EDITORIAL

# OBESITY - THE GENETICS PERSPECTIVE

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There is a growing perception that there are too many obese people in the world and that they are increasing at an alarming rate, in 'epidemic proportions', with the predictions that the world of tomorrow will be overrun by overly fat people. Who are these swarms of overly fat people? They are said to be bulgy with redundant thick waistlines of fat deposits, a feature used in a Relative Fat Pattern Index (RFPI) evaluating the ratio of dorsal armpit (subscapular) skinfold thickness to the sum of dorsal armpit and waist (suprailiac) skin fold thickness. They are also grossly overweight, a parameter used in the Body Mass Index *(BMI = (weight, kg)/(height, m)$^2$)* where the obese male has BMI ≥ 28.6. Family studies have shown that 35% of the adjusted variation in BMI are due to a single recessive locus with a major effect. Polygenic loci in continuous variation (multifactorial inheritance) account for an additional 42% of the variation. About 23% of the variation are not explained by genetic factors. Thus genetic factors in a combination of major genes (Mendelian inheritance) and minor genes (polygenes, Galtonian inheritance), seem responsible for most (77%) of the BMI correlations[1]. Similar conclusions have been drawn from direct parent/child correlations and monozygotic-dizygotic twin studies[2]. Apparently, childhood environment has little or no influence on the BMI score of later life. With established, clear and strong genetic influence, the perception of tomorrow's world dominated by obese people could only be true if the obese are also biologically more fit, ie have a higher reproductive index. A further implication that can be drawn from a predominant genetic component is that the "waistline and weight" problem cannot be adequately managed by instructing abstinence, strenuous physical workouts, healthclub subscriptions and lifestyle changes. Obesity is a symptom of an array of minimal deviations and defined disease syndromes.

## SIMPLE OBESITY

This is usually perceived as a consequence of overfeeding in excess of nutritional requirements or gorging indulgence. However, nutritional requirements are known to be modulated by 3 major categories of metabolic pathways. They are: (1) anabolic pathways involved in the synthesis of compounds to maintain the structure and function of the body, viz., proteins, carbohydrates, lipids, nucleic acids, etc.; (2) catabolic pathways involved in oxidative processes that release the required free energy, usually in the form of high-energy phosphates or reducing equivalents, viz., the respiratory chain and oxidative phosphorylation; and (3) amphophilic pathways that have more than one function, acting as links between anabolic and catabolic routes, viz., the citric acid cycle. "Feeding" these metabolic processes are traits related to ingestion, digestion, absorption and satiation. Minimal deviations in this metabolic route may not produce individually identifiable phenotypes, but could have profound effects cumulatively and with time. Since the time of Sir Francis Galton (cousin of Charles Darwin) and Karl Pearson of University College London, in the late 19th century, weight and stature have been recognised as metrical or quantitative traits under continuous variation due to the cumulative effect of "minor" gene activity, each of which does not produce any major effect. They are the polygenes. The frequency distribution of quantitative traits is "Gaussian" or the bell-shaped normal curve, and the inheritance is Galtonian genetics (blending inheritance) where parent-child correlation is always highly significant, in contradistinction to the all-or-none phenomena of Mendelian genetics where there is some difficulty in conceptualizing "no weight" or "no height". The child of an obese father will have a high tendency to become obese due to inheritance of the minimal deviations from "minor" or polygene effects, a tendency that can be expressed as $\sigma = rH^2$ where $r$, the statistical coefficient of relationship (coined by Galton), gives the proportion of genes in common; and $H^2$, the heritability factor that defines the extent to which the trait is controlled by $r$. It is also important to note that BMI does not have a 100% genetic correlation. Environmental factors do have a degree of modulating influence. Environmental covariation with obese relatives would favour obesity. Outside of family covariations, the invariable bell-shaped frequency distribution of metrical traits also means that there is a strong, so-called, "population pressure" by the environment towards the median or average which is the highest frequency in the population. If on the other hand, most of the people in the population are obese, then all is lost with no escape from destiny.

## OBESITY AS A FEATURE OF DEFINED DISEASES

### 1. Non-insulin dependent diabetes mellitus (NIDDM, maturity onset diabetes, Type II diabetes)

NIDDM is a major health problem affecting some 5% of the world population and even higher in some countries, reaching 6% or more in the United States. It is characterized by obesity of late onset without ketosis, insulin resistance and glucose intolerance. A strong familial tendency is well established. Concordance in monozygotic twins is almost 100% (in contradistinction to the low 25%-50% concordance rate in insulin-dependent diabetes mellitus, IDDM). For NIDDM, risk in siblings increases with age, reaching the theoretical 50% by the age of 80 years. Despite of overwhelming evidence of genetic predisposition, genetic markers have so far failed to identify any major gene effect in NIDDM. Insulin receptor defect producing insulin resistance and glucose intolerance appears to be a central issue in NIDDM. Insulin initiates its physiological effect by binding to a receptor (insulin receptor). When bound to insulin, the insulin receptor functions as an enzyme and phosphorylates tyrosine in the target proteins. This is the intracellular signal for the metabolic processes induced by insulin. Multiple factors along this pathway have been suggestd in risk models for NIDDM or maturity onset diabetes, and commonly cited as a multifactorial trait[3] where the predisposition is quasi-continuous, dependent on threshold penetrance in the "Gaussian" distribution of

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Galtonian inheritance.

