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Metabolic Health and Weight: Understanding metabolically unhealthy normal weight or metabolically healthy obese patients

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Obesity is most commonly defined as a BMI of over 30kg/m^2. Typical classification is into categories of Class I (BMI >30 kg/m^2), Class II (BMI equal to or over 35 kg/m^2) and Class III (equal to or over 40 kg/m^2), with the latter also known as severe obesity. While this method is most frequently utilized by clinicians, it has limitations-such as in those individuals with high muscle to fat ratios or those of Asian descent. Alternate methods for obesity definition and classification include data such as waist circumference, hip to waist ratio, or body fat percentage.

Using the BMI criteria for obesity, over 600 million people worldwide, including one third of adults in the United States meet criteria for obesity [1]. In the United States, this translates to mounting healthcare costs (estimated close to 128 billion dollars in 2008) and increased mortality compared to normal weight individuals [2]. Cardiovascular disease and secondarily malignancies has long been identified as the primary reason for these increases in mortality and costs. This in turn has been attributed to a worse metabolic profile which includes various combinations of impaired glucose tolerance/type 2 diabetes, dyslipidemia, hypertension and systemic inflammation.

However, hidden amongst traditional obesity related concerns, there lies a subset of patients without the expected sequelae of their weight. These patients circumvented the classic models of metabolic and cardiovascular risk, and are known as the “metabolically healthy obese” (MHO). Simultaneously, there are individuals who despite having “normal” weights, shoulder an increased burden of these risks. Accurate classifications and mechanistic understandings for individuals with these conditions would be required to ensure the best health care and appropriate treatments as well as to decrease health care costs due to

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improper treatments and requisite subsequent medical interventions. Here we discuss the current knowledge surrounding these two groups, and highlight important features for provider management.

Historically, the primary concern regarding obesity was due to the concurrent metabolic and cardiovascular risk. Yet, in recent years increased notice has been made of those individuals who do not fit into this traditional phenotype. Instead, metabolically healthy obese (MHO) and metabolically unhealthy normal weight (MUHNW) patients are generating important discussions regarding the classification of metabolic, and thus cardiovascular risk in patients. These cohorts have been previously highlighted in Metabolism, with discussions in recent years ranging from the association with diabetes, liver enzymes and vitamin D to the role of weight status and inflammation [3–9]. Here we discuss these two phenotypes, highlight current knowledge regarding their classification, development and management features for healthcare providers.

Presently, beyond cutoffs for surgical intervention, obesity guidelines do not distinguish between management of the various subclasses of obesity despite the fact that there has not been evidence for increased mortality in simple Class II Obesity [10]. In fact, while studies have shown that individuals with Grade II-III have greater mortality, there is evidence that Class I obesity patients may have lower all-cause mortality than normal weight patients [11]. Furthermore, existing guidelines also fail to individualize the management of MHO or metabolically unhealthy/abnormal obese (MUHO/MAO) patients. This is further complicated by a gap in the recognition and appropriate management of those normal weight individuals, who demonstrate high risk metabolic risk profiles.

Here we highlight these subtypes of obesity and metabolic profiles for providers, as well as ongoing research in the field.

Metabolically Healthy Obese (MHO)

Since 1982, there has been recognition of a group of patients who, despite meeting traditional BMI criteria for obesity, do not demonstrate high risk metabolic profiles. These individuals have been deemed as the “metabolically healthy obese” (MHO) [12–14]. Broadly, this categorization is described as an absence of metabolic disorders such as insulin resistance, type 2 diabetes, dyslipidemia and hypertension in those patients with BMIs greater than 30kg/m^2[15]. More specific classification schemes vary by study/research group, with variable cutoffs for blood pressure, and cholesterol (HDL, LDL, TC, TG or TG/HDL ratios) [16–18]. Further conflict is introduced by variable definitions for insulin resistance, which can include fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), and/or homeostasis model assessment (HOMA). For instance, one study showed that over 30% of patients were not correctly diagnosed with impaired glucose tolerance/T2DM when fasting plasma glucose was used as the primary criteria [19]. Thus, clearer and more consistent criteria are needed to determine whether an individual is MHO.

