Gastaldi L, Baldelli S, Cortinovis M, Bitto A, Perna A, Motterlini N.](#)
- Department of Medicine and Transplantation, Ospedali Riuniti-Mario Negri Institute for Pharmacological Research, Bergamo, Italy.
 Cyclosporine A (CsA) is a substrate of P-glycoprotein, an efflux transporter encoded by the **ABCB1 gene**. Compared with carriers of the wild-type gene, carriers of T allelic variants in exons 21 or 26 have reduced P-glycoprotein activity and, secondarily, increased intracellular concentration of CsA; therefore, carriers of T variants might be at increased risk for CsA-related adverse events.
- We evaluated the associations between ABCB1 genotypes (in exons 12, 21, and 26) and CsA-related outcomes in 147 renal transplant recipients who were receiving CsA-based immunosuppression and were included in the Mycophenolate Steroids Sparing study. During a median of 65.5 mo follow-up, carriers of T allelic variants in exons 21 or 26 had a three-fold risk for delayed graft function (DGF), a trend to slower recovery of renal function and lower GFR at study end, and significantly higher incidences of new-onset diabetes and cytomegalovirus reactivation compared with carriers of the wild-type genotype. T variants in both exons 21 and 26 were independently associated with 3.8- and 3.5-fold higher risk for DGF, respectively (P = 0.022 and P = 0.034).
- The incidence of acute rejection and the mean CsA dose and blood levels were comparable in genotype groups.
- **In conclusion, renal transplant recipients with T allelic variants in ABCB1 exons 21 or 26 are at increased risk for CsA-related adverse events.**

Defesa anti-oxidante da parede vascular

Mutat Res. 2009, May 22.

A novel Real Time PCR strategy to detect SOD3 SNP using LNA probes.

Brugè F, Littarru GP, Silvestrini L, Mancuso T, Tiano L.

Department of Biochemistry, Biology and Genetics, Polytechnic University of Marche, Via Ranieri, 60100, Ancona, Italy.

Extracellular **superoxide dismutase (SOD3)** is the primary enzymatic antioxidant defence of the vascular wall.

The **physiopathological role of SOD3** has been examined in vascular-related diseases, atherosclerosis, hypertension, diabetes, ischaemia-reperfusion injury, lung disease, various inflammatory conditions, and neurological diseases.

An important single nucleotide polymorphism (**SNP**), **nt.760 G>C of the SOD3 gene** (rs#1799895) leads to the amino acid substitution Arg(213)Gly (R213G) in the center of the heparin-binding domain and consequently to a lowered affinity for the endothelium.

This mutation, which occurs with a relatively high frequency in the population (4% of Swedish, 3% of Australian and 6% of Japanese people), is associated with **decreased tissue antioxidant defences and increased risk of ischaemic heart disease.**

The identification of patients carrying this mutation is therefore of great interest in order to highlight lowered antioxidant defences at a vascular level which could lead to increased susceptibility toward coronary artery disease and atherogenesis. Here we describe a method to detect the 760 G>C single nucleotide polymorphism based on Real Time PCR strategy using locked nucleic acid (LNA) probes. This technique, a modification of classic TaqMan probes SNP genotyping, amplifies and detects the mutation in a single reaction tube. Moreover, the implementation of LNA probes remarkably increases the specificity of the reaction.

The proposed method enables unambiguous and rapid discrimination of wild type and mutant genotype both in plasmid and genomic DNA samples. In light of the role of SOD3 polymorphism, the genotyping of 760 G>C mutant has important clinical implications. The proposed assay combines rapidity, high specificity, can be easily automated and overall reduces labor and cost of analyses. Moreover,

Efeito poligénico

- Hum Hered. 2009;68(2):131-8.

- Genetic analysis of age-at-onset for cardiovascular risk factors in a Brazilian family study.

Ruiz Giolo S, Pereira AC, de Andrade M, de Oliveira CM, Krieger JE, Soler JM.

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BACKGROUND/AIMS: Statistical analysis of age-at-onset involving family data is particularly complicated because there is a correlation pattern that needs to be modeled and also because there are measurements that are censored. In this paper, our main purpose was to evaluate the effect of genetic and shared family environmental factors on age-at-onset of three cardiovascular risk factors: hypertension, diabetes and high cholesterol.

- **METHODS:** The mixed-effects Cox model proposed by Pankratz et al. [2005] was used to analyze the data from 81 families, involving 1,675 individuals from the village of Baependi, in the state of Minas Gerais, Brazil.
- **RESULTS:** The analyses performed showed that the polygenic effect plays a greater role than the shared family environmental effect in explaining the variability of the age-at-onset of hypertension, diabetes and high cholesterol. The model which simultaneously evaluated both effects indicated that there are individuals which may have risk of hypertension due to polygenic effects 130% higher than the overall average risk for the entire sample. For diabetes and high cholesterol the risks of some individuals were 115 and 45%, respectively, higher than the overall average risk for the entire population.
- **CONCLUSIONS:** Results showed evidence of significant polygenic effects indicating that age-at-onset is a useful trait for gene mapping of the common complex diseases analyzed. In addition, we found that the polygenic random component might absorb the effects of some covariates usually considered in the risk evaluation, such as gender, age and BMI.

