+ MODEL

Genes & Diseases (2024) 11, 100995

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.keaipublishing.com/en/journals/genes-diseases

RAPID COMMUNICATION

Genetic association analysis-based networks and classification of human *UCP1* polymorphisms

Uncoupling protein 1 (UCP1, also known as thermogenin or SLC25A7) plays an important role in the uncoupling of oxidative phosphorylation and adaptive non-shivering thermogenesis (NST). The genomic location for *UCP1* is chromosome 4 q31.1:140,555,770–140,568,961 (GRCh38/hg38) and its size is 13,192 bases split into 6 exons. In dbSNP, 3650 short genetic variations of human *UCP1* are documented. In this study, *UCP1* serves as an example to construct polymorphism-trait networks and enable a functional classification.

A total of 26 *UCP1* polymorphisms were collected. It is believed that there is an association between *UCP1* polymorphisms and the risk of overweight, obesity, and type 2 diabetes mellitus (T2DM). Also, certain *UCP1* genotypes have been found to be associated with the risk of type 1 diabetes mellitus (T1DM)/T2DM complications including coronary heart disease (CHD), diabetic nephropathy (DN), and diabetic retinopathy (DR). −112A/C (rs10011540), −1766A/G (rs3811791), −3826A/G + *UCP2* exon 8 deletion/insertion (del/ins), g.IVS4-208T/G (rs1494808), rs2071415, rs6536991, rs1800592-involved genetic predisposition score (GPS), haplotype, and UCP1 level are related to overweight, obesity, and T2DM (Fig. S1). −3826A/G and *B3AR* (Trp64Arg) (at least three minor alleles), rs1800592, −112A/C (rs10011540), −412A/C (rs3811787), Ala64Thr (rs45539933, g.940G/A), and certain genotypes showed association with complications (CHD, DN, DR (T1DM/T2DM), microvascular late complication, obesity, overweight, proliferative DR). −3826A/G, anthropometry, and haplotype analysis are usually detected or done in genetic association studies and 8–14 nodes connect them (Fig. S1). Longevity, climate, and oxidative stress (glucotoxicity) belong to those nodes. Figure S1 shows the relationship of −3826A/G (rs1800592), rs12502572, and rs3113195 with brown adipose tissue (BAT) activity, NST, and thermogenesis. Notably, a higher rs1800592-involved GPS could provide a greater metabolic benefit of Roux-en-Y gastric bypass. Genetic variants in the regulatory region of certain gene(s) may decrease downstream transcription, and thus non-coding regulatory −3737C/A and −3826A/G are involved in UCP1 expression. Clinical biochemistry, carotid parameters, and genetic interaction were found to be associated with some polymorphisms.

Of 13 controversial polymorphisms, −3826A/G polymorphism mainly contributes to Figure S3. A meta-analysis study determined the association of obesity phenotype with −866G/A, ins/del, Ala55Val (*UCP2*, Europeans), −55C/T (*UCP3*, Asians), but not with −3826A/G. −3826A/G polymorphism is analyzed by a wealth of countries, including Australia, Belgian, Brazil, China, Czech Republic, Denmark, Finland, France, Germany, India, Iran, Japan, Korea, Malaysia, Netherland, Poland, Spain, Sweden, and the USA.[1,2] Therefore, inconsistent results could be caused by ethnic differences. Other potential factors include small samples, sample differences (*e.g.*, age, gender, and BAT distribution), environmental factors, experimental conditions, genetic interaction (*e.g.*, −3826A/G and Trp64Arg in *B3AR*), and specific analysis (*e.g.*, obesity-related haplotype analysis). A single report could also provide inconsistent data such as −3826A/G-related anthropometry (Fig. S3). Contradictory results from a single report are caused by conditional differences, including methodology [SNP (single nucleotide polymorphism) *vs.* genotype combination], seasonal effects (adult mainly sampled from winter to spring/outdoor temperature-dependent effect *vs.* adult sampled during the hot season), gender effects (females *vs.* males), treatment effects [doenjang (a Korean fermented soy paste) *vs.* placebo treatments], diet effects (mixed rice diet *vs.* white rice diet), anthropometric parameters (abdominal subcutaneous fat areas *vs.* thigh fat areas and visceral fat areas) and weight loss after bariatric

Peer review under responsibility of Chongqing Medical University.

https://doi.org/10.1016/j.gendis.2023.04.028

surgery *vs*. a family history of obesity and early weight gain during childhood and adolescence. Beside −3826A/G (−3826A/G, −3826A/G (rs1800592), −3826A/G (Bcl 1 site), −3826C/T (rs1800592) and rs1800592), other overweight-, obesity-, and T2DM-related controversial nodes are −1766A/G (rs3811791), Ala64Thr (rs45539933, g.940G/A), Met229Leu (rs2270565), rs12502572, rs6536991, and haplotype (analysis). In haplotype analysis, Korean females and Chinese adult subjects were genotyped and four-allele haplotype analysis was derived from different polymorphisms [−3954A/G, −1766A/G, Ala64Thr, Met229Leu *vs*. rs45539933, rs2270565, rs1494808, −3826A/G (rs1800592)].