Metabolically Unhealthy Normal Weight (MUHNW)/Metabolically Obese Normal Weight (MONW)

In contrast to those metabolically healthy obese, there are also of subsets of patients who are considered “normal/healthy” weight, but demonstrate increased metabolic/cardiovascular risk. However, these patients have been even harder to define or characterize than the aforementioned group. First suggested by Ruderman in the 1980s, these individuals were described as hyperinsulinemic, insulin resistant, hypertriglyceremic and predisposed to subsequent development of type 2 diabetes mellitus and coronary artery disease [20, 21]. Broadly, these patients have been categorized by body mass indices of less than 25 kg/m^2, but have metabolic abnormalities more commonly associated with their obese counterparts, including abdominal fat distribution and elevated blood pressure. Most studies set the cutoff as three or more metabolic derangements to fulfill “metabolic unhealthy” definition. More recently, *Lee et al*. [22] proposed utilizing the TyG index-a product of the fasting blood glucose and triglyceride levels to identify patients who are MONW.

Classification is further complicated by the limitations associated with utilizing BMI in definitions. The metabolically abnormal phenotype has been associated with increased waist circumference and body fat percentage in normal weight individuals, which may not be picked up with standard BMI measurements [23].

In coming years, it will be increasingly important to identify consistent criteria for these metabolic states/body phenotypes. With the ability to accurately and precisely classify these patients, healthcare providers will be better able to assess prevalence and study the predisposing factors for metabolic disease-and target therapies accordingly.

Prevalence

Given the inconsistency of MHO definitions, there is high degree of variability surrounding the estimated prevalence of this phenotype. In 2010, one analysis found that the prevalence of MHO varied from 3.3–32.1% in men and 12.2 to 57.5% in women, largely depending on which criteria for MHO patients was applied [18]. Another study found a prevalence of 53.7% for MHO amongst overweight adults when classified by visceral-to-subcutaneous fat ratio and this further related to lipoprotein subfraction analyses particularly for small dense LDL particles [7]. A study coming out of Korea found that the prevalence was 14.9% in the entire or 47.7% amongst obese individuals [4]. More recently, a systematic review by *Rey-Lopez et al.*[24] evaluated 27 prospective studies and found that prevalence ranged from six to 75%, depending on classification scheme used. The prevalence of MHO varies widely depending on how it has been defined, yet again underscoring the importance of establishing a clear definition and criteria.

Without one standardized definition, however, the true prevalence of the MUHNW phenotype is difficult to quantify. Using criteria of two or more metabolic abnormalities, *Wildman et al.* [25] reviewed NHANES data from 1999–2004 to find that 23.5% of normal weight adults were metabolically abnormal. Similarly, a Korean study, using data from the third national Korean National Health and Nutrition survey, found a prevalence of 8.7% for

the MUHNW phenotype [26]. There is some evidence that race may contribute to MUHNW, as for certain races, central adiposity is high despite low overall BMI. One study has shown that Asian Americans have a 5× prevalence of being lean as compared to obese with diabetes mellitus, suggesting that they are more likely to be MUHNW than typically obese [27]. African and Latino Americans had the highest overall prevalence of lean body weight with diabetes in the same study, suggesting higher overall levels of MUHNW, although they showed similar rates with obesity and diabetes, suggesting higher levels of metabolic dysfunction regardless of body weight [27]. These differences are likely due to differences in central adiposity. For instance, lean (defined by BMI) Asian Indians show lower insulin sensitivity than other races of Asian descent but also higher body fat percentage and waist circumference [28]. Similarly, lean Chinese participants have NAFLD which also correlates with higher waist circumference and poorer metabolic outcomes such as blood glucose, blood pressure, and insulin levels [29]. One should keep in mind that for a given BMI, Chinese subjects tend to accumulate fat intra-abdominally and thus even lean subjects may have ectopic fat deposition and intra-abdominal obesity. With varying prevalence, it becomes more difficult to identify at risk populations and subsequently dedicate research into the genetic and lifestyle factors that contribute to their presentations.

Genetic Factors

Obesity as a whole has and continues to undergo extensive study into the underlying genetic mechanisms contributing towards its development. Notable findings have been monogenic obesity presentations secondary to disruptions of the POMC, leptin and MCR4 loci [30] in addition to minor contributions by several other genes [31]. In general, overall obesity is a polygenic disorder and gene-environment interactions play a very important role. The genetic and pathophysiologic development of metabolically healthy obesity remains an area of continued study. As suggested before, MHO patients are noted to have less central and visceral obesity. These studies have also alluded to reduced adipocyte hypertrophy, fibrosis and stress as potential contributors to this presentation.

