Genetic Analysis of Low BMI Phenotype in the Utah Population Database

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Abstract

The low body mass index (BMI) phenotype of less than 18.5 has been linked to medical and psychological morbidity as well as increased mortality risk. Although genetic factors have been shown to influence BMI across the entire BMI, the contribution of genetic factors to the low BMI phenotype is unclear. We hypothesized genetic factors would contribute to risk of a low BMI phenotype. To test this hypothesis, we conducted a genealogy data analysis using height and weight measurements from driver’s license data from the Utah Population Data Base. The Genealogical Index of Familiality (GIF) test and relative risk in relatives were used to examine evidence for excess relatedness among individuals with the low BMI phenotype. The overall GIF test for excess relatedness in the low BMI phenotype showed a significant excess over expected (GIF 4.47 for all cases versus 4.10 for controls, overall empirical p-value < 0.001). The significant excess relatedness was still observed when close relationships were ignored, supporting a specific genetic contribution rather than only a family environmental effect. This study supports a specific genetic contribution in the risk for the low BMI phenotype. Better understanding of the genetic contribution to low BMI holds promise for weight regulation and potentially for novel strategies in the treatment of leanness and obesity.

Introduction

Genetic factors increase the risk for a high body mass index (BMI), overweight and obesity [1]. The role of genetic factors in low BMI is less well understood.

Family studies have found family clustering for low BMI [2–4]. However, family studies cannot distinguish between genetic and familial factors. Twin studies have estimated the heritability of BMI across the entire BMI range at between 50 and 74% [5–6].

Molecular genetic studies have identified a series of candidate genes for low BMI including a thyrotropin-releasing hormone (TRH) receptor polymorphism [7], the Ser23 allele of the genes for low BMI including a thyrotropin-releasing hormone receptor, and one copy number variant identified as gcn1l1 [10]. Allelic variants of the FTO gene linked to obesity risk are frequently found in thin individuals [11].

Understanding the genetic and environmental contributions to low BMI are important because low BMI has been linked to medical and psychiatric illnesses as well as increased mortality. In females, low BMI during childhood and adolescence increases women’s risk for later endometriosis [12], preterm birth [13], low infant birth weight [14] and increased risk for placental abruption [15]. Infants born to mothers with low BMI have an increased risk for atrial septal defect, genital abnormalities including hypospadias [16].

The psychiatric illness anorexia nervosa is defined by a low BMI in association with extreme fear of becoming fat [17].

Mortality rates across BMI categories in many studies display a U-shaped curve with increased death rates for the low BMI as well as those with a high BMI. Mortality rates are higher by an estimated 73% in those with BMI below 18.5 [18]. A Japanese study estimated the mortality risk increased by 78% in those with a BMI<18.5 and increased by 155% in those with a BMI<16 [19]. The exact mechanism for the mortality increase in low BMI populations is unclear. Some of the increase may be due to higher rates of death in severe illness and surgical procedures such as lung transplantation [20].

A study of excess deaths related to being low BMI and high BMI in the United States provides a reference for the relative contribution of low BMI to mortality [21]. High BMI was estimated to contribute to 111,909 deaths in the U.S. in 2000 while low BMI was estimated to be associated with 33,746 deaths. Thus, low BMI is estimated to contribute about three deaths for every ten deaths related to being high BMI.

To further understand the prevalence and genetic contributions of leanness, we examined the low BMI phenotype in the Utah Population Data Base (UPDB). The UPDB provides a strategy to...
examine the possibility of both environmental and genetic contributions to a phenotype by estimating risk in both close and distant relatives and by testing for excess familial clustering. An observation of excess close relationships alone would not have allowed discrimination between shared genes and shared environment, but the UPDB allows us to consider more distant relationships that are unlikely to represent lifestyle sharing beyond what is expected in the Utah population. We hypothesized that low BMI individuals would demonstrate near and distant familial clustering consistent with a genetic contribution.

