Considerations Regarding the Genetics of Obesity

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The genetics of human body fat content (obesity) are clearly complex. Genetic and physiological analysis of rodents have helped enormously in pointing to critical molecules and cells in central nervous system and "peripheral" pathways mediating the requisite fine control over the defense of body fat. Human and animal studies are consistent with inferences from evolutionary considerations that the strengths of defenses against fat loss are greater than those against gain. Many of the genes participating in these pathways have reciprocal effects on both energy intake and expenditure, though different genes may have primary roles in respective responses to weight gain or loss. Such distinctions have important consequences for both research and treatment strategies. The body mass index (BMI) is a useful gross indicator of adiposity, but more refined measurements of body composition and energy homeostasis will be required to understand the functional consequences of allelic variation in genes of interest. Phenotypes related to energy intake and expenditure—which clearly are the major determinants of net adipose tissue storage—are not salient when individuals are in energy balance (weight stable); measurements obtained during weight perturbation studies are likely to provide more revealing phenotypes for genetic analysis. The advent of high-density genome-wide scans in large numbers of human subjects for association analysis will revolutionize the study of the genetics of complex traits such as obesity by generating substantial numbers of powerful linkage signals from smaller genetic intervals. Many of the genes implicated will not have been previously related to energy homeostasis (e.g., recent experience with *FTO*/*FTM* as described below), and will have relatively small effects on the associated phenotype(s). The mouse will again prove useful in determining the relevant physiology of these new genes. New analytic tools will have to be developed to permit the necessary analysis of the gene × gene interactions that must ultimately convey aggregate genetic effects on adiposity.

In this article we discuss selected topics relevant to the genetics of obesity.

DO GENES PARTICIPATE IN THE REGULATION OF BODY WEIGHT?

Human adiposity resolves complex interactions among genetic, developmental, behavioral, and environmental influences (1). Evidence for potent genetic contributions to human obesity is provided by familial clustering of increased adiposity, including a three- to sevenfold increased relative risk (λ_s) among siblings (2). Genetic factors are currently estimated to account for 40–70% of the variance in human adiposity (2).

Human twin studies

Based on twin studies, the heritability (fraction of the total phenotypic variance of a quantitative trait attributable to genes in a specified environment) of measures of adiposity is higher than for most other complex diseases or quantitative traits. Estimates of heritability range from 0.50 to 0.70 for body mass index (BMI) (3,4), 0.71 to 0.86 for total and regional body fat distribution (5), 0.75 to 0.8 for total body fat (6–8), 0.72 to 0.82 for skinfold thickness and waist circumference, 0.36 to 0.61 for waist–hip ratio (9), 0.59 for cognitive restraint in eating, 0.60 for emotional eating, and 0.45 for uncontrolled eating (10). The high heritability of phenotypes related to increased adiposity supports the contribution of genes, but does not indicate the number of genes or how those genes interact with modifiable environmental factors.

Rodent and human monogenic obesities

As with other complex phenotypes, there are rare examples of mono/oligogenic causes of obesity that serve as models for understanding the complex hormonal and neural networks that regulate adiposity, and also provide insight into pathways that may account for more common causes of obesity. There are over 25 human genetic syndromes associated with obesity as a cardinal feature of the condition including Prader Willi, Alstrom, Bardet-Biedl, Cohen, Albright hereditary osteodystrophy, Borjeson Forssman Lehmann, and MEHMO (11). In addition, there are several nonsyndromic monogenic forms of obesity in humans due to mutations in *LEP*, *LEPR*, *MC4R*, *POMC*, and *PCSK1*. Mutations in many of these same genes, or

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other members of their molecular pathways, were first identified in rodents: *Lep, Lepr, Agrp*, and *Cpe*. The phenotypes in humans and rodents are remarkably similar in all cases (12,13). Additional monogenic causes/modifiers of obesity in rodents include mutations in *Tub, Atrn*, and *Mgrn1*.

Mouse genetics

There are >244 genes that when altered in the mouse affect body weight or adiposity (14). Transgenic and knockout mice support roles for a diverse array of genes and pathways (15) in the regulation of energy homeostasis.

