彰化午餐秘書研習課程

肥胖基因在體重管理之飲食策略探討

Gene, obesity and dietary patterns.

功能醫學營養師 呂美寶

FB粉專：食物的力量．呂美寶營養師

2025.8.6

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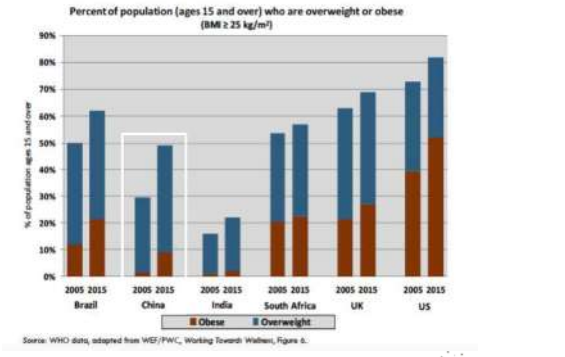
肥胖比率 10年大躍進



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體重跟基因遺傳有關?

3

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Intrapair resemblance in very low calorie diet-induced weight loss in female obese identical twins

V Hainer[1]*, AJ Stunkard[2], M Kunešová[1], J Parízková[1], V Štich[1] and DB Allison[3]

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OBJECTIVE: To assess intrapair resemblance in changes of body weight, total body fat, fat distribution, resting metabolic rate, fasting respiratory quotient and cardiovascular disease risk factors in response to therapeutic weight loss in female obese identical twins.

DESIGN: Patients stayed for 40 days on an inpatient metabolic unit under careful supervision. The stay was divided into three parts: an initial period of 7 days for adjustment to the hospital environment and for baseline measurements, 28 days of the weight reduction regimen when negative energy balance was achieved mainly by a very low calorie diet (1.6 MJ per day) and 5 days of testing after weight reduction.

SUBJECTS: Fourteen pairs of premenopausal female obese identical twins (age: 39.0 ± 1.7 y; body weight (BW): 93.9 ± 21.2 kg; body mass index (BMI): 34.2 ± 7.8 kg/m²) participated in the study.

MEASUREMENTS: Before and after weight loss, the following measurements were made: body composition by anthropometry and hydrodensitometry, intra-abdominal fat by ultrasonography, resting metabolic rate by indirect calorimetry. Total cholesterol, high-density lipoprotein-cholesterol, triglycerides and uric acid were determined by standard laboratory procedures. Blood pressure was measured in the morning in the recumbent position.

RESULTS: Subjects lost 8.8 ± 1.9 kg of weight, from 93.9 ± 21.2 to 85.1 ± 10.9 kg ($P < 0.0001$) and 6.5 ± 2.3 kg of body fat ($P < 0.001$). Weight losses varied widely among subjects, with a high correlation between losses of members of twin pairs for body weight ($r = 0.85$; $P < 0.001$) and for body fat ($r = 0.88$; $P < 0.0001$). Changes in uric acid resulting from weight loss were also correlated among members of twin pairs whereas changes in blood pressure, cholesterol and triglycerides were not.

CONCLUSION: The great intrapair resemblance observed in very low calorie diet-induced weight and fat losses in female obese identical twins suggests an important role of genetic factors in response to the weight reduction regimen.

International Journal of Obesity (2000) **24**, 1051–1057

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14對女性雙胞胎 接用極低熱量飲食減重 雙胞胎減重成效 具有高度相似性

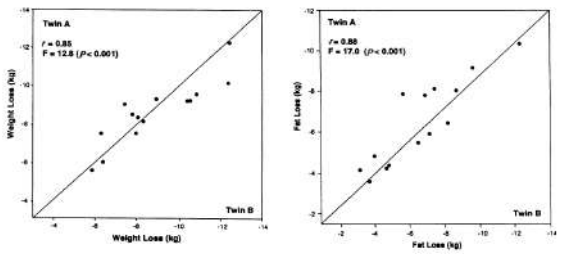

Figure 1 Similarity within pairs with respect to decrease in body weight in 14 pairs of obese female twins in response to 28 days of very low calorie diet (1.6 MJ). Each point represents one pair of twins (A and B).

Figure 2 Similarity within pairs with respect to decrease in body fat in 14 pairs of obese female twins in response to 28 days of very low calorie diet (1.6 MJ). Each point represents one pair of twins (A and B).