Implicated genes include those involved in transcription related to adipogenesis [32]. With the knowledge that white adipose tissue plays a role both lipid and glucose regulation, *Das et al.* [33] looked to identify difference in RNA transcripts of MHO and MAO patients. They found that those patients with metabolic derangement had upregulation of 141 genes and downregulation of 17 genes. Highlighted differences included the upregulation of matrix metallopeptidase 9 (MMP 9 and osteopontin (SPP1), as well as downregulation of NDRG4 (N-myc downstream-regulated gene family member 4) and GINS3 (GINS complex subunit 3) [33]. Another study revealed that MHO as compared to metabolically unhealthy obese patients had differential gene expression for amino acids and for branched-chain amino acid catabolism in subcutaneous adipose tissue [34]. Particularly, levels of glutamic acid, valine and isoleucine correlated with HOMA-IR where MHO had less expression and lower HOMA-IR [34]. Further underscoring the role in genetic variation within adipogenesis in MUHNW patients, *Yaghootkar et al.* looked to compare genetic risk scores against disease outcomes, and were able to identify 11 genetic variants/risk alleles which were found to lead to increased hypertension, type 2 diabetes, and coronary artery disease. The identified loci were primarily associated with transcription factors involved in

adipogenesis [35]. With specific focus on the development of T2DM, *Scott et al.* tested associations between genetic risk scores and incident diabetes, finding that a genetic score for insulin resistance mirrored monogenic models for lipodystrophy, and was predictive, regardless of weight status [36]. Additionally, adipocyte storage capacity has been a complementary avenue for study, as this may hold the key in subsequent development of metabolic risk.. Previously, to explain the transition from normal adipose tissue to that which leads to metabolic derangements, studies proposed the "adipose tissue expandability hypothesis." This postulated that once adipocytes reached a threshold capacity for storage, they begin to promote insulin resistance with lipotoxicity and adipokine release. This was supported by knockout studies with PPARγ, lipodystrophy models, alterations in adipokine secretion following saturation of adipose tissue [37]. Investigating this led to further characterization of genetic contributors to the pathways of adipogenesis (SFRP-1, Wnt, S14), apoptosis (TRAIL, TWEAK, BCL2, CASP 3/7), and angiogenesis (VEGF-A,B,C,D). Expanding the understanding of adipose tissue in the context of MHO patients, *Tinahones et al.* looked at genes associated with both lipolysis and lipogenesis and BMI, insulin and HOMA-IR. They found a positive correlation in PPARγ, DGAT1, AQP7, GK, ATGL, HSL, and perilipin and the BMI, insulin, and HOMA-IR in both subcutaneous and visceral fat tissue. Additionally, they demonstrated a negative correlation between genes-ACC1, PEPCK, ACSS2, FABP4, and the aforementioned measures of metabolic risk [38]. Future studies should examine these in more depth to determine their influence over and/or interaction with typical obesity.

Mouse models for MHO

There are several mouse models which may serve as models for MHO. For instance, adiponectin transgenic mice on an *ob/ob* background become obese on a normal diet but remain insulin sensitive and show fewer inflammatory markers without liver steatosis [39]. Indeed, elevated adiponectin has been observed in humans with MHO [40]. Similarly, *TBP2* knockout mice show weight gain and high adiposity but remain insulin sensitive [41]. *HcB19* mice crossed with *ob/ob* become very obese, but also retain peripheral insulin sensitivity and do not show β-cell apoptosis [42]. Additionally, a leaky knockout of the *Brd2* gene in mice do show liver steatosis and elevated levels of circulating insulin, but they have less inflammatory markers, hypoglycemia and normal glucose infusion rates [43, 44].

While study of MUHNW mouse models is more limited, work in Goto-Kakizaki rats has implicated Major Histocompatibility Complex (MHC) genes *RT1-Ba, Bb, and Db1* in development of insulin resistance and inflammation with a lack of obesity [32] and may serve as models for further study. Careful study of appropriate animal models is needed to propel this field forward.