Chemical mutagenesis using ethylnitrosourea (ENU) has also been used to obtain new single gene mutations associated with obesity. Currently, many of the obese mice resulting from ENU mutagenesis are in the process of being crossed and mapped, although no genes have yet been identified using this strategy. Additionally, 408 quantitative trait loci (QTL) for obesity and body weight have been mapped in mice (14,15). These QTLs map to every chromosome except the Y chromosome, with highest density and replication in different crosses on chromosomes 1, 7, and 11. In general, most of these QTLs have modest effects, but a few contribute as much as 20% of the phenotypic variance in a cross. Many of these genetically manipulated or naturally occurring alleles demonstrate effects of background strain, differential response to a high-fat diet, and interactions with each other to modify the phenotype underscoring the ability to model some of the genetic complexity of human studies in more readily studied rodent models.

Linkage and candidate gene associations and recent genome-wide association studies

The number of genes implicated in human obesity continues to grow. The 253 QTLs for human obesity have been identified from 61 genome scans (14). Fifty-two of these genomic intervals have been replicated in two or more studies. Positive association studies have been reported in 127 genes with 22 of those genes supported by at least five studies (14).

In the past year, the decrease in the cost of genotyping on large, robust single-nucleotide polymorphism genotyping platforms, and advances in our understanding of the patterns of sequence variation in the human genome provided through the International Hap Map Consortium, have led to a flurry of reports from genome-wide association studies for complex diseases, the first among which those reported were for obesity and type 2 diabetes (T2DM). For T2DM, five independent groups of investigators performed genome-wide association studies (GWAS), and three groups have collaborated and combined their data sets to increase their power (16–20). In each study, ~1,000–2,000 cases and controls were used in the first stage followed by at least as many subjects in the second stage replication study. This two-staged strategy is the optimal approach to maximize sensitivity and eliminate false positive results from the first stage. Across both stages of all five studies, >55,000 subjects were analyzed. The large sample size attained through the combined analysis was essential for robust detection of susceptibility genes with modest effects. Due to the large number of tests performed in the GWAS, P values of $<5 \times 10^{-7}$ are necessary to provide a study-wide $P < 0.05$. These GWAS have identified 11 confirmed genomic regions and found six new replicated regions for diabetes susceptibility within Europeans. Five of the six genes were replicated across at least three studies. Implicated regions demonstrated statistical confidence ranging from 1×10^{-12} to 1×10^{-19}. Although the statistical significance of these loci was great, the risk conferred by the individual variants was modest, with the odds ratio ranging from 1.10 to 1.20 for all but one of the loci. The exception was transcription factor *TCF7L2* which had previously been implicated in diabetes susceptibility (21), and has the highest odds ratio of 1.37 for each T allele and was the most statistically significant with $P < 1 \times 10^{-48}$. Of the other 10 loci implicated in the GWAS, *PPARG, KCNJ11, TCF2*, and *WFS1* had been previously implicated in diabetes, but the other six genes *HHEX-IDE, SLC30A8, CKAL1, CDKN2A-2B, IGF2BP2*, and *FTO* were novel genes for diabetes/obesity susceptibility. Several genes that have been previously implicated in diabetes susceptibility such as *Calpain 10* were not identified in the GWAS and may indicate ethnic-specific difference or insufficient power even in these large studies. For the five loci for which there are data for mechanism of action, all five show effects through altered insulin secretion and provide evidence that a substantial portion of the genetic susceptibility to T2DM is conveyed through decreased insulin production (β-cell genes), with excess insulin resistance conveyed through increased adiposity produced through a combination of genes and environmental factors.

Through the GWAS of T2DM has come the first GWAS of obesity. While analyzing ~30,000 European adults to identify novel genes for T2DM, *FTO* was found to be associated with T2DM, but the effect was eliminated after controlling for BMI. *FTO* was then found to be associated with increased adiposity, independent of diabetes (22). Sixteen percentage of the European population carries two copies of the at-risk allele and were 1.0 kg/m^2 or 2.3 kg heavier than those homozygous for the protective alleles (22), with an attributable risk of 22% (23). Furthermore, studying 5,000 children at 9 years of age suggests that the association is with fat mass with no effect on lean body mass (22). The association between *FTO* and weight and hip circumference has also been replicated in Hispanic Americans but not African-Americans (24). This region of chromosome 16 had been previously implicated in obesity based on a case of a syndromic form of obesity characterized by obesity, anisomastia, mental retardation, and dysmorphic features associated with an interstitial duplication in this region (25). Meta-analysis of nonparametric genome-wide linkage studies with BMI from 37 studies of 31,000 subjects and >10,000 families demonstrated only nominal evidence of linkage with 16q12.2 around *FTO*, although this was one of the most significant findings of the meta-analysis. This result suggests that even large linkage studies may be insufficiently powered to identify genes with modest risk for obesity susceptibility, that genetic heterogeneity may limit the utility of such meta-analyses, and/or that association studies may identify different