Intrapair resemblance in very low calorie diet-induced weight loss in female obese identical twins. *Int J Obes* **24**, 1051–1057 (2000).

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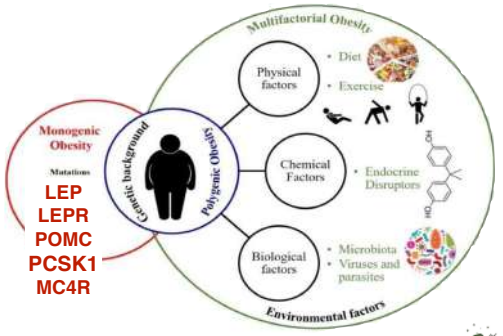
天生基因變異性
將影響每個人的減重成效

7

遺傳性單基因變異 基因影響頗大 < 多基因變異 環境是主要關鍵



Austin J Nutr Metab. 2017; 4(3): 1052.

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Original Article
PEDIATRIC OBESITY

Obesity

Genetic Variants in *LEP*, *LEPR*, and *MC4R* Explain 30% of Severe Obesity in Children from a Consanguineous Population

LEP, LEPR與MC4R基因變異 可解釋30%嚴重肥胖兒童的原因

Objective: Single gene mutations leading to severe obesity have so far been identified in 3-5% cases in European populations. However, prevalence of these pathogenic mutations has not systematically been examined in specific consanguineous populations. Here we describe the incidence of obesity-associated mutations through a step-wise sequence analysis, in a cohort of 73 Pakistani children with severe obesity from consanguineous families.

Methods: Initially, all subjects were screened for mutations in coding regions of leptin (*LEP*) and melanocortin 4 receptor (*MC4R*) genes by direct sequencing. Subjects negative for mutation in these genes were screened using microdroplet PCR enrichment and NGS. Genomic structural variation was assessed by genotyping. Serum leptin, insulin, and cortisol were determined by ELISA.

Results: Among 73 children with severe obesity (BMI SDS > 3.0), we identified 22 probands and 5 relatives, carrying 10 different loss-of-function homozygous mutations in *LEP*, leptin receptor (*LEPR*), and *MC4R* genes, including 4 novel variants. Hypercortisolemia was significantly emphasized in *LEP* mutation carriers.

Conclusions: The prevalence of pathogenic mutations in genes known to directly influence leptin-melanocortin signaling is 30% in our cohort. The results of this study emphasize the desirability of undertaking systematic and in-depth genetic analysis of cases with severe obesity in specific consanguineous populations.

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Chiang *et al. BMC Genetics* (2019) 20:97
https://doi.org/10.1186/s12863-019-0797-x

BMC Genetics

RESEARCH ARTICLE Open Access

Genome-wide association study of morbid obesity in Han Chinese

Kuang-Mao Chiang[1†]
Wei-Jei Lee[5*] and We

FTO基因變異為 台灣肥胖症最為相關的遺傳基因

Abstract

Background: As obesity is becoming pandemic, morbid obesity (MO), an extreme type of obesity, is an emerging issue worldwide. It is imperative to understand the factors responsible for huge weight gain in certain populations in the modern society. Very few genome-wide association studies (GWAS) have been conducted on MO patients. This study is the first MO-GWAS study in the Han-Chinese population in Asia.

Methods: We conducted a two-stage GWAS with 1110 MO bariatric patients (body mass index [BMI] ≥ 35 kg/m^2) from Min-Sheng General Hospital, Taiwan. The first stage involved 575 patients, and 1729 sex- and age-matched controls from the Taiwan Han Chinese Cell and Genome Bank. In the second stage, another 535 patients from the same hospital were genotyped for 52 single nucleotide polymorphisms (SNPs) discovered in the first stage, and 9145 matched controls from Taiwan Biobank were matched for confirmation analysis.

Results: The results of the joint analysis for the second stage revealed six top ranking SNPs, including rs8050136 (p-value = 7.80×10^{-15}), rs9939609 (p-value = 1.32×10^{-5}), rs1421085 (p-value = 1.54×10^{-8}), rs9941349 (p-value = 9.05×10^{-8}), rs1121980 (p-value = 7.27×10^{-7}), and rs9937354 (p-value = 6.65×10^{-7}), which were all located in *FTO* gene. Significant associations were also observed between MO and *RBFOX1*, *RP11-638 I3.1*, *TMTC1*, *CBLN4*, *CSMD3*, and *ERBB4*, respectively, using the Bonferroni correction criteria for 52 SNPs ($p < 9.6 \times 10^{-4}$).

