Genetics of common obesity and type 2 diabetes: please forget diseases and study pathogenic traits

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The main enemy for the geneticist may not be the complexity, but the heterogeneity of common diseases like obesity or Type 2 diabetes (T2D). The pragmatic approach of this heterogeneity is that of every general practitioner who decides to treat a thin T2D patient with insulin or insulin secretagogues and an obese hyperglycemic patient with an hypocaloric diet and insulin sensitizers. The geneticists who track T2D genes do not care with such medical subtleties. They think of T2D as an entity. They use DNA samples from the two previous categories of patients for association studies with candidate genes of all sorts, or pour these samples into various types of genome screens to find new diabetogenic loci. While a number of genomic and computational tools are available for sophisticated association and linkage studies [1], the phenotypic approach of common obesity or T2D remains often limited to have or not to have the disease. To have the disease, unfortunately, gives no indications with respect to pathogenic processes. Obesity as well as T2D are defined by thresholds on the distribution of continuous traits (BMI, blood glucose). These thresholds are derived from long term morbidity and mortality data under the auspices of consensus conferences. Obesity being defined by a BMI > 90th percentile, more than 10% of the Western adults can be classified as obese 'cases'. T2D being defined by a fasting glucose level of 126 mg/dl or higher, or a 2h glucose superior to 200 mg/dl, approximately 6% of the US population are T2D 'cases'. The majority of the prevalent cases of these 'diseases' are likely to be a consequence of context-dependent effects of allelic variations. Geneticists have used these public health definitions and therefore have included in their genome screens or association studies heterogeneous cohorts of patients, lean or obese, insulin resistant or insulin deficient, with large ranges of ages at diagnosis, in a effort to enlarge the number of 'cases'. Pathogenic and genetic heterogeneity between individuals of such cohorts is likely to be major.

Unlike asthma, Crohn's ileitis, schizophrenia, or autoimmune diabetes, it is interesting that obesity and T2D can be dissected into traits that are amenable to quantitative genetic studies. We are not speaking here of 'descriptive' traits, such as body fat mass, skinfolds, or BMI, that simply reflect the current degree of obesity. We are not speaking either of insulin, leptin or free fatty levels, that are implicated in both the causal mechanisms and the secondary consequences of obesity or diabetes in adult patients.

Instead, our proposition is to select quantitative traits that are pathogenic to the disease, that reflect its natural history, that can be measured long before disease is diagnosed, and are of the lowest possible phenotypic level. Physiological systems such as the regulation of blood glucose have a hierarchical component to them, leading from the gene to its product, to 'low level' then 'intermediate' phenotypes of greater complexity, to the ultimate phenotypes (BMI, glycemia) used to diagnose disease *(Fig 1)*. To reduce the effects of the many factors (genetic, environmental) compounding the phenotypic effect of individual genes, quantitative traits that have a low level of complexity should be preferred. We think that candidate genes can be more accurately tested against traits that are proximal to them, for example the insulin gene and plasma insulin level [2]. Another argument for the 'pathogenic trait - candidate gene' approach is the power of association studies [3], as exemplified in Oji-Creek Indians *versus* genome scan approaches [4].

The genetic architecture of health, and therefore of a given disease, is expected to be population- specific. Different combinations of susceptibility genes appear to contribute to the development of T2D in Pima Indians, Mexican-Americans or Finnish patients [5]. The genetic heterogeneity of obesity and T2D at a population level explains the localization of susceptibility loci to different regions of the genome and the disparate results of the genome scan approach. The study of physiological traits in the perspective of candidate polymorphisms can be expected to diminish this degree of heterogeneity.

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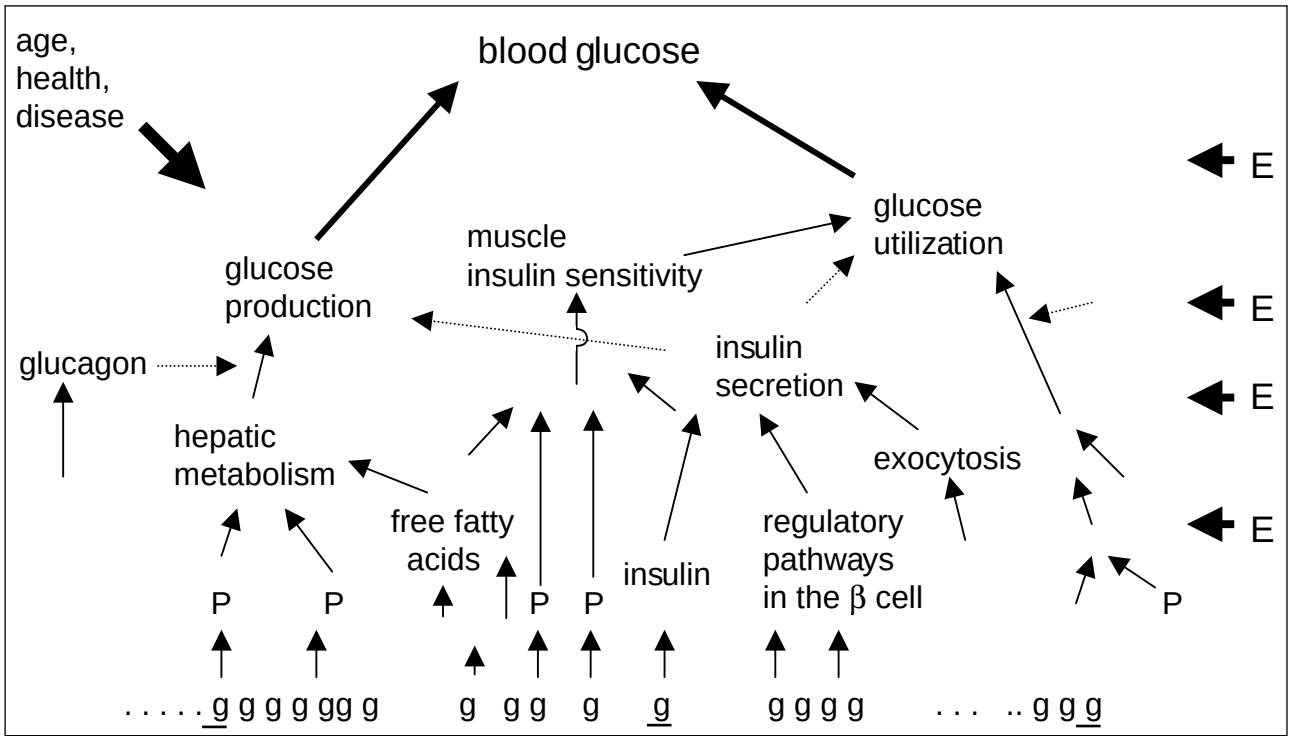