loci than linkage studies due to the inherent power limitations and sampling bias of family studies (26).

Gene × environment interactions

Clearly, changes in our genes cannot account for the recent trends toward increased adiposity. However, what is likely genetically determined is the relative rank of adiposity of an individual within a population living in a specific environment. As the environment becomes more, or less, conducive to the development of obesity (ease of access to food, need for physical exertion to obtain it, putative intrauterine and perinatal influences), the median adiposity of the population shifts accordingly. The distribution of adiposities representing the population would not be expected to shift in perfect Gaussian symmetry around this median. In other words, as a population is exposed to these environmental "pressures," the "tails" of the distribution may not change proportionately. Those who are thinnest may show disproportionate resistance to upward pressure by the environment, while those who are fattest may show greater sensitivity to the upward bias imposed by the environment (27). The opposite responses would characterize these tails in the context of environmentally mediated restriction of access to food. There are reasonable evolutionary arguments for such asymmetries in response, based on the likelihood that strong selective pressure in favor of energy efficiency and proclivity in the acquisition and storage of calories has prevailed. The phenotypic differences among individuals at these extremes of adiposity presumably reflect allelic variation at genes that affect energy intake, expenditure, and the chemical form in which excess calories are stored ("partitioning").

WHERE IN REGULATORY CASCADES ARE THE CRITICAL GENES LIKELY TO RESIDE?

Physiology of control of body weight

At one level, the physiology underlying the control of body weight (body fat) is quite simple. The degree of balance between energy intake and expenditure, over time, determines whether body weight will change. In children—especially during the periods of rapid somatic growth in infancy and adolescence—positive balance is required to enable deposition of new body mass. The arithmetic in all instances is a biological version of the first law of thermodynamics: energy in – energy out = delta body mass. The average adult ingests about 700,000 kcal/year. Hence, even small imbalances in this relationship can lead to large changes in body mass. For example, assuming an energy equivalence of 6,000 kcal/kg of body weight, a 3% difference between intake and expenditure will result in a 3.5 kg weight change in 1 year. These effects are mitigated in the upward direction by the gain of metabolic mass, and in the downward direction by a reduction in energy expenditure per unit of metabolic mass. A salient point of this calculation is the substantial effect on body mass of sustained, very small differences between intake and expenditure. Neither energy intake nor expenditure in free-living humans can be measured to these tolerances, making it difficult to directly quantify the respective contributions of these mechanisms to any specific instance of obesity (28). In addition, it seems to be frequently forgotten that obese individuals—when weight stable—are in precise energy balance, with energy expenditure rates that are superimposable on those of never-obese subjects when adjusted for the larger metabolic mass of the obese; at such equilibrium points, the obese are ingesting calories that are perfectly matched to energy expenditure (29). Hence, efforts to identify mechanistically relevant differences between obese and nonobese individuals by examining them when stable at their customary weights are not likely to be revealing. Prospective analysis of the relevant phenotypes in the dynamic phase of weight gain or characterizations of responses to experimental weight perturbations are required.

Some of the genes underlying the physiological pathways governing energy expenditure and intake are known (30). However, the apparent contribution of many genes of relatively small effect on net body mass and composition indicates that we have certainly not identified all the relevant genes in either pathway.

The genes involved in energy homeostasis will have primary effects on:

1. Energy expenditure
2. Energy intake: regulatory, hedonic, reward, executive control
3. Partitioning: the proclivity to store calories ingested in excess of expenditure as fat, protein, carbohydrate.