Conclusion: The most significantly associated locus of MO in the Han-Chinese population was the well-known *FTO* gene. These SNPs located in intron 1, may include the leptin receptor modulator. Other significant loci, showing weak associations with MO, also suggested the potential mechanism underlying the disorders with eating behaviors or brain/neural development.

Keywords: Morbid obesity, Body mass index, Genome-wide association study, FTO

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單一基因變異 就能說明肥胖 的原因?

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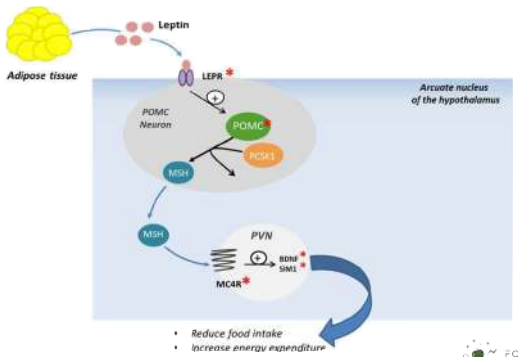
多種基因共同影響能量代謝



Int. J. Mol. Sci. **2020**, *21*(23), 9035

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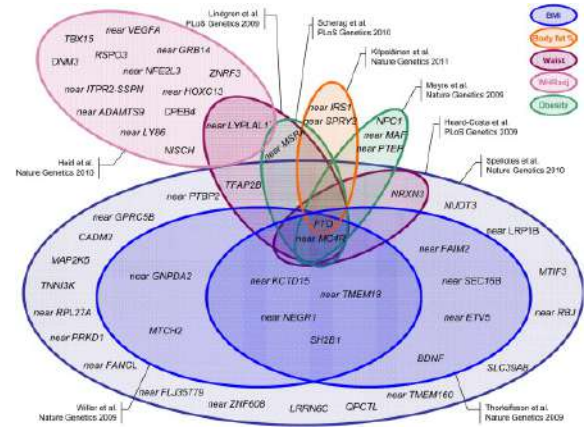

Best Practice & Research Clinical Endocrinology & Metabolism, Volume 26, Issue 2, 2012, Pages 211-226,

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肥胖基因
進一步分型

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1. 我老是吃不飽！

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飽足感 / 食慾控制 有關的基因型

表徵	基因名稱	影響面
飽足感 食慾控制	ANKK1	受到高油脂飲食的調控，影響多巴胺分泌，容易造成食物上癮。
	BDNF	受MC4R調控，影響食慾與熱量消耗。
	LEPR	參與大腦下視丘食慾促進和抑制調節，並影響全身能量代謝。
	MC4R	參與大腦下視丘食慾促進和抑制調節，並影響全身能量代謝。

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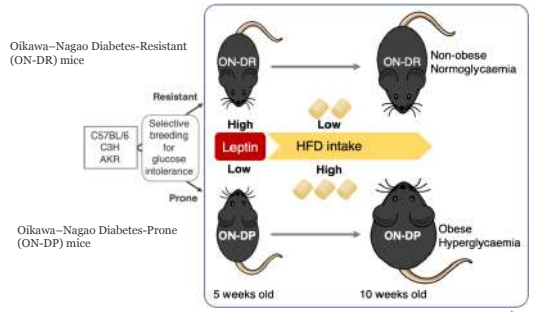
動物試驗：先天Leptin分泌較低
有助於預測未來肥胖與糖尿病的可能性



Diabetologia **63**, 1836–1846 (2020).

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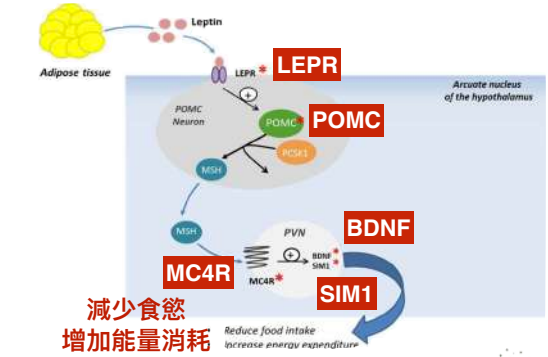
多種基因共同影響能量代謝