Methods

Ethics Approval

The protocol for this study was approved by the University of Utah Institutional Review Board and the Resource for Genetic and Epidemiologic Research. The Resource for Genetic and Epidemiologic Research is the oversight board for the Utah Population Data Base. All data used in this research study contains no individual identifiers. A waiver of consent was approved for this study due to the lack of individual identifiers for all subjects. Consent requirements were waived for this study since obtaining consent would have unnecessarily identified individuals in the anonymous database. Review of this protocol by the University of Utah Institutional Review Board and the Resource for Genetic and Epidemiologic Research includes a review and approval of consent issues and other ethical aspects of the research.

Utah Population Data Base (UPDB)

The UPDB is a unique computerized database primarily representing the pioneer founders of Utah and their modern day descendants. It includes up to 15 of genealogy data dating back to the original Utah founding pioneers [22], as well as current generations. The genealogy data has been linked to statewide data including driving license (DL) data, births, deaths, the Utah Cancer Registry, and Utah Hospital Discharge Data, among other data sets (www.huntsmancancer.org/groups/ppr). The DL data includes height and weight and is available for over three million Utah drivers.

For the genetic analyses performed here we selected only from those 1,192,768 individuals in the UPDB who have genealogy data for both parents, all four grandparents, and six of their eight great grandparents and whose genealogy connects to the original Utah genealogy, and the 593,704 of these individuals who have Utah Drivers License data. These strict criteria allow for appropriate matching of cases and controls in terms of quality and quantity of genealogical data.

The oversight board for the UPDB encourages collaboration with outside investigators and institutions. Researchers with interest in using the UPDB to test hypotheses may contact the board or one of the authors for information about methods to apply for access.

The UPDB has been successfully used to define familial clustering and genetic influences in a variety of disorders including cancer [23–27], coronary artery disease [20], diabetes [29] rotator cuff disease [30], and deaths due to influenza [31] and asthma [32]. The methods used to identify phenotypes, assess familial and genetic effects and identify pedigrees using UPDB data have been described in detail in these studies. The study of high-risk pedigrees identified in the UPDB has led to multiple gene identifications, including BRCA1 [33], BRCA2 [34], CDKN2A (melanoma) [35–36] and HPC2/ELAC2 [37].

Low BMI phenotype

The phenotype of adult leanness was established using Utah DL data available for 593,704 individuals (with acceptable genealogy data as described) included in the UPDB. We identified all male and female drivers whose most recent calculated BMI (from height and weight provided) was <18.5. Rates for the low BMI phenotype were calculated by age group and are shown in Table 1, which includes the age group, the number of lean individuals in the age group, the total number of individuals with DL data in the age group, the leanness prevalence and the 95% confidence interval for prevalence by age group, estimated by the method of Clopper and Pearson [38].

Statistical Analysis

The Genealogical Index of Familiality (GIF) statistic was used to test the hypothesis of excess relatedness among individuals in the low BMI phenotype. The GIF was developed specifically for the UPDB [39–40]. Briefly, the GIF measures the average pair-wise relatedness of a set of individuals and compares that measurement to the average pair-wise relatedness expected in the Utah population. The GIF test differs from relative risk (RR) in that it includes analysis of all genetic relationships, both close and distant. The GIF utilizes the Malecot coefficient of kinship to measure pair-wise relatedness. The coefficient is defined as the probability that randomly selected homologous genes from two individuals are identical by descent from a common ancestor [41]. The coefficient is 0.50 for parent/offspring, 0.25 for a sibling pair, 0.125 for an uncle/nephew pair, 0.0625 for a first cousin pair, and so forth. The contribution to the GIF statistic is therefore smaller for individual pairs with greater genetic distance between them; more closely related pairs contribute more.

To evaluate the significance of the GIF test, we estimated the average pair-wise relatedness for 1,000 sets of controls matched to the cases by birth year, sex, and birthplace (Utah or not). These controls are chosen from among the 593,704 individuals with acceptable quality genealogy data who also have DL data. The empirical significance of the GIF test is measured by comparing the case GIF to the distribution of 1,000 control GIF values.

The GIF statistic measures familial clustering, which can be due to genetic (genes related to low BMI phenotype), or to shared environmental factors.