Single genes may influence one or more of these, a phenomenon that might be predicted from the importance of integrating these physiologic responses in the organism. An example of such protean effects of a single gene is the impact of leptin deficiency in the *Lep*^{ob} mouse (31) that shows reduced energy expenditure, increased energy intake, and strong partitioning of stored calories toward fat. Other genes—such as *Mc4r*, *Mch*, *Cnr1*—shown by mouse and/or human genetics to play a role in the control of energy homeostasis have effects on both energy intake and expenditure, resulting in coordinate effects that favor weight loss (*Mc4r*) or gain (*Mch*, *Npy*, *Cnr1*). These reciprocal effects are consistent with evolutionary and physiological considerations that would favor selection of genes with reciprocal actions on the major pathways regulating energy balance, hence energy storage (32,33).

What do genetics and natural history suggest regarding the most likely major locus of physiology among these three processes?

The bias in energy homeostasis would be expected to favor the storage of some excess of calories against environmental vicissitudes and the cost of gestation and breast-feeding. Some of the data supporting this inference are described later. The physics and biochemistry of energy homeostasis make the choice of predominant mechanism for such physiology simple: energy intake will be the quantitatively most important means for such control. The amount by which *energy expenditure* can be safely lowered in service of favoring weight/fat gain is far less than

the ease with which *calorie intake* can be increased for the same purpose. A few thousand extra calories of intake can be readily achieved, whereas reduction of energy expenditure—necessarily comparatively mild—to achieve this same end would, at best, have to be imposed for a much longer period of time with possible adverse collateral impact on muscle and other aspects of metabolic performance. The use of "partitioning" —i.e., the preferential shifting of calories toward fat—would deprive the organism of critical lean mass in muscle and the brain. This partitioning phenotype is, in fact, seen in pair-fed *Lep*^{ob} mice. Based on such arguments, the main genes with major impact on facultative energy balance are likely to have their largest, though not necessarily exclusive, effects on energy intake.

ARE THE GENES REGULATING RESPONSES TO NUTRIENT EXCESS THE SAME AS THOSE MEDIATING RESPONSES TO CALORIC DEFICIENCY?

What does the physiology of response to over- or underfeeding indicate about this question and the nature of participating genes?

This is a very important question from both a basic physiological perspective as well as the framework for the design of intervention strategies. There is general acceptance of the idea that movement of body weight (fat) in either direction is to some extent opposed by physiological adjustments whose apparent purpose is to prevent excessive gain or loss of body fat. Studies in rodents, nonhuman primates, and humans support this general idea, though the magnitude and nature of the responses are contested (34–37). Assuming that the evolutionary history of our mammalian predecessors involved greater exposure to environments in which available calories were more often restricted than in excess, and that considerable physical effort was required to access such calories, it would seem likely that selection would favor genes conserving energy. From a physiological perspective this certainly seems to be the case in modern humans, who have little difficulty gaining body fat when exposed to a predisposing environment, but who experience great difficulty in the maintenance of reduced body weights. The current increase in the prevalence of obesity proves the point but does not, of course, define the underlying molecular physiology.

Elsewhere we have suggested that the central nervous systems subserving the regulation of energy balance comprise a threshold-like mechanism for the assessment of humoral and other peripheral signals that denominate the amount of adipose tissue and any acute changes in that mass (38). Leptin is a major signal in this pathway, but insulin, fatty acids, and various gut hormones also play a role in these processes that are mediated in part via neurons in the hypothalamus and brain stem (39–41). Genes that control the development of the constituent neurons, their connections, and the expression of neuropeptides (e.g., NPY/AGRP, POMC, MCH) and other neuromediators (e.g., endocannabinoids) and their cognate receptors—interacting with developmental processes—determine the threshold for signals of body fat below which increases in energy intake and reductions in energy expenditure are invoked to "defend" body fat. This threshold determines the physiological "floor" for each individual's body fat. The strength of the compensatory responses is equal in obese and never-obese individuals, indicating that both types are appropriately and effectively defending minimum amounts of body fat that are determined by these genetic and developmental forces (42). The response to reductions of fat mass below the threshold is powerful, involves effects on both intake and expenditure, and accounts for the high recidivism to initial weight of normal weight or obese individuals who lose weight due to illness or therapeutic interventions. The defense against gain in body fat is weaker due to presumed lower evolutionary pressure to develop such responses, and, in fact, the survival and reproductive advantages of carrying some additional adipose tissue (42,43).