Int. J. Mol. Sci. **2020**, *21*(23), 9035

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飽足感 / 食慾控制基因變異 飲食與營養策略
(eg. ANKK1、BDNF、LEPR、MC4R)

飲食策略	原因	營養補充
增加膳食纖維	增加飽足感，減緩食慾，維持腸道健康	膳食纖維 Omega-3 B群 Vit.C 5-HT血清素 鎂離子
足夠蛋白質，足夠抗炎好油，避免低油飲食	增加飽足感，減緩食慾，穩定情緒	
充足的水分	有助增加飽足感，降低熱量	
健康低熱量零食選擇，指導分次少量食用技巧	預防無意識暴量攝取	
正念飲食技巧，進食速度減慢	預防無意識暴量攝取，增加對飲食的意識感	
避免極低熱量飲食	無法支持身心滿足感，復胖機率更高	

2. 我吃什麼都好容易胖！

醣類代謝 / 脂肪儲存 有關的基因型

表徵	基因名稱	影響面
醣類代謝 / 脂肪儲存	FTO	促進脂肪細胞轉為白色脂肪，與第二型糖尿病有相當高度連結性
	PPARG	調節血糖平衡與脂肪代謝，調節脂肪前驅細胞分化到脂肪細胞。
	PPARGC1B	調節血糖平衡與脂肪代謝，調節脂肪前驅細胞分化到脂肪細胞。
	SH2B1	影響血糖平衡，熱量消耗不足造成代謝型肥胖 。

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An Obesity-Associated FTO Gene Variant and Increased Energy Intake in Children

Jeanne E. Cecil, Ph.D., Roger Tavendale, Ph.D., Peter Watt, Ph.D., Marion M. Hetherington, Ph.D., and Colin N.A. Palmer, Ph.D.

Article Figures/Media

30 References 500 Citing Articles Letters

December 11, 2008
N Engl J Med 2008; 359:2558-2566
DOI: 10.1056/NEJMoa0803839

Abstract

帶有FTO變異基因(A)的兒童，攝食量增加，傾向吃更多高密度/高熱量食物，並與BMI成正相關

BACKGROUND
Variation in the fa
associations with
specific compone

METHODS
We studied 2726 Scottish children, 4 to 10 years of age, who underwent genotyping for FTO variant rs9939609 and were measured for height and weight. A subsample of 97 children was examined for possible association of the FTO variant with adiposity, energy expenditure, and food intake.

RESULTS
In the total study group and the subsample, the A allele of rs9939609 was associated with increased weight (P<0.001 and P=0.049, respectively) and body-mass index (P<0.001 and P=0.03, respectively). In the intensively phenotyped subsample, the A allele was also associated with increased fat mass (P=0.01) but not with lean mass. Although total and resting energy

Obesity, FTO Gene Variant, and Energy Intake in Children

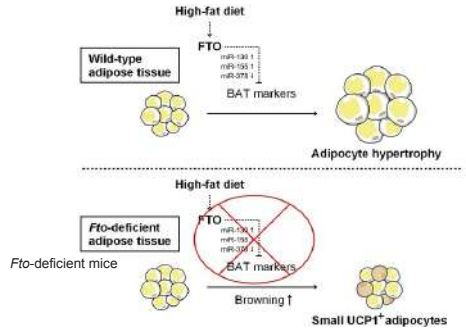
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

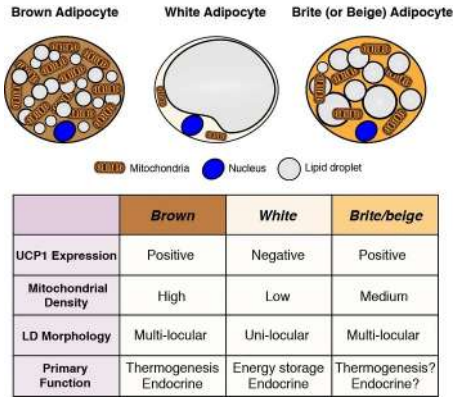
FTO Obesity Variant Circuitry and Adipocyte Browning in Humans

Melina Claussnitzer, Ph.D., Simon N. Dankel, Ph.D., Kyoung-Han Kim, Ph.D., Gerald Quon, Ph.D., Wouter Meuleman, Ph.D., Christine Haugen, M.Sc., Viktoria Glunk, M.Sc., Isabel S. Sousa, M.Sc., Jacqueline L. Beaudry, Ph.D., Vijitha Puviindran, B.Sc., Nezar A. Abdennur, M.Sc., Jannel Liu, B.Sc., Per-Arne Svensson, Ph.D., Yi-Hsiang Hsu, Ph.D., Daniel J. Drucker, M.D., Gunnar Mellgren, M.D., Ph.D., Chi-Chung Hui, Ph.D., Hans Hauner, M.D., and Manolis Kellis, Ph.D.