There is a distinct form of NIDDM called maturity-onset diabetes of the young (MODY) which has 3 subforms called MODY I, MODY II and MODY III. MODY I is caused by mutation in chromosome 20, at 20q13; MODY II by a mutation in the glucokinase gene in chromosome 7, at 7p15-p13; and MODY III by a point mutation at the 24th position of the beta chain of the insulin gene resulting in substitution of serine for phenylalanine, the Phe24Ser mutation in the insulin gene in chromosome 11 at 11p15.5. In contrast to the multifactorial transmission of the general NIDDM phenotype, MODY phenotypes are inherited as clear autosomal dominant traits[4].

In addition, there is the maternally transmitted mitochondrial-inheritance form of NIDDM which is NIDDM with deafness (non-insulin dependent diabetes mellitus with deafness, diabetes-deafness syndrome, Ballinger-Wallace syndrome) that is a strictly maternally transmitted. NIDDM with deafness is not a genomic DNA disease. The cause of NIDDM with deafness is a deletion in the mitochondrial DNA in the cytoplasm of the cell, causing loss of O(L), the origin of light chain for mtDNA replication, hence the obligate maternal transmission. Only the egg of the mother has the cytoplasm to transit to the offspring in the formation of the zygote with sperm fertilization. Onset of diabetes is between 20 to 30 years with deafness generally preceding diabetes.

## 2. Rodent homologues of human obesity

All the Mendelian recessive rodent models of obesity with associated type II diabetes mellitus (NIDDM), viz., the "tubby" mouse (tub/tub), the "obese" mouse (ob/ob), and the "fatty" rat (fa/fa), appear to have conserved homologies in man. The human homologue of the mouse "tubby" mutant (tub gene) seems located in human chromosome 11 at 11p15 region, where the insulin (Ins) gene is found. The tub gene is also said to be mapped to only 2.4 cM from the human haemoglobin beta (Hbb) gene in 11p15, so that Hbb is said to be a useful linkage marker for studies on familial obesity in humans[5]. The recently announced cloning of the mouse ob gene[6] has been publicly hailed as a decisive advance in the genetics of obesity in both mouse and man. The human homologue of ob has been assigned to chromosome 7q31.3[7] and seems to be overexpressed in the obese and regulated by insulin. The normal counterpart of the ob gene produces the leptin protein/hormone (derived from the Greek world *leptos* for thin) whose soluble portion acts on the hypothalamus as a satiety factor[8]. It seems that mutation of the normal leptin gene produces the ob gene, making the poor animals insatiable. Obesity from ob/ob expression is therefore gorging obesity. The fa/fa "fatty" rats are obese apparently with ob gene expression[9]. However in man dissociated responses have been observed, ob expression is reportedly without any role in the susceptibility to NIDDM in Mexican-Americans[10].

## 3. Prader-Willi syndrome

Unlike obesity with NIDDM, Prader-Willi obesity is not a major social issue, but illustrates the diversity of genetic mechanisms involved in obesity. This is an early onset obesity, developing in the first and second years of life. The Prader-Willi syndrome and its alternate form called Angelman ("happy puppet") syndrome are the classical examples illustrating a fundamental mode of genetic transmission that deviates totally from Mendelian inheritance. It is caused by distrubances in an "imprinted" genomic domain at chromosome 15q11-q13. Quite apart from the X and Y sex chromosomes, autosomal domains of higher eukaryotic genomes are not necessarily functionally equivalent because some of the genomic regions are marked by the phenomenon called "parental or genomic imprinting" which distinguishes the parental origin, resulting in allele-specific differences in methylation, transcription and replication between maternal and paternal geomic domains. The term "imprinting" was coined in 1950 by Helen Crouse who found that "the chromosome which passes through the male germ line acquires an imprint that results in behaviour exactly opposite to the imprint conferred on the same chromosome by the female germ line[11]. This epigenetic modulation has recently been demonstrated to be the causation of a known cytogenetic phenomenon called "homologous pairing", often observed in induced interphase cell fusions, in which there is preferential association of the imprinted maternal and paternal chromosomes or chromosomal domains in interphase nuclei[12]. A number of conditions are known to alter normal imprinting of the imprinted gene or locus, viz., uniparental disomy inheritance, hemizygous deletion or mutation. In the present case a deletion, for example, at 15q11-q13 of the paternal chromosome without corresponding deletion in the maternal chromosome produces the Prader-Willi syndrome that is characterized by obesity. If, on the other hand, there was deletion at 15q11-q13 in the maternal chromosome without corresponding deletion in the paternal chromosome, produces the angelman ("happy puppet") syndrome which is not characterized by obesity. The Prader-Willi syndrome is therefore said to be from "maternal imprinting" due to paternal loss, where a nonmanifesting male transmits the loss of paternal imprinting to the manifesting offspring. The Angelman ("happy puppet") syndrome is said to be from "paternal imprinting" due to maternal loss, where females transmit the trait, being nonmanifesting carriers themselves. "Homologous pairing" is lost in cells from either Prader-Willi or Angelman syndrome. Imprinting loss affects homologous pairing with devastating results.