Figure 1
A simplified view of some pathogenic traits involved in the determination of a complex, highly regulated, trait, blood glucose. **g** represents the many genetic loci, **g** those that have common variants. p represents the proteins coded at the given loci. **E** represents the environmental factors influencing the system.

There are several possibilities to quantify pathogenic traits: one can use the mean value and distribution of each trait, or the regression between relevant traits [2], or phenotypic matrices in which hundreds of traits are quantified in each subject then inter-correlated at a cohort level to develop a physiological model of the relationships between these phenotypes [6]. To match the term 'genomics' associated with purely genetic research, Schork coined the term 'phenomics' to describe the connections and networks among genes, gene products, physiological and regulatory pathways, and ultimately complex traits or diseases [7].

Other characteristics that should in the future feed genetic studies are the pathogenic relevance of traits and their developmental aspects. In patients exposed to a disease for a prolonged period, physiology tends to follow new rules to compensate for accumulating dysfunctions. The traits no longer reflect their primary genetic determinism. This is true for both obesity and T2D, where traits are altered by diets, drugs and disease consequences such as hyperglycemia. For example, insulin secretion and resistance can follow a variety of changes before and during disease evolution. These variations are seen in a given individual, as well as between different individuals [8]. Statistical tools certainly help the investigators to adjust phenotypic values with respect to age, sex, physical activity at time of study and DNA sampling, etc but will never be able to recapitulate the natural history of the trait in the pre-disease phase *(Fig 2)*, when the genetic predisposition to T2D is expected to develop. For this reason, we elected to study traits during the early dynamic phase of juvenile obesity, when the β cells, the insulin sensitive tissues, and all metabolic pathways are adjusting their function to the burden of fat accumulation.

It is likely that insulin regulation, fuel homeostasis, and storage of calories have been of primary importance to the survival of our species [9], and that genetic evolution has mostly worked on the metabolic phenotype of young people, given the limited life span of our ancestors. Therefore, measuring insulin secretion and sensitivity early in adolescence may more closely reflect the influence of genetic variants on these physiological traits. The genetic architecture of diseases like obesity or T2D cannot be separated from the study of the genetic architecture of normal variation in healthy individuals [10]. Juvenile obesity, which has become very frequent in our societies and carries a high risk of T2D, provides geneticists with a unique model to unravel the genetic roots of metabolic functions and of alterations leading to T2D. These genetic associations and mechanisms may be

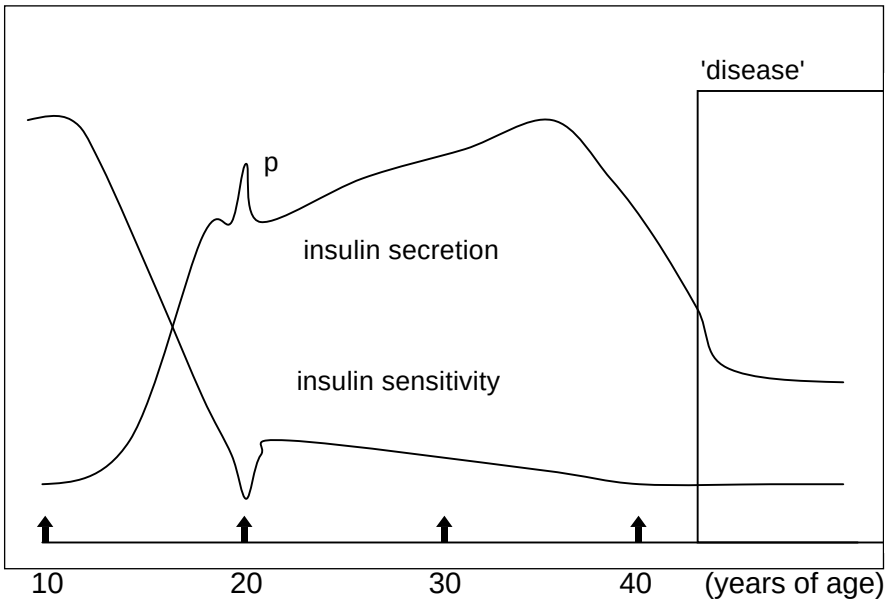

Figure 2
Hypothetical history of insulin sensitivity and secretion in a woman who developed Type 2 diabetes in adulthood. She had early obesity, and hyperinsulinemia. She carried out one pregnancy (p). Near 39 yrs of age, her insulin secretion passed under the level needed to compensate her massive insulin resistance. Hyperglycemia developped progressively and Type 2 diabetes was diagnosed around 45 yrs of age.

relevant to millions of individuals, in whom modern life has become associated with common diseases.

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