特定FTO基因
促進脂肪細胞在成熟過程 轉為白色脂肪



Int. J. Mol. Sci. **2016**, *17*(11), 1851



	Brown	White	Brite/beige
UCP1 Expression	Positive	Negative	Positive
Mitochondrial Density	High	Low	Medium
LD Morphology	Multi-locular	Uni-locular	Multi-locular
Primary Function	Thermogenesis Endocrine	Energy storage Endocrine	Thermogenesis? Endocrine?

https://www.umassmed.edu/guertinlab/research/adipocytes/

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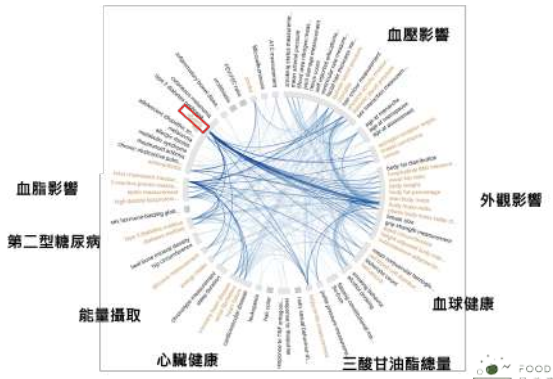
FTO基因變異 不只影響肥胖



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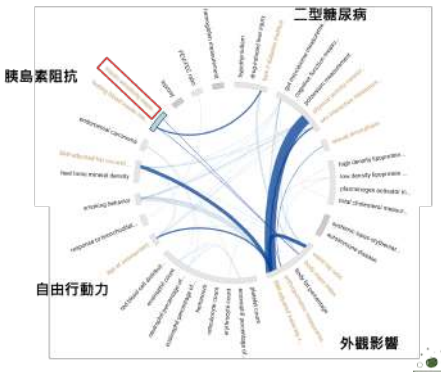
PPARG基因變異 也與胰島素有關



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醣類代謝 / 脂肪儲存基因變異 飲食與營養策略 (eg. FTO, PPARG, PPARGC1B, SH2B1)

飲食策略	原因	營養補充
低GI飲食	維持血糖穩定，增加飽足感	膳食纖維 鉻離子 山苦瓜萃取物 武靴葉萃取物 葫蘆巴萃取物 魚油 vit.D 薑黃素
增加水溶性膳食纖維	維持血糖穩定，增加飽足感	
足夠的蛋白質	確保維持肌肉質量，幫助平衡血糖，增加飽足感	
攝取健康脂肪 Omega-3/9	維持細胞膜訊息傳導功能，緩解發炎，避免反式脂肪損害細胞	
辣椒素、白藜蘆醇、薑黃、黃連素、薄荷	提高棕色組織活性	

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3. 脂肪總是對我不離不棄！

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脂肪代謝 有關的基因型

表徵	基因名稱	影響面
脂肪細胞增生	ADIPOQ	血糖調節、影響胰島素抗性，調控影響脂肪細胞增生或減少。
	APL15	影響Adiponectin含量而影響脂肪細胞增生。
脂肪細胞分解	ADRB2	幫助脂肪滴中三酸甘油酯分解成脂肪酸。
	APOA2	參與人體脂肪合成代謝，易造成脂肪囤積。
	APOA5	參與人體脂肪合成代謝，易造成脂肪囤積。