Dietary and Lifestyle Contributions

Along with ongoing research into genetic determinants, there remain questions surrounding the environmental or external factors leading to MHO presentations. Most commonly, studies have examined diet and fitness for potential contributions, but also for consideration of age, alcohol, tobacco and other factors.

Drawing from National Health and Nutrition Examination Surveys (NHANES) data from two separate time periods, *Camhi et al.* examined dietary quality (using the Healthy Eating Index) in obese patients, and found that adolescents and MHO women 19–44 years of age, had higher dietary quality with increased fruit, grain, meat and bean intake [45]. Previously, data had not shown marked differences, other than increased adherence to food pyramid recommendation in MHO individuals [10].

Similarly, investigation into exercise/fitness regimens has been conducted. One cross sectional study from the Cork and Kerry Diabetes and Heart Disease Study, did not show any effect of physical activity, smoking, alcohol intake or calorie intake on development of the MHO phenotype, whereas there was positive evidence for dietary quality[i] [10]. Alternately, data from the Korean National Health Study demonstrated the MHO phenotype was less likely with advanced age, male gender, and with any history of tobacco smoking [26].

With regards to factors influencing the development of metabolic syndrome/unhealthy metabolic profiles, several studies have examined the influence of lifestyle contributors. While multiple studies identify age, alcohol intake and activity levels as likely contributors, there is differing evidence surrounding the influence of gender [46, 47]. Smoking status and lower education levels have also been identified as potential contributors to this phenotype [26]. This will need to be better defined by large epidemiology studies in the future.

Metabolic Outcomes

Given concern surrounding obesity as a public health epidemic lies within cardiovascular risk and disease, this has also been an important question for MHO patients. However, the data surrounding this has been conflicting and inconsistent.

Despite variable criteria, certain anthropometric and other characteristics have been associated with the MHO phenotype. Most notably, distinct fat distribution patterns (with less ectopic and visceral fat), and favorable inflammatory profiles (with lower concentrations of inflammatory markers) are seen with MHO [48]. Furthermore, in another study, MHO women had lower blood pressure, triglycerides, and glucose but higher HDL cholesterol, adiponectin and LDL size than MUHNW women [6]. *Phillips et al.* found that MHO patients had lower levels of complement component 3, TNF-a, IL-6 and CRP, as well as a reduced white blood cell count and higher adiponectin [49]. Multiple studies have suggested this “favorable” inflammatory profile in MHO development [50–52], though the degree of profile is not universally agreed upon [19]. MHO show higher free fatty acid (FFA), IL-6, and CD4+ T cell levels and macrophage infiltration into adipose tissue [9]. Liver enzymes, but not vitamin D, have been shown to be independently associated with MHO in the Korean population [4]. Another study also showed that MHO individuals have lower levels of liver enzymes such as ALT, AST, and GGT in addition to less fat in the liver [53]. This was further supported by *Chen et al.*, who stratified insulin resistant and sensitive groups, subsequently finding that lower visceral adiposity, liver fat, blood sugar levels, and

[i]With closer adherence to current food pyramid recommendations

blood pressures were all associated with insulin sensitive obesity [54]. Altogether, there appears to be a normal/healthy metabolic profile that sets MHO patients apart from their metabolically unhealthy obese counterparts.