## 4. Cohen syndrome

Characterized by truncal obesity, prominent incisors and gaping mouth and has been mistaken several times for Prader-Willi 15q11-q13 defect (see above). Cohen syndrome involves an apparently balanced reciprocal translocation between chromosome 5 and 7, viz., t(5q;7p)(q33.1;p15)[13]. Here classical chromosome inheritance forces are pertinent.

## 5. Cushing's syndrome

Obesity in Cushing's syndrome can be iatrogenic or the result of Mendelian transmitted neoplasia. It is characterized by obesity of special distribution, viz., moonface, truncal obesity and matchstick limbs. The symptoms are directly related to chronic administration of cortisone, cortisol, corticotrophic hormones and their synthetic analogues, or excessive secretion of glucocorticoid hormones with nodular hyperplasia of the adrenals and adenoma of the adenohypophysis which may be subclinical, and transmitted as a Mendelian recessive trait. Onset of the obesity may be at any age, but is usually seen in the 3rd or 4th decades with a higher incidence in women than in men. Cushing's syndrome is also seen in multiple endocrine neoplasia type I (MEN I, Wermer's syndrome with Zollinger-Ellison syndrome included), and multiple endocrine neoplasia type II (MEN II) which are Mendelian autosomal dominant traits.

## 6. Familial polycystic ovarian disease (PCO, Stein-Leventhal syndrome)

This is a Mendelian dominant trait where the fundamental defect in many causes is increased 5-alpha-reductase activity in the liver and skin. As a result, testosterone is converted to the more potent androgen dihydrotestosterone, leading to hirsutism[14]. Here obesity is associated with hirsutism, amenorrhea and ovarian

enlargement from polycystic disease.

### 7. Borjeson syndrome (Borjeson-Lehmann syndrome; mental deficiency, epilepsy and endocrine disorders; Borj syndrome)

X-linked obesity illustrates male-restricted phenotypes. This syndrome of marked obesity with fatty face and cheeks, gynaecomastia, hypogenitalism and small testicles, is due to a mutation or deletion at the distal end of the long arm of X chromosome, Xq26-27, which contains the testis-determining factor (SRY)-related HMG-box gene, 3 (SOX3). The mammalian genome contains a family of genes related to SRY, the testis-determining gene of Y chromosome, by a DNA binding-motif of the high mobility group (HMG) box class of non-histone chromosomal proteins, and are called SOX genes for SRY-related HMG-box genes. Deletion of the SOX3 gene in X chromosome at Xq26-27 results in small testicles from partial primary testicular failure but sufficient testicular function for male development. Males are obligate hemizygotes and invariable expressors for X-linked traits (in contrast to the complications of X-inactivation [Lyonization] and loci that escape inactivation in females[15]).

### 8. Bardet-Biedl syndrome (BBS; Bardet-Biedl syndrome type I and II; BBS1 and BBS2)

Obesity can also be a problem of genetic heterogeneity. BBS is characterized by obesity with polydactyly of hands and feet, hypogenitalism and pigmented retinopathy. Two subforms of Bardet-Biedl syndrome have been documented, and named BBS type I and BBS II, both documented as Mendelian recessive traits. The BBS type I locus is said to be at chromosome 16q21 while BBS type 2 locus is at chromosme 11q. However BBS families involving other chromosomal loci have also been documented[16]. BBS has been mistaken for Laurence-Moon syndrome and until recently the two syndromes were named conjointly as Laurence-Moon-Biedl syndrome, since 1925. Laurence-Moon syndrome itself does not present with obcsity.

## POSTSCRIPT

Obesity is clearly a problem in genetics. The diversity of genetic mechanisms involved in obesity ensures that the problem cannot be morally eradicated. Predictions of the world being overrun by obese people also cannot be justified since there is no evidence in any of the obesity-associated genetics traits that the affected has a higher biological fitness, in fact quite to the contrary.

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