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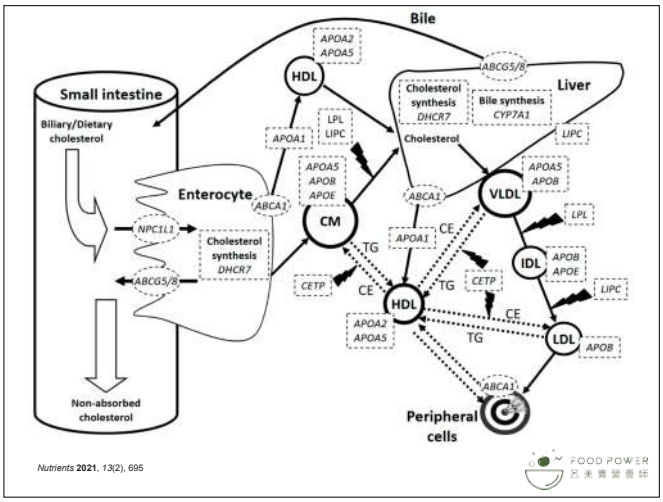

Nutrients 2021, 13(2), 695

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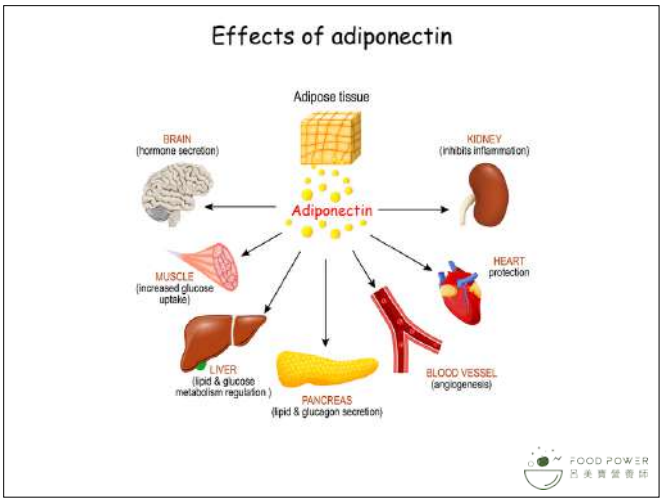

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脂肪代謝基因變異 飲食與營養策略
(eg. ADIPOQ, APL15, ADRB2, APOA2, APOA5)

飲食策略	原因	營養補充
地中海型飲食	預防心血管疾病	魚油 (高劑量EPA) Vit.E B群 膳食纖維 吲哚類I3C 薑黃 朝鮮薊 膽鹼
攝取健康脂肪 Omega-3/9	保護血脂與血管健康，增加胰島素敏感性，緩解發炎，減少飽和脂肪與反式脂肪	
多攝取植物蛋白	保護心血管功能健康	
增加膳食纖維	降低膽固醇與脂肪吸收	
彩虹飲食、十字花科蔬菜、含硫豐富蔬菜	保護肝臟功能	
間歇性斷食	增長脂肪氧化的時間，提升adiponectin濃度	

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4. 血糖老是降不下來！

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脂肪細胞肥大 / 血糖代謝有關的基因型

表徵	基因名稱	影響面
脂肪細胞肥大	ADCY5	此基因調控胰島素分泌與敏感度，影響血糖值與脂肪生成。
	GIPR	此基因調控胰島素分泌與敏感度，影響血糖值與脂肪生成。
	GNB3	此基因調控胰島素分泌與敏感度，影響血糖值與脂肪生成。
	TCF7L2	此基因調控胰島素分泌與敏感度，影響血糖值與脂肪生成。

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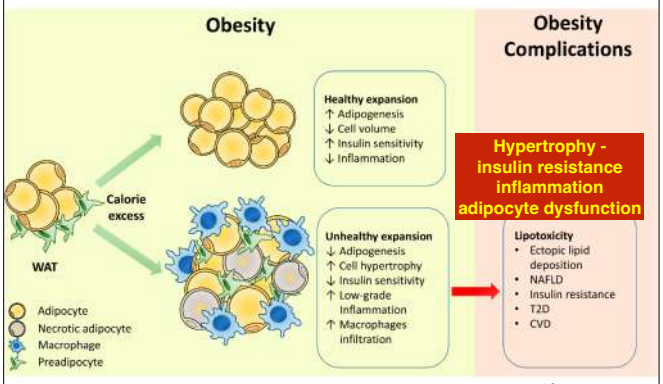
脂肪細胞肥大 誘發胰島素阻抗



Int. J. Mol. Sci. 2019, 20(9), 2358

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脂肪細胞肥大 / 血糖代謝基因變異 飲食與營養策略 (eg. ADCY5, GIPR, GNB3, TCF7L2)