To evaluate cardiovascular risk, *Pimentel et al.* [55] applied the well validated Framingham Risk Score (FRS) in a Brazilian population, and found that there was some indication that metabolically unhealthy obese patients were at increased cardiovascular risk as compared to MHO patients. However, this was specifically noted to hold true when ATP III criteria (alone or in conjunction with HOMA), but not with HOMA model alone [55]. This was in opposition to data gleaned from the London based Whitehall II cohort, which showed decreased when development of T2DM in MHO patients, but also demonstrated an increased risk of cardiovascular disease compared to their metabolically unhealthy counterparts [56]. To compare MHO patients to their non-obese counterparts, *Hamer et al.* [57] followed MHO patients over a 7-year time period. They found that in this case, MHO patients were not at comparatively increased cardiovascular risk [57]. Most recently, and potentially most comprehensively-another prospective study, the Nord-Trøndelag Health Study (HUNT) specifically evaluated risk of acute myocardial infarctions (AMIs), as well as heart failure (HF). After initial metabolic and anthropometric measurements, patients were followed for an average of 12.2 years, with AMIs and HF being identified by hospitalization data. Using this data, *Morkedal et al.* [58] found that these patients were not at significantly increased risk of AMI compared to their normal weight counterparts, but heart failure was increased in obese patients regardless of metabolic status. Another study found that MHO were at less risk of angiographic coronary artery disease as compared to metabolically unhealthy obese and even MUHNW [8]. To comprehensively assess both clinical and subclinical cardiovascular disease, *Stefan et al.* [59] performed a systematic review of the literature, which further emphasized variable evidence in this area. Of note, on analysis of MHO patients, they were found to have significant increase in subclinical markers, such as carotid intimal thickness. More recently, *Kim et al.* found that lipid and LDL particle subfraction profiles were significantly different between MHO and non-MHO in a Korean population. Specifically, small dense LDL particles were associated with increased metabolic abnormalities in obese adults [7]. The prospective Framingham Heart Study suggested lower risk of obesity-related cancers in MHO patients with normal glucose levels as compared to those with elevated glucose levels [60].

Limited studies have looked at longer-term outcomes in MUHNW patients. One study observed higher waist circumference, higher HbA1c, triglyceride, and CRP levels, and lower HDL and adiponectin in individuals who were MUHNW [61]. Some studies have found less cardiovascular disease risk in MUHNW than MHO [57, 62–64], while others have not [65, 66]. In an elderly Korean population over an average of 10 years, MUHNW patients had significantly higher all cause and cardiovascular mortality than MHO patients [67]. These patients have also been found to have increased markers of atherosclerosis [68]. Another study has shown that MUHNW participants have worse cardiovascular outcomes than MHO including higher levels of fatty liver and of subclinical systolic and diastolic dysfunction, suggesting that these outcomes are not dependent on BMI but rather on overall metabolic health [62]. MUHNW women have been shown to have increased risk for cardiovascular

disease with higher blood pressure, triglycerides and glucose as well as lower adiponectin, HDL, and LDL size than MHO women [6]. MONW has also been shown to be associated with angiographic coronary artery disease after controlling for potential confounders [8]. There are several mechanisms through which this may be occurring. Fatty liver has been associated with increased fat in the pericardium [69–71] which in turn leads to lipotoxicity and apoptosis of cardiac myocytes [72]. MUHNW individuals also show higher levels of inflammatory markers which is associated with cardiovascular disease risk [73, 74]. Future studies will be needed to explore this more fully.

Conversion of MHO to metabolically unhealthy obesity

There remains suggestion that despite "healthy" metabolic profiles, these patients may still be at increased risk for adverse long term outcomes, though data behind this does not account for confounding factors on smoking, physical activity, age and sex [11]. Further confounding considerations include the possibility that as many as 30% of these patients may convert to a MAO/MUHO phenotype, with resultant increase cardiovascular risk [48]. Additionally, while MHO patients have been shown to have better vascular reactivity than patients with metabolic syndrome, they have poorer reactivity compared to metabolically healthy people of normal weight [75], further suggesting deficits that may evolve over time. This too, has been conflicting in its evidence, with an underlying question being whether MHO presentations simply represent an early snapshot in the timeline of metabolic health. One group found that nearly 50% of MHO patients transitioned to metabolically unhealthy phenotypes when followed longitudinally for 10 years [76]. A theory then could be that MHO would eventually transition to being metabolically unhealthy given enough time, but large, longitudinal studies would be required to determine this possibility. By studying a large longitudinal sample of individuals who are MHO at baseline and monitoring the development of diabetes, cardiovascular disease, hypertension, and fatty liver disease over a long period of time, it would be possible to determine whether there are indications that individuals who are MHO would develop the typical metabolic complications of obesity.