In studies in which mono- and dizygous twins pairs have been either overfed for up to 6 weeks or put into negative energy balance via an exercise regime, the resulting changes in body weight are highly correlated within twin pairs, but range widely among these pairs (44). The strength of the inter-twin correlations is stronger for weight loss than for gain, suggesting tighter biological control of the response to the hypocaloric state.

Are defenses against movement of weight in both directions mediated by reciprocal actions/effects of the same genes, the actions of direction-specific genes, or a combination of both?

This is an important basic question in molecular physiology, but also has implications for the development of effective therapeutic interventions (for both obesity and cachexia) and, perhaps, for predicting specific biologic responses of individuals to weight perturbation. Genes protecting against excessive weight gain seem most likely to have been selected for as a mechanism for preventing the organism from experiencing incessant and possibly overwhelming drives to eat—interrupting other behaviors critical to survival, for example reproduction and attention to offspring. Short-to-intermediate satiety signals, such as those emanating from the gut (GLP1, PYY, CCK, ghrelin), mediate meal-to-meal variation in frequency and size. Molecules sensitive to longer-term changes in energy stores (leptin, insulin) have effects that are to some extent proportional to their circulating concentrations, but the responses to their lowering (reflecting reduced energy intake or stores) are stronger than those to their elevation. Cell bodies of the hypothalamus, brain stem, and rostral projections express receptors for these circulating peptides, as well as endogenous neuropeptides with powerful orexigenic (NPY/AGRP, MCH) and anorexigenic (POMC) effects. These neuropeptides and circuits presumably underlie the region-specific effects of ablative and stimulatory manipulation of the hypothalamus. We have argued elsewhere that in the basal/weight steady state, the catabolic "tone" of this regulatory system is somewhat greater than the anabolic tone due to ambient levels of leptin and insulin (45). Caloric restriction suppresses catabolic and increases anabolic tone, the strength and speed of response enhanced by the fact that both pathways are reciprocally affected. The

response to weight loss, in this formulation, is stronger than that to weight gain because weight loss lowers the tonically increased anorexic tone, while driving orexigenic signals upward. The response to weight gain is weaker because anorexic signals are already activated in the basal state and orexigenic tone is low in the basal state and stays that way with weight gain. This formulation would suggest that separate genes—though necessarily acting in coordinate fashion—have primary roles in responses to weight gain or loss.

HOW TO FIND AND VET RELEVANT GENES IN HUMANS

Example of T2DM

Given the foundation of previously defined single gene mutations, linkage studies, and genes/regions identified by association studies, what is the optimal strategy to identify and validate genes relevant to the pathogenesis and maintenance of obesity? The goal of identifying such genetic susceptibilities is both to stratify risk for disease development and to individualize therapeutic intervention, as well as to identify molecular mechanisms for energy homeostasis that can be ultimately used as targets for intervention. The elucidation of the genetic basis for obesity in humans has many parallels to that of the genetic basis for T2DM. Susceptibility to T2DM is mediated by effects on beta cell mass, beta cell function and insulin secretion, and insulin resistance (which is affected by adiposity as well as fat distribution). In addition to genetic complexity, there are developmental determinants that are imposed in part by maternal effects during gestation and early postnatal environment, as well as the timing of development of obesity. To date, the preponderance of genes identified for T2DM susceptibility have been those presumably affecting beta cell mass and function. The genetics of increased adiposity are likely to be similar but probably even more complicated.

Why is finding obesity genes harder?

The phenotype of increased adiposity is much less specific than T2DM, and the mechanisms governing the excess storage of calories relate to the three endophenotypes listed earlier. The mechanisms governing these processes are complex and encompass the neurological circuits governing myriad aspect of ingestive behaviors, energy expenditure, and their interactions with social contexts. Similar to diabetes, there are likely to be intrauterine effects on the fetus that will have long-standing impact on the neural circuitry underlying control of energy homeostasis, the number and location of adipocytes, and genetic and metabolic imprinting of molecules participating in these processes (46–48). The phenotype most commonly used to assess obesity, the BMI, is actually a composite of fat and nonfat mass which can reflect varying degrees of adiposity among individuals even with the same BMI. Finally, it is likely that the genetics of obesity are complicated and heterogeneous. There may be genetic heterogeneity among ethnic groups, ages, and sexes. There are also likely to be complex gene by gene, gene by environment, and gene by development interactions that could involve epigenetics and copy number variations that have heretofore been little studied in relationship to obesity.