- Pancreas. 2009 May 11

- Association Between the Peroxisome Proliferator-Activated Receptor gamma Pro12Ala Variant and Haplotype and Pancreatic Cancer in a High-Risk Cohort of Smokers: A Pilot Study.

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OBJECTIVES:: The Pro12Ala variant in the peroxisome proliferator-activated receptor gamma (PPARG) gene has been associated with diabetes and several cancers. This pilot study tested for the association between Pro12Ala and pancreatic cancer risk in a high-risk sample of smokers.

- **METHODS::** A nested case-control study was conducted in 83 incident cases of pancreatic cancer and 166 matched controls originally recruited into a cohort chemoprevention study of lung cancer. Associations between Pro12Ala and pancreatic cancer risk were measured using conditional logistic regression.
- **RESULTS::** Carriers of the G allele (Ala) of the Pro12Ala variant had a borderline increased relative risk of pancreatic cancer compared with homozygous carriers of the C allele (Pro), with an odds ratio of 1.79 (95% confidence interval [CI], 0.96-3.33; P = 0.06). Among subjects randomized to high-dose vitamin A, the odds ratio was 2.80 (95% CI, 1.16-6.74; P = 0.02) versus 1.20 (95% CI, 0.45-3.23; P = 0.71) in the placebo group. A haplotype including Pro12Ala was also significantly associated with pancreatic cancer risk in all subjects and in subjects randomized to vitamin A.
- **CONCLUSIONS::** This analysis presents the first evidence that **PPARG** may be associated with pancreatic cancer risk, and this candidate gene should be investigated in future, larger studies.

Apolipoprotein C3 (APOC3) gene polymorphisms and impaired lipid and glucose metabolism

PLoS One. 2009;4(5):e5465.

Apolipoprotein C3 polymorphisms, cognitive function and diabetes in Caribbean origin Hispanics.

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BACKGROUND: Apolipoprotein C3 (APOC3) modulates triglyceride metabolism through inhibition of lipoprotein lipase, but is itself regulated by insulin, so that **APOC3 represents a potential mechanism by which glucose metabolism may affect lipid metabolism.** Unfavorable lipoprotein profiles and impaired glucose metabolism are linked to cognitive decline, and all three conditions may decrease lifespan. Associations between apolipoprotein C3 (APOC3) gene polymorphisms and impaired lipid and glucose metabolism are well-established, but potential connections between APOC3 polymorphisms, cognitive decline and diabetes deserve further attention.

METHODS: We examined whether APOC3 single nucleotide polymorphisms (SNPs) m482 (rs2854117) and 3u386 (rs5128) were related to cognitive measures, whether the associations between cognitive differences and genotype were related to metabolic differences, and how diabetes status affected these associations. Study subjects were Hispanics of Caribbean origin (n = 991, aged 45-74) living in the Boston metropolitan area.

RESULTS: Cognitive and metabolic measures differed substantially by type II diabetes status. In multivariate regression models, APOC3 m482 AA subjects with diabetes exhibited lower executive function (P = 0.009), Stroop color naming score (P = 0.014) and Stroop color-word score (P = 0.022) compared to AG/GG subjects. APOC3 m482 AA subjects with diabetes exhibited significantly higher glucose (P = 0.032) and total cholesterol (P = 0.028) compared to AG/GG subjects. APOC3 3u386 GC/GG subjects with diabetes exhibited significantly higher triglyceride (P = 0.004), total cholesterol (P = 0.003) and glucose (P = 0.016) compared to CC subjects.

CONCLUSIONS: In summary, **we identified significant associations between APOC3 polymorphisms, impaired cognition and metabolic dysregulation in Caribbean Hispanics with diabetes.** Further research investigating these relationships in other populations is warranted.

Esteatose Hepática não Alcoólica (NASH) associada à obesidade e diabetes: Lipólise e lipogénese aumentadas; oxidação beta diminuída Associação com Haplótipo HLA - A33, B14, DR1

Diabetes Metab. 2008 Dec;34(6 Pt 2):643-8.

The role of the lipogenic pathway in the development of hepatic steatosis.

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Non-alcoholic fatty liver disease (NAFLD) represents a wide spectrum of diseases, ranging from simple fatty liver (hepatic steatosis) through steatosis with inflammation and necrosis to cirrhosis. NAFLD, which is strongly associated with obesity, insulin resistance and type 2 diabetes, is now well recognized as being part of the metabolic syndrome.

The metabolic pathways leading to the development of hepatic steatosis are multiple, including enhanced non-esterified fatty acid release from adipose tissue (lipolysis), increased de novo fatty acids (lipogenesis) and decreased beta-oxidation.

Recently, several mouse models have helped to clarify the molecular mechanisms leading to the development of hepatic steatosis in the pathogenesis of NAFLD. This review describes the models that have provided evidence implicating lipogenesis in the development and/or prevention of hepatic steatosis.