Treatments and Interventions

With contradicting evidence surrounding the factors leading to, and longitudinal risks of, MHO, there remains limited data surrounding appropriate long-term management and interventions for patients with MHO. On review, a handful of trials have been conducted in these patients, with the majority focusing on exercise/lifestyle changes as the intervention modality. In 2009, *Arsenault et al.*[77] examined metabolically healthy overweight or obese postmenopausal women with elevated blood pressures. This cohort underwent a six month intensive exercise program, after which there was no significant change noted in metabolic profile [77]. *Janiszewski* [78] expanded weight loss interventions to also evaluate diet along with exercise interventions in MHO men and women, as well as MAO patients. While all patients had improvements in anthropometric measurements, only insulin sensitivity/fasting insulin were noted as cardiometabolic improvements in MHO patients [78]. A similar study did not show this improvement in insulin sensitivity, though did find it in metabolically unhealthy individuals [79]. Recently, a 12-week energy restricted diet intervention demonstrated significant improvements in insulin, as well as hepatic enzyme, fatty liver and

leptin measurements [80]. Thus, these studies suggest that exercise and lifestyle modifications might be therapeutic for MHO individuals in terms of long-term insulin sensitivity, but as there are conflicting results, future, larger studies will need to determine if this is indeed the case.

Specialized treatments specific for the MUHNW phenotype do not exist, but they are instead treated as metabolically unhealthy obese patients with lifestyle modification and exercise in addition to the appropriate therapeutics for their metabolic abnormalities. Indeed, there are a number of pharmaceutical therapies effective for the comorbidities typically associated with obesity, such as diabetes, hypertension, and cardiovascular disease, which may be effective in treating the metabolic dysfunction associated with MUHNW [81–85]. There are also dietary and exercise therapies generally recommended for obesity which may benefit this phenotype as well [86–91]. Indeed, even small changes in weight and/or waist circumference seem to benefit biomarkers for cardiometabolic risk [92]. Upon more complete definitions of the MUHNW phenotype, targeted therapies may be warranted.

Future directions

Altogether, there is clear evidence towards the existence of MHO and MUHNW individuals with distinct phenotypes and metabolic outcomes. Clear definitions are needed in order to classify these individuals across research and clinical studies. Additionally, time relationships should be studied in terms of the possibility that MHO may all eventually develop metabolic dysfunctions typically associated with obesity. Regardless, it appears that MHO individuals cross-sectionally and over brief periods of time are at less risk of metabolic dysfunction, including diabetes, cardiovascular disease, and obesity-related cancers; while individuals who are MUHNW display increased risks for these conditions despite a normal weight. After these conditions are well-defined, targeted therapies should be developed to target these unique metabolic disorders.

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Abbreviations

BMI	Body Mass Index
T2DM	type 2 Diabetes Mellitus
MHO	Metabolically healthy but obese
MUHNW	Metabolically unhealthy normal weight
MUHO	Metabolically Unhealthy Obese
MAO	Metabolically Abnormal Obese
LDL	Low density lipoprotein
HDL	High densisty lipoprotein

TC	Total cholesterol
TG	Triglycerides
FPG	Fasting plasma glucose
HbA1c	Hemoglobin A1c
TyG	Triglycerides
MONW	Metabolically obese but normal weight
POMC	Pro-opiomelanocortin
MCR4	Melanocortin receptor 4
RNA	Ribonucleic acid
SPP1	Osteopontin
NDRG4	N-myc downstream-regulated gene family member 4
GINS3	GINS complex subunit 3
SFRP1	secreted frizzled-related protein 1
Wnt	Wingless-type mammary tumor virus integration site
TRAIL	TNF-related apoptosis-inducing ligand
TWEAK	TNF-related weak inducer of apoptosis
BCL2	B-cell lymphoma-2
CASP3/7	Caspase 3/7
VEGF	Vascular Endothelial Growth Factor
HOMA-IR	Homeostatic model assessment for insulin resistance
PPARγ	peroxisome proliferator-activated receptor alpha
DGAT1	Diacylglycerol-O-Acyltransferase
AQP7	Aquaporin 7
GK	glycerol kinase
ATGL	Adipose triglyceride lipase
HSL	Hormone sensitive lipase
ACC1	Acetyl-CoA carboxylase 1
PEPCK	Phosphenolpyruvate carboxykinase
ACSS2	Acyl-CoA synthetase short chain family member 2
FABP4	Fatty acid binding protein 4
TBP2	Thioredoxin-binding protein-2
HcB19	HcB19/Dem mouse strain

Brd2	Bromodomain-containing protein 2
RT1-Ba, Bb	Rat1 locuse Ba/Bb
Db1	didemnin-B 1

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