Use of endophenotypes should help

An important aspect to addressing this problem is a refinement of the phenotype. Ideally, phenotypes would include total caloric intake, composition of food intake, ingestive behavior, taste preferences, tasting ability, hedonic characterizations of food ingestion, body weight, BMI, body composition, fat distribution, energy expenditure, energy expenditure in response to diet challenges, metabolic profiles, and functional imaging to understand the neurological response to feeding cues. The cost of such intensive endophenotyping must ultimately be balanced against the potentially large numbers of subjects necessary to statistically demonstrate association.

Study the cell biology and molecular genetics of responses to perturbations of body weight—naturally occurring and drug-induced

An additional strategy involves intentionally perturbing the system to determine the differential response to the perturbation. This approach was used in the weight perturbation studies of twins mentioned earlier. An important clinical example of this is the weight gain among schizophrenics in response to the second generation antipsychotics (49). By focusing on a single drug and differential response among nonobese patients to an equivalent pharmacological intervention, researchers can identify a subset of subjects predisposed to substantial weight gain with concomitant insulin resistance, diabetes, and lipid abnormalities. Early studies in this area have suggested that genetic variation at the 5-hydroxytryptamine 2C and adrenergic alpha 2a receptor genes may play a role in the differential responses to antipsychotic treatment (50). Other challenges can be studied such as differential responses to overfeeding, or "doses" of exercise (44), changes in diet palatability/composition, etc. Although difficult to accomplish on a large scale, elimination of environmental variability can be achieved by placing subjects in a uniform environment such as an in-patient setting for short periods of time and may be most useful in provocative studies such as those using antipsychotics. Quantification of relevant social networks (51) may enable control for some important environmental influences.

Study the effects of genes prospectively in subjects selected by genotype, prior to onset of obesity or other relevant endophenotypes

Many novel genes and alleles have been and will continue to be identified in the GWAS. Follow-up of these initial leads will require replication in additional populations. In addition, studies of other ethnic groups, African-Americans specifically, will be used in some instances to refine the genomic intervals containing the disease-causing variations due to their smaller regions of linkage disequilibrium. Additionally, it will be necessary to analyze association between these genetic variants and multiple endophenotypes, longitudinally across the lifespan. Longitudinal and/or prospective data will be particularly important to enable understanding of the primary effects of these variants rather than the secondary and tertiary effects occurring once obesity is established. Once a small

number of these potentially pathogenic variants are identified and validated, *in vitro* and *in vivo* studies in tissue culture and animal models will be necessary to prove causality. We have already performed similar experiments and have created a mouse model to examine the Gln(223)Arg genetic variant in *LEPR* (52) and propose using similar strategies as new genes are identified.

In addition to the strategies of linkage and GWAS, analysis of copy number variation in syndromic and nonsyndromic forms of obesity will provide novel genes and regions for analysis. We are only now beginning to characterize normal copy number variation (53,54), but the research tools have been developed to analyze copy number variation in the same data sets that were used to generate genotypes for the GWAS. Analysis of these copy number variants may identify additional genetic susceptibilities for increased adiposity. Additionally, although rarer, larger genomic deletions or duplications incorporating multiple contiguous genes are likely to be a common cause of syndromic obesity and can be readily detected by array comparative genomic hybridization and/or SNP oligonucleotide microarray analysis (55,56). Identification of specific genotypes and genes associated with these deletions/duplications may be extremely useful in identifying genes and pathways important in energy homeostasis and ingestive behavior and will be amenable to intensive endophenotypic characterization to elucidate the mechanisms mediating contributions to adiposity.

Finally, we will need to develop sophisticated, complex algorithms for studying gene-by-gene interactions, gene networks, and integration of inherited genetic variation with gene expression profiles, metabolite profiles, and multiple endophenotypes. Such analyses will require large numbers of subjects, but as the data from multiple GWAS become publicly available and as the cost of genotyping DNA sequencing continues to decrease, and computing power to increase, such experiments will be feasible.

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DISCLOSURE

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