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Evaluating the Association of *FAAH* Common Gene Variation with Childhood, Adult Severe Obesity and Type 2 Diabetes in the French Population

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Key Words
Genetics · Obesity · Type 2 diabetes

Summary
Objective: The endocannabinoid pathway is involved in eating behavior and body weight regulation in both animals and humans. The association of a missense polymorphism (Pro129Thr) in *FAAH* gene with overweight/obesity has been recently questioned. **Subjects and Methods**: To evaluate the contribution of the *FAAH* gene variation in polygenic obesity and type 2 diabetes mellitus (T2DM) in the French population, we investigated the entire *FAAH* locus. We selected and genotyped ten tagged single nucleotide polymorphisms (SNPs) in 635 obese children, 896 morbidly obese adults, 2,238 T2DM subjects and 1,340 control subjects, all of French European origin. Case control association tests were performed using logistic regression models. **Results**: Nominal evidences of association were observed for rs6429600, rs324419, rs324418, rs2295633, rs7520850 and risk for class III adult obesity ($0{,}001 < p < 0.04$). The rs324420 (Pro129Thr) was nominally associated with class III adult obesity ($OR_{additive} = 0.79$ (95% CI 0.67–0.93), $p = 0.005$; $OR_{dominant} = 0.76$ (95% CI 0.63–0.92), $p = 0.005$), Pro129 being the obesity risk allele. These associations did not remain significant after Bonferroni correction for multiple testing. There was no significant association between FAAH SNPs and risk for childhood obesity or T2DM. **Conclusion**: Our results in 5,109 subjects suggest that FAAH Pro129Thr polymorphism may modestly contribute to class III adult obesity in the French population. Further validation is needed to precise the role of this gene variant in obesity susceptibility background.

Introduction

Fatty acid amide hydrolase (FAAH) is the principal inactivating enzyme of endogenous cannabinoid degradation of the most important endocannabinoid ligand, anandamide, and hydrolyses other long fatty acids, especially 2-arachidonoylglycerol (2-AG) [1–3]. Endocannabinoids are lipid mediators derived from membrane phospholipids or triglycerides with complex effects on body weight and metabolic regulation [4]. It has been shown that both exocannabinoid and endocannabinoid are associated with an increased food intake and weight gain in animals through the central endocannabinoid pathway [5, 6].

Mice deficient in FAAH display reduced anxiety and ethanol sensitivity [7, 8], and have reduced levels of the orexigenic peptide CART in several regions of the brain implicated in appetite control [9]. The *FAAH* gene is located in a region of linkage for dietary energy and nutrient intakes on chromosome 1p33 in human populations [10]. In addition, FAAH mRNA expression in adipose tissue is negatively correlated with circulating endocannabinoid and visceral fat mass, and is increased in mature adipocytes compared with preadipocytes [11–13]. A functional missense polymorphism Pro129Thr has been associated with drug use [14–16] and with reduced cellular expression and activity of human FAAH in T lymphocytes and COS-7 cells [17]. In addition, the Pro129Thr polymorphism has been associated with overweight and obesity in a cohort of European and African ancestry, but this association was not confirmed in Asian [18] and was borderline associated with overweight in Danish population-based cohorts [19] but in the

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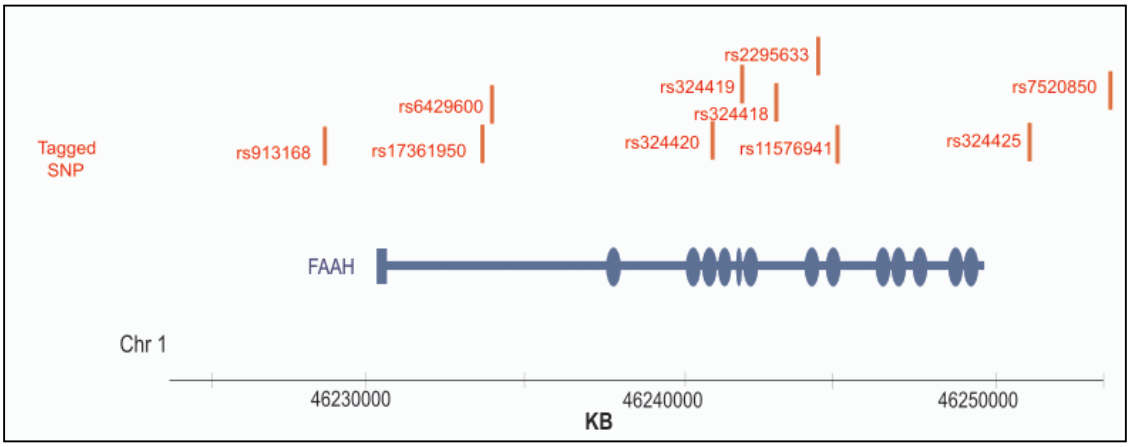

Fig. 1. Schematic representation of the *FAAH* gene in the 30kb studied interval and the tagged SNPs selected from Hap Map II (data Rel19/ phaseII Oct05, on NCBi B34 assembly).

opposite direction of the initial report of Sipe et al. [18]. These conflicting data might indicate that both findings are spurious and highlight the need for further validation studies.

More recently, Murdolo et al. [20] found that hyperinsulinemia induced by a euglycemic hyperinsulinemic clamp led to a two-fold increase in the level of FAAH mRNA in subcutaneous abdominal adipose tissue of lean but not obese subjects. However, the effect of the Pro129Thr functional polymorphism on the risk of type 2 diabetes mellitus (T2DM) has not been assessed to date. Our aim was to investigate the possible role of the whole *FAAH* gene variations in susceptibility to polygenic severe obesity as well as to T2DM using a tagged single nucleotide polymorphism (SNP) approach in the French population.

Subjects and Methods

Subjects

Subjects in the case control studies were all French Caucasian, and an informed consent was signed by each subject before participating in the studies which were approved by local ethics committees.

The control subjects were recruited by the CNRS-UMR8090 or came from the general-population D.E.S.I.R. study [21]. We selected 1,340 unrelated adults, with BMI < 25 kg/m^2, age ≥ 40 years, fasting glucose < 6.1 mmol/l and with no treatment for hyperglycemia (men/women 444/896; mean BMI 21.8 ± 1.6 kg/m^2; mean age 55 ± 10 years).

The CNRS-UMR8090 recruited obese children. Childhood obesity was defined according to the European Childhood Obesity Group (ECOG) [22] as BMI exceeding the 97th percentile for gender and age in a French reference population. We selected 635 obese children (mean zBMI 4.3 ± 1.2; mean age 11 ± 3 years; men/women 296/339).

Obese adults were recruited by the CNRS-UMR8090 and by the Department of Nutrition of the Hotel Dieu Hospital in Paris. Class III obesity status was defined as BMI ≥ 40 kg/m^2 in adults. The obese adult group included 896 subjects (men/women 