Table 1. Prevalence Rates for Low BMI (<18.5) in the UPDB.

| Age     | BMI<18.5 | N   | Prevalence (%) | 95% CI   |
|---------|----------|-----|----------------|----------|
| 15–19   | 6,259    | 57,010 | 11.0           | 10.7, 11.2 |
| 20–24   | 2,847    | 62,070 | 4.6            | 4.4, 4.8  |
| 25–29   | 1,629    | 63,548 | 2.5            | 2.4, 2.7  |
| 30–34   | 922      | 49,069 | 1.9            | 1.8, 2.0  |
| 35–39   | 544      | 39,353 | 1.4            | 1.3, 1.5  |
| 40–44   | 400      | 36,097 | 1.1            | 1.0, 1.2  |
| 45–49   | 311      | 40,719 | 0.8            | 0.7, 0.9  |
| 50–54   | 258      | 42,998 | 0.6            | 0.5, 0.7  |
| 55–59   | 176      | 38,040 | 0.4            | 0.3, 0.5  |
| 60–64   | 135      | 26,947 | 0.5            | 0.4, 0.6  |
| 65–69   | 191      | 27,076 | 0.7            | 0.6, 0.8  |
| 70–74   | 255      | 26,207 | 1.0            | 0.9, 1.1  |
| 75–79   | 354      | 25,122 | 1.4            | 1.3, 1.6  |
| 80 or older | 569    | 26,979 | 2.1            | 1.9, 2.3  |

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familial environmental effects (i.e. familial preference for low calorie diet or rigorous physical exercise), or to a combination of both. In order to better distinguish these effects, we recalculate the case GIF and the control GIF’s while ignoring close relationships (first and second degree). If this distant GIF (dGIF) test is significant, it provides strong evidence that there is significant distant excess relatedness that is unlikely to be due to shared environment.

The calculation of RR in relatives provides the more traditional mechanism for identifying genetic effects. A genetic contribution to a phenotype is supported when both close and distant relatives have elevated risk. RRs for the low BMI phenotype were estimated for first-, second- and third degree relatives of low BMI individuals as follows. First-degree relatives include parents, siblings and offspring; second-degree relatives are the first-degree relatives of the first-degree relatives (e.g. uncle, grandmother); third-degree relatives are the first-degree relatives of the second-degree relatives (e.g. first cousin, great grandchild). All 593,704 individuals in the UPDB with acceptable quality and quantity genealogy data are summarized by age and birthplace cohort-specific rates for low BMI among all UPDB individuals per cohort by the total number of individuals with DL data per cohort. Expected numbers of low BMI first-degree relatives were estimated by counting the number of first-degree relatives with DL data and genealogy data by cohort (without duplication), multiplying by the rate of low BMI in each cohort, and summing over all cohorts. Observed numbers of low BMI individuals (BMI<18.5) among relatives were counted without duplication. RRs were estimated for each degree of relationship as observed/expected number of low BMI cases and controls while ignoring close relatives (genetic distance <4). Although the pairwise relatedness distributions for cases and matched controls cross at some points, as seen in Figure 1, the pairwise relatedness distributions for cases and controls, by pairwise genetic distance where genetic distance 1 = parent/offspring, 2 = siblings, 3 = avunculars, 4 = first cousins, and so forth for the low BMI individuals aged 25–64 years. As seen, the distribution of relatedness for cases is in excess up to genetic distance = 4 (e.g. first cousins) and beyond genetic distance = 9 (e.g. second-cousins once-removed). Although the pairwise relatedness distributions for cases and matched controls cross at some points, as seen in Figure 1, the pairwise relatedness for cases is significantly elevated over that for matched controls when all genetic distances are considered as determined by distant GIF test (dGIF p=0.031).

### Relative Risks (RRs)

Estimates of relative risks in relatives of lean adults are shown in Table 3. The table shows the total number of each type of relative with BMI data (# relatives), the observed number of those relatives with BMI<18.5 (obs), and the expected number of relatives with BMI<18.5 (expected) based on birth year, sex, and birthplace cohort-specific rates for low BMI among all UPDB individuals per cohort by the total number of individuals with DL data per cohort. Expected numbers of low BMI first-degree relatives were estimated by counting the number of first-degree relatives with DL data and genealogy data by cohort (without duplication), multiplying by the rate of low BMI in each cohort, and summing over all cohorts. Observed numbers of low BMI individuals (BMI<18.5) among relatives were counted without duplication. RRs were estimated for each degree of relationship as observed/expected number of low BMI cases and controls while ignoring close relatives (genetic distance <4). Although the pairwise relatedness distributions for cases and matched controls cross at some points, as seen in Figure 1, the pairwise relatedness distributions for cases and controls, by pairwise genetic distance where genetic distance 1 = parent/offspring, 2 = siblings, 3 = avunculars, 4 = first cousins, and so forth for the low BMI individuals aged 25–64 years. As seen, the distribution of relatedness for cases is in excess up to genetic distance = 4 (e.g. first cousins) and beyond genetic distance = 9 (e.g. second-cousins once-removed). Although the pairwise relatedness distributions for cases and matched controls cross at some points, as seen in Figure 1, the pairwise relatedness for cases is significantly elevated over that for matched controls when all genetic distances are considered as determined by distant GIF test (dGIF p=0.031).

### Results

#### Prevalence Rates and Proband Selection

The prevalence of BMI<18.5 in the UPDB individuals with acceptable quality and quantity genealogy data are summarized by age and birthplace cohort-specific rates for low BMI among all UPDB individuals per cohort by the total number of individuals with DL data per cohort. Expected numbers of low BMI first-degree relatives were estimated by counting the number of first-degree relatives with DL data and genealogy data by cohort (without duplication), multiplying by the rate of low BMI in each cohort, and summing over all cohorts. Observed numbers of low BMI individuals (BMI<18.5) among relatives were counted without duplication. RRs were estimated for each degree of relationship as observed/expected number of low BMI cases and controls while ignoring close relatives (genetic distance <4). Although the pairwise relatedness distributions for cases and matched controls cross at some points, as seen in Figure 1, the pairwise relatedness distributions for cases and controls, by pairwise genetic distance where genetic distance 1 = parent/offspring, 2 = siblings, 3 = avunculars, 4 = first cousins, and so forth for the low BMI individuals aged 25–64 years. As seen, the distribution of relatedness for cases is in excess up to genetic distance = 4 (e.g. first cousins) and beyond genetic distance = 9 (e.g. second-cousins once-removed). Although the pairwise relatedness distributions for cases and matched controls cross at some points, as seen in Figure 1, the pairwise relatedness for cases is significantly elevated over that for matched controls when all genetic distances are considered as determined by distant GIF test (dGIF p=0.031).

| Group       | N     | Case GIF | Control GIF | GIF p-value | dGIF p-value |
|-------------|-------|----------|-------------|-------------|--------------|
| All BMI<18.5| 14,867| 4.47     | 4.10        | <0.001      | 0.031        |
| BMI<18.5, ages 25–64 | 4,375 | 4.84     | 4.19        | <0.001      | <0.001        |

Table 2. GIF Test for Low BMI (<18.5) in the UPDB.
individuals with BMI data. RRs for adult leanness were significantly elevated among first-, second-, and third-degree relatives of lean adults. The smaller number of second degree lean adults observed is not unexpected, given that second degree relatives are primarily in different generations (avunculars, grandparent/child), while first and third-degree relatives occur in the same generation (siblings and cousins, respectively) as well as in different generations (parent/offspring). Since the DL data exist only after 1980, there is a very narrow window that limits observations across generations; however, our results support the GIF results, where the contribution from first- (genetic distance 1 and 2), second- (genetic distance = 3) and third-degree relatives (genetic dis-

**Figure 1. The contribution to the GIF statistic by genetic distance for 4,375 low BMI cases aged 25–64 years old compared to 1,000 sets of matched UPDB controls with BMI data.** Genetic distance between pairs is shown on the x-axis and represents an increasing measure of relatedness (1 = parent/offspring; 2 = siblings, e.g.; 3 = uncle/niece, e.g.; 4 = first cousins, e.g.) from close to distant; the most distant relationships noted (genetic distance = 16) could represent, for example, two individuals who have a common ancestor 8 generations past. The cumulative contribution to the GIF statistic for each relatedness (as measured by genetic distance) for all pairs identified at that genetic distance is represented on the y-axis. The contribution to the GIF statistic for each larger genetic distance is one-half as large; the contribution for genetic distance 2 = \( \frac{1}{4} \), and so forth. The distribution for controls represents the expected relatedness of a group of individuals just like the cases (ignoring BMI) and is smoother because it is averaged over 1,000 different sets of controls tested. The distribution for cases represents only the analysis of the single set of cases and is more irregular. The peak at genetic distance = 2 (e.g. siblings) in comparison with genetic distance = 1 (parent/offspring) is seen for both cases and controls and represents that we observe more sib pairs than parent/offspring pairs in our data. A similar peak for cases at genetic distance 4 also indicates that we observed more cousins (same generation) than avunculars, for example.

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**Table 3. Relative Risk of Low BMI (<18.5) in Relatives of All Lean Utah Adults.**

| Relatives    | N   | Observed | Expected | p-value | Relative Risk | 95% CI    |
|--------------|-----|----------|----------|---------|---------------|-----------|
| First-degree | 54,324 | 3,565 | 1,615.5 | <0.00001 | 2.21 | 2.13, 2.28 |
| Second-degree | 96,151 | 2,236 | 1,799.7 | 2.1 e-23 | 1.24 | 1.19, 1.30 |
| Third-degree | 175,286 | 5,204 | 4,546.0 | 7.7 e-22 | 1.14 | 1.11, 1.18 |
| Fourth-degree | 317,807 | 6,897 | 6,773.4 | 0.133 | 1.02 | .99, 1.04 |
| Fifth-degree | 501,420 | 12,417 | 12,271.5 | 0.191 | 1.01 | .99, 1.03 |
| Sixth-degree | 571,643 | 14,180 | 14,147.9 | 0.788 | 1.00 | .99, 1.02 |
| Seventh-degree | 588,223 | 14,796 | 14,772.6 | 0.849 | 1.00 | .99, 1.02 |

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Table 4. Relative Risk of Low BMI (<18.5) in Relatives of Lean Utah Adults Ages 25–65 Years.

| Relatives    | N     | Observed | Expected | p-value   | Relative Risk | 95% CI   |
|--------------|-------|----------|----------|-----------|---------------|----------|
| First-degree | 20,551| 1,177    | 1,468.0  | <0.00001  | 2.57          | 2.42, 2.72|
| Second-degree| 32,849| 1,056    | 775.4    | <0.00001  | 1.36          | 1.28, 1.45|
| Third-degree | 63,856| 1,668    | 1,363.8  | 7.0e-16   | 1.22          | 1.17, 1.28|
| Fourth-degree| 153,915| 3,597   | 3,427.9  | 0.0039    | 1.05          | 1.02, 1.08|
| Fifth-degree | 309,372| 6,899    | 6,774.1  | 0.130     | 1.02          | 0.99, 1.04|
| Sixth-degree | 474,053| 11,512   | 11,376.2 | 0.204     | 1.01          | 0.99, 1.03|
| Seventh-degree| 562,037| 12,984   | 13,955.3 | 0.809     | 1.00          | 0.99, 1.02|

Pedigree Identification

We identified all possible clusters of the 4,375 low BMI individuals between 25 and 65 years of age. These clusters merely represent all related sets of individuals with low BMI, they are not necessarily high-risk for BMI. We further evaluate each cluster by testing for an excess of low BMI among all the descendants of the founding pair of the cluster using the low BMI rates estimated from the UPDB. We identified over 4,000 clusters of low BMI relatives, ranging in size from 2 related cases (n = 789 clusters) to size 168 (n = 1 cluster).

We were able to identify thousands of individual pedigrees that may assist in future molecular genetic studies of the low BMI phenotype. As an example, we have identified 63 pedigrees with a significant excess of individuals with low BMI (p<0.0001) with at least 10 cases. An example of one of these pedigrees is shown in Figure 2. As can be observed, Utah driver’s license data is only available for the most recent two or three generations of the Utah genealogy; earlier generations remain unknown for the phenotype of interest.

Discussion

Familial clustering of the low BMI phenotype in the UPDB is consistent with both genetic as well as environmental contributions to low BMI humans. Increased relative risks for the low BMI phenotype in first-, second-, and third-degree relatives suggests that genetic factors contribute to the familial clustering pattern.

The GIF analysis confirms a genetic contribution to low BMI in relatives with an even more distant degree of relatedness. Excess relatedness among close relatives could represent either shared environment or shared genetics, or a combination. However, the finding of excess relatedness in distant relatives is much more likely to result from shared genes than shared environment.

Our study represents the largest genealogical population genetics study of low BMI to date. There are no comparable low BMI studies using a similar methodology. However, our identification of a genetic contribution to low BMI is consistent with findings in family studies [2–4] and in a single adoption study [43].

A primary limitation of this study is the reliability and validity of Department of Motor Vehicle height and weight self-reported measures. There is limited study of the accuracy of self-reported height and weight in DL data. Self-reported weights in overweight and obese individuals might be significantly underestimated due to the social stigma of obesity. In contrast, social stigma issues in reporting an accurate weight in the low BMI may be less than in obesity. Nevertheless, it remains possible that there is some social pressure to overestimate weight among the low BMI.

Utah driver’s license BMI data from the Utah Population Data Base has been compared to BMI data obtained by the CDC Behavioral Risk Factor Surveillance System (BRFSS). This analysis found BMI means generally varied in males by only three percent between the databases with no bias toward over or underestimation across age categories. In younger female age groups (between 25 and 34 years), BMI means from Utah driver’s license data was 5 to 8% lower than means from the BRFSS [44].

Figure 2. Example UPDB pedigree with a statistical excess of low BMI (<18.5) individuals. Individuals with bmi <18.5 are fully shaded and BMI is shown beneath subjects where available.

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We compared rates of low BMI in the UPDB to the National Health and Nutrition Examination Survey (NHANES) to look for evidence of a self-report bias. [45–46]. The NHANES includes data from direct measurement of weight and height in a representative sample of individuals in the United States. The overall NHANES estimated prevalence of low BMI (BMI<18.5) is 13% in the U.S. adult population.

Prevalence rate estimates of low BMI in the UPDB generally are in close agreement with estimates from the NHANES. Rate estimates for BMI<18.5 by age group for the UPDB and (NHANES) were: 20 to 39 years of age, 3.3% (2.6%), 40 to 59 years of age, 9.9% (12.2%), 60 to 74 years of age, 9.0% (9.3%), 75 years of age and older, 2.0% (1.7%). This agreement supports the validity of the low BMI phenotype in the UPDB. Nevertheless, there is no easy method to directly measure the reliability and validity of the drivers license self-reported weight and height in the UPDB.

Some degree of inaccurate self-report of weight may be present and contribute to variance in our relative risk estimates. However, weight self-report bias would likely lead to underestimation of the estimates for BMI. The UPDB cohorts cross several generations. Environmental dietary and physical exercise patterns likely change across generations and may have influenced a portion of BMI data.

Despite these potential limitations, this study finds excess clustering of the low BMI phenotype among both close and distant relatives supporting a significant genetic contribution. Environmental factors are also likely to contribute to familial clustering of low BMI. Families often share diet, exercise and other lifestyle patterns that contribute to body weight.

Pedigrees in the UPDB with a significant excess of low BMI individuals among the descendants of founder couples have been identified. These pedigrees could prove valuable for additional molecular genetic studies of low BMI. Figure 2 shows an example pedigree with a significant excess of individuals with low BMI. The pedigree founder has 257 descendants with BMI data. Eighteen of these individuals have a BMI<18.5. This is significantly greater than 5.3, the number expected in the pedigree (p = 1.13 e-5).

Further studies to confirm our results and to explore the molecular genetics of the low BMI phenotype are needed. Such studies may uncover the mechanisms for increased morbidity and mortality in low BMI populations. Additionally, further understanding of the genetic and environmental contributions to low BMI may provide insight for prevention and treatment of both low BMI as well as obesity.

Author Contributions

Conceived and designed the experiments: WRY CJ PM LACA. Performed the experiments: LACA. Analyzed the data: LACA. Contributed reagents/materials/analysis tools: LACA. Wrote the paper: WRY.

References

1. Day FR, Loos RJ. (2011) Developments in obesity genetics in the era of genome-wide association studies, J Nutrigenet Nutrigenomics 24:222–38.
2. Laskarzewski PM, Klouy P, Morrison JA, Kelly, Melliess MJ, et al. (1983) Familial obesity and leanness. Int J Obes 1983; 7:505–27.
3. Magnusson PKE, Rasmussen F (2002) Familial resemblance of body mass index and familial risk of high and low body mass index. A study of young men in Sweden. Int J Obesity 26:1225–1231.
4. Borecki IB, Higgins M, Schreiner PJ, Arnett DK, Mayer-Davis E. (1998) Evidence for multiple determinants of the body mass index: The National Heart, Lung, and Blood Institute Family Heart Study. Obes Res 6:107–14.
5. Stunkard AJ, Harris JR, Pedersen NL, McClearn GE (1990) The body mass index of twins who have been reared apart. N Engl J Med 322:1483–7.
6. Dubois L, Ohm Kyvik K, Girard M, Taïone-Tokuda F, Perusse D (2012) Genetic and environmental contributions to weight, height, and BMI from 0 to 19 years of age: an international study of over 12,000 twin pairs. PLoS One 7(2):e30153.
7. Liu XG, Tan LJ, Lei SF, Liu YJ, Shen H, et al. (2009) Genome-wide association and replication studies identified TRIBR as an important gene for lean body mass. Ann Hum Genet 74:418–23.
8. Bahj, Westberg L, Bagnac H, Hemmingson S, Rosmond R, et al. (2010) Further exploration of the possible influence of polymorphisms in HTR2C and 5HTT on body weight. Metabolism 59:1156–63.
9. Jacquemont S, Reymond A, Zufferey F, Harewood L, Walters RG, et al. (2011) Mirror extreme phenotypes associated with gene dosage at the chromosome 14q12.3 region between D9S736 and D9S171. Genomics 23:265–8.
10. Hai R, Pei YF, Shen H, Zhang L, Liu XG, et al. (2012) Genome-wide association study of copy number variation identified grem1 as a candidate gene for lean body mass. J Hum Genet 57:33–7.
11. Hunt SC, Stone S, Xin Y, Scherer CA, Magness CL, et al. (2000) Association of the FTO gene with BMI. Obesity (Silver Spring) 16:902–4.
12. Vitone AF, Bard J, Hankinson SE, Lauffer MR, Mismari SA (2010) A prospective study of body size during childhood and early adulthood and the incidence of endometriosis. Hum Reprod 5:1325–34.
13. Khaskan AS, Kenny LG (2009) The effects of maternal body mass index on pregnancy outcome. Eur J Epidemiol 24:907–703.
14. Kalk P, Gauthmann F, Krause K, Keller C, Godes, et al. (2009) Impact of maternal body mass index on neonatal outcome. Eur J Med Res 14:216–22.
15. Deutsch AB, Lynch O, Alo AP, Sallou HM, Spellacy WN (2010) Increased risk of placental abruption in low BMI women. Am J Perinatol 27:235–40.
16. Sallou HM, Lynch O, Alo AP, Mbaah AK, Kornovsky JL, et al. (2009) Extreme maternal low BMI and feto-infant morbidity outcomes: a population-based study. J Matern Fetal Neonatal Med 22:426–34.
17. American Psychiatric Association. (2000) Diagnostic and Statistical Manual of Mental Disorders, 6th ed, text rev. Washington, DC: American Psychiatric Association.
18. Ohpama HM, Berthelot JM, Kaplan MS, Feeny DH, McFarland B, et al. (2010) BMI and mortality: results from a national longitudinal study of Canadian adults. Obesity (Silver Spring). 18:214–8.
19. Tamakoshi A, Yatsuha Y, Lin Y, Tamakoshi K, Kondo T, et al. (2010) JACC Study Group. BMI and all-cause mortality among Japanese older adults: findings from the Japan collaborative cohort study. Obesity (Silver Spring). 18:362–9.
20. Lederer DJ, Wilt JS, D’Orlando F, Barcetta MD, Shafl L, et al. (2009) Obesity and low BMI are associated with an increased risk of death after lung transplantation. Am J Respir Crit Care Med 180:807–13.
21. Hleg HL, Grabau BL, Williamson DF, Gall MH (2005) Excess deaths associated with low BMI, overweight, and obesity. JAMA 293:1061–7.
22. Skodnick M (1980) The Utah genealogical database: a resource for genetic epidemiology. In: Cairns J, Lyon JL, Skolnick M, editors. Cancer incidence in defined populations. Cold Spring Harbor, NY: Cold Spring Harbor Laboratories pp 285–97.
23. Cannon LA, Bishop DT, Skodnick MH (1986) Segregation and linkage analysis of breast cancer in the Dutch and Utah families. Genet Epidemiol Suppl 1:45–8.
24. Cannon-Albright LA, Goldgar DE, Neuhauizen S, Grun NA, Anderson DE, et al. (1994) Localization of the 9p melanoma susceptibility locus (MLM) to a 2-cM region between D9S736 and D9S171. Genomics 23:263–5.
25. Shrirs BH, Burt RW, Matilbh SJ, Cannon-Albright LA (2010) A population-based description of familial clustering of pancreatic cancer. Clin Gastroenterol Hepatol 8:812–6.
26. Mauj JS, Burt RW, Cannon-Albright LA (2007) A familial component to human rectal cancer, independent of colon cancer risk. Clin Gastroenterol Hepatol 5:16–4.
27. Teerlink C, Farnham J, Allen-Brady K, Camp NJ, Thomas A, et al. (2012) A unique genome-wide association analysis in extended Utah high-risk pedigrees identifies a novel melanoma risk variant on chromosome arm 10q. Hum Genet 131:77–85.
28. Horne BD, Camp NJ, Muhlestein JB, Cannon-Albright LA (2010) Familiality of diabetes mellitus. Exp Clin Endocrinol Diabetes 115:634–45.
29. Tashjian RZ, Farnham JM, Albright FS, Teerlink CC, Cannon-Albright LA (2009) Evidence for an inherited predisposition contributing to the risk for rotator cuff disease. J Bone Joint Surg Am 91:1136–42.
31. Albright FS, Orlando P, Pavia AT, Jackson GG, Cannon Albright LA (2008) Evidence for a heritable predisposition to death due to influenza. J Infect Dis 197:18–24.
32. Teerlink CC, Hegewald MJ, Cannon-Albright LA (2007) A genealogical assessment of heritable predisposition to asthma mortality. Am J Respir Crit Care Med 176:865–70.
33. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, et al. (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66–71.
34. Tavtigian SV, Simard J, Rommens J, Couch F, Shattuck-Eidens D, et al. (1996) The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. Nat Genet 12:333–7.
35. Cannon-Albright LA, Goldgar DE, Meyer LJ, Lewis CM, Anderson DE, et al. (1992) Assignment of a locus for familial melanoma, MLM, to chromosome 9p13–p22. Science 256:1148–52.
36. Kamb A, Shattuck-Eidens D, Edes R, Liu Q, Grus NA, et al. (1994) Analysis of the p16 gene (CDKN2) as a candidate for the chromosome 9p melanoma susceptibility locus. Nat Genet 8:23–6.
37. Vesprini D, Nam RK, Trachtenberg J, Jewett MA, Tavtigian SV, et al. (2001) HPC2 variants and screen-detected prostate cancer. Am J Hum Genet 68:912–7.
38. Clopper CJ, Pearson ES (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26:404–413.
39. Hill JR (1980) A survey of cancer sites by kinship in the Utah Mormon population. In: Cairns J, Lyon JL, Skolnick M, editors. Cancer incidence in defined populations. Cold Spring Harbor, NY: Cold Spring Harbor Laboratories pp 299–318.
40. Cannon-Albright LA (2008) Utah family-based analysis: past, present and future. Hum Hered 65:209–20.
41. Malecot G (1948) Les mathematiques de l'heredite. Paris: Masson & Cie.
42. Agresti A (1990) Categorical Data Analysis. New York: Wiley.
43. Costanzo PR, Schifman SS (1989) Thinness—not obesity—has a genetic component. Neurosci Biobehav Rev 13:53–58.
44. Centers for Disease Control and Prevention (CDC) (2008) Behavioral Risk Factor Surveillance System Survey Data. Atlanta, Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.
45. Centers for Disease Control and Prevention (CDC) (2011) National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Available: http://www.cdc.gov/nchs/nhanes/about_nhanes.htm
46. Center for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS). Health E-Stat. Prevalence of Low BMI Among Adults: United States, 2003–2006. Available: http://www.cdc.gov/nchs/data/hestat/low_BMI/low_BMI_adults.htm