飲食策略	原因	營養補充
低GI飲食	維持血糖穩定	膳食纖維 鉻離子 山苦瓜萃取物 武靴葉萃取物 魚油 vit.D3 薑黃
增加水溶性膳食纖維	維持血糖穩定	
精緻碳水、果糖需更加控制	避免發炎加成胰島素阻抗，避免過多TG累積於脂肪細胞	
地中海型飲食	預防心血管疾病	
攝取健康脂肪 Omega-3/9	維持細胞膜訊息傳導功能，緩解發炎，避免反式脂肪損害細胞	
適量脂肪，不過度攝取，避免生酮飲食？	減少過多TG累積於脂肪細胞	

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5. 努力運動 卻成效不彰？

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基礎代謝 / 運動代謝 有關的基因型

表徵	基因名稱	影響面
基礎代謝 / 運動代謝	CLOCK	體內晝夜節律調節，影響飲食行為、能量代謝與脂質和醣類代謝。
	TRHR	肌肉發育與代謝。
	UCP1	褐色脂肪代謝調節。

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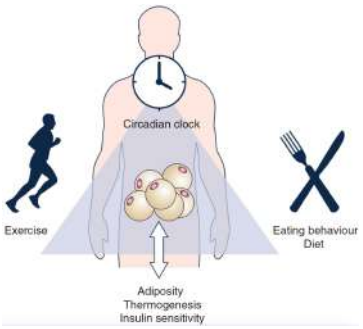
晝夜節律 主控進食運動與代謝



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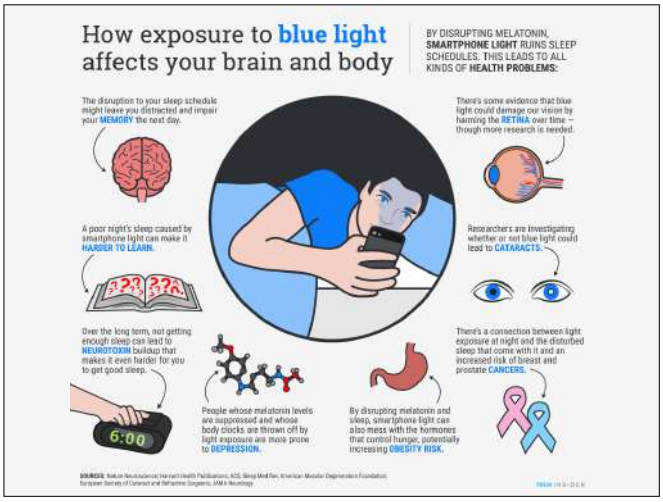

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基礎代謝 / 運動代謝 飲食與營養策略 (eg. CLOCK, TRHR, UCP1)

飲食策略	原因	營養補充
需控制飲食熱量	避免高熱量/高脂肪食物，增加儲存負擔	維生素B群 CoQ10 L-carnitine 鉻離子 血清素5-HT
辣椒素和茶多酚	有助刺激UCP-1，增加能量消耗	

運動策略

1. 運動強度要夠
2. 中高強度有氧運動：如慢跑、游泳、跳繩等，提高能量消耗
3. 間歇性高強度運動（HIIT）：增加代謝率，並在運動後保持熱量消耗
4. 肌力訓練：提高基礎代謝率

生活型態

1. 規律作息：確保充足睡眠
2. 保持較低室溫，洗冷水澡：增加熱量消耗
3. 夜間暗燈：減少藍光刺激而抑制褪黑激素分泌

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肥胖基因分型因應對策

	1. 永遠吃不飽	2. 脂肪易儲存	3. 脂肪難分解	4. 血糖居高不下	5. 運動成效差
基因	LEPR (leptin) MC4R	FTO PPARG	ADIPOQ (adiponectin) APOA2/5	TCF7L2	CLOCK UCP1
代謝狀態	食慾無法抑制 能量合成降低	血糖調節失衡 容易儲存脂肪 白色脂肪多	脂肪增生 脂肪分解慢/ 利用度差	脂肪肥大 脂肪發炎 胰島素阻抗 脂肪功能受損	晝夜節律差 褐色脂肪產熱 效能差
因應對策	增加飽足感 的食物與技巧	控制血糖 維持肌肉量	保護心血管 保護肝臟 緩解發炎	控制血糖 保護心血管 緩解發炎	控制飲食熱量 運動強度拉高 規律作息 低溫
需避免	避免 低熱量飲食			生酮飲食？	

FOOD POWER 呂美寶營養師

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