Two papers from one laboratory studied carotid plaque in stroke-free subjects from the Northern Manhattan Study. Controversial source is from plaque presence *vs*. plaque number, men (C-carrier) *vs*. women (C-carrier), and stroke-free women *vs*. stroke-free subjects. Other sources for controversy include age, gender, geographical area [*e.g.*, China *vs*. Japan, India *vs*. Japan, South Indians (genotype, allele) *vs*. North Indians], stratification [*e.g.*, moderate-obese (BMI: 30−39.9 kg/m^2) patients *vs*. extreme obese (BMI $\geq$ 40 kg/m^2) patients], parameters in anthropometry or clinical biochemistry [*e.g.*, abdominal subcutaneous fat (ASF) areas (Korean females) *vs*. thigh fat areas, visceral fat areas (Korean females), HbA1c level (Japanese type 2 diabetes patients) *vs*. insulin resistance, hepatic lipid content (Japanese type 2 diabetes patients)], treatment (*e.g.*, high carbohydrate meal *vs*. high-fat meal), confounding conditions [*e.g.*, adult (Germany) *vs*. childhood or adolescence (Denmark)].

Non-association network and genetic interactions were described in the supplementary data. Based on (non-)association networks and relative traits, *UCP1* polymorphisms were divided into five classes: (I) activity and thermogenesis, (II) genetic interaction, (III) health status, (IV) measurement, and (V) treatment (Fig. 1). Association polymorphisms in class II (genetic interaction) and class V (treatment) are all shared with other classes. −3826A/G (rs1800592) is shared in 5 classes. Activity and thermogenesis-measurement and health status-treatment are connected by rs12502572 and a group of polymorphisms (−112A/C (rs10011540), −1766A/G (rs3811791), −412A/C (rs3811787), and Ala64Thr (rs45539933, g.940G/A)), respectively. rs1800592-involved GPS contributed to health status, measurement, and treatment. Haplotype analysis

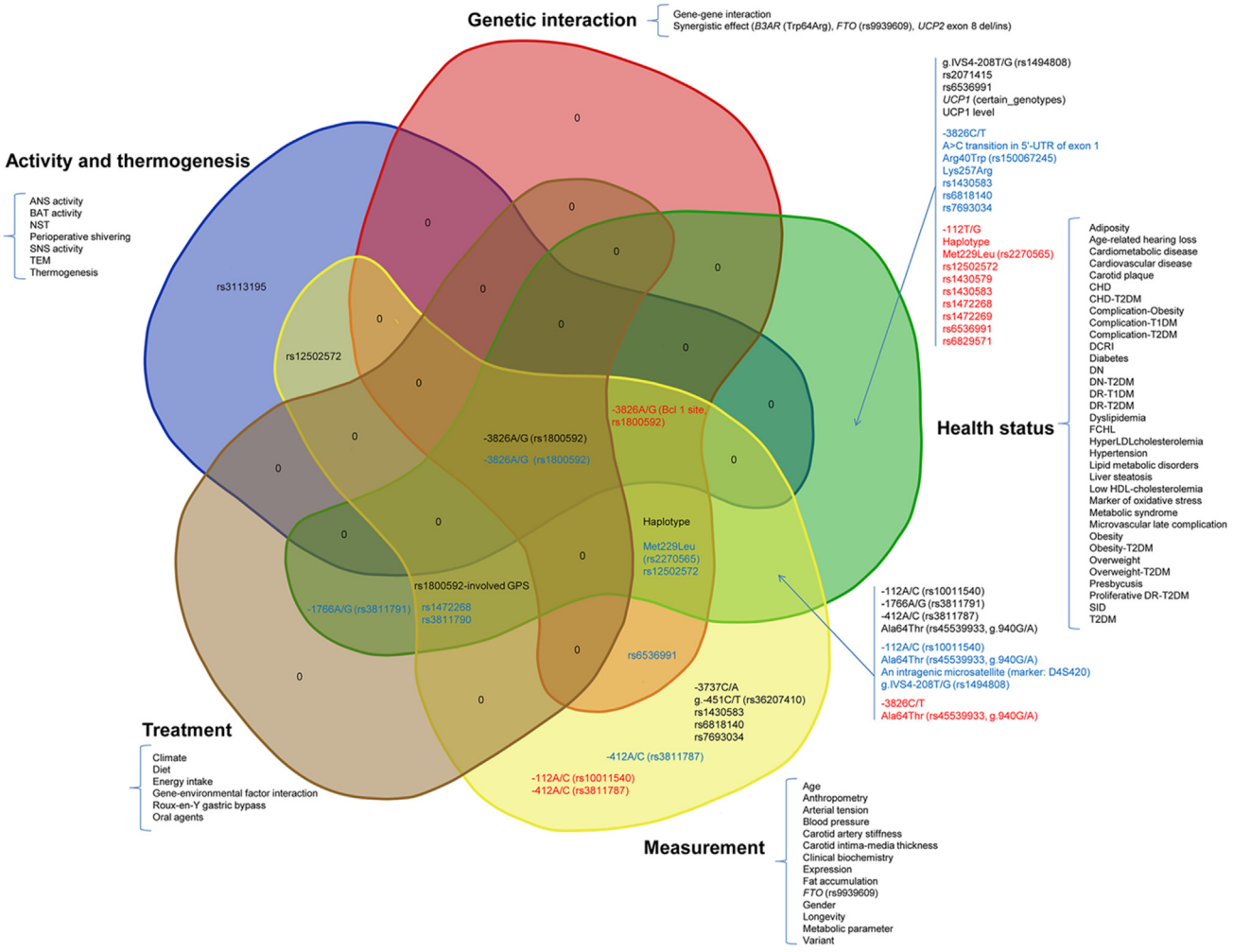

Figure 1 Venn diagram and classification of *UCP1* polymorphisms. Polymorphisms in black, cyan, and red are derived from association network, non-association network, and controversial (non-)association network, respectively.

suggested the relationship between genetic interaction, health status, and measurement. Specific polymorphisms are found in classes I, III, and IV. Of note, these classes and analyses are totally based on class IV (measurement). Theoretically, the results and conclusions are completely obtained from various measurements such as variant (genotype distribution, allele frequency), *UCP1* expression, anthropometry, and clinical biochemistry. However, the point was not emphasized further for polymorphism classification due to the complexity of genetic association analysis. Meanwhile, non-association and controversial (non-)association networks were further classified. Obviously, there is differential distribution found in association, non-association, and controversial (non-)association classifications, indicating that polymorphic classes are dependent on association analysis.

Genetic association studies are utilized to assess the association between polymorphisms and phenotypes on a population scale. Case-control study design is a common strategy. To solve a bias from population stratification, family-based association tests are designed. Six reports (Canada, Finland, France, Poland, and the USA) collected family-related subjects to study the genetic association of *UCP1* polymorphisms (−3826A/G, an intragenic microsatellite (marker: D4S420)). Two reports (Sweden and the USA) performed sibling- and twins-based studies. Contradictory results also exist due to the factors described above (Fig. S3). Environmental factors could influence human phenotypes, and gene−environment interaction and environmental treatment were also analyzed to identify polymorphisms in class V. Only −3826A/G (rs1800592) is shared in gene−gene interaction (genetic interaction) and gene−environment interaction (treatment), suggesting that −3826A/G (rs1800592) has functional complexity which may cause inconsistent conclusion (Fig. 1). Common errors of association studies have been summarized.[3]

In 2021, sex differences in BAT activity and cold-induced thermogenesis were investigated in a large cohort of males and females.[4] The results showed active BAT prevalence was non-significantly higher in pre-menopausal females than males, and that females had higher cold-induced thermogenesis, partially associated with estradiol. Human Obesity Gene Map has reported that *UCP1* has a positive association with obesity phenotypes. However, it is known that human adaptive thermogenic capacity is limited and small effects may be found. In most cases, obesity is a multifactorial phenotype related to polygene. T1DM and T2DM are also polygenic metabolic diseases. To identify and characterize *UCP1* polymorphisms, in-depth analysis is needed. This study is the first report on association analysis-based networks and functional classification of *UCP1* polymorphisms. The strategy would accelerate the annotation of functional polymorphisms and assist in genomics and genetics studies.

Conflict of interests

The author declares no conflict of interests.

Funding

This work was supported by the National Natural Science Foundation of China (No. 31470716, 31000323 and 31070672) and the Natural Science Foundation of Jiangsu Province, China (No. BK20131272).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2023.04.028.

References

1. Pravednikova AE, Shevchenko SY, Kerchev VV, et al. Association of uncoupling protein (Ucp) gene polymorphisms with cardiometabolic diseases. *Mol Med*. 2020;26(1):51.
2. Oppert JM, Vohl MC, Chagnon M, et al. DNA polymorphism in the uncoupling protein (*UCP*) gene and human body fat. *Int J Obes Relat Metab Disord*. 1994;18(8):526−531.
3. Cardon LR, Bell JI. Association study designs for complex diseases. *Nat Rev Genet*. 2001;2(2):91−99.
4. Herz CT, Kulterer OC, Prager M, et al. Sex differences in brown adipose tissue activity and cold-induced thermogenesis. *Mol Cell Endocrinol*. 2021;534, 111365.

Donghai Li *

State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University, Jiangsu 210023, China

*Corresponding author.
E-mail address: donghaili@nju.edu.cn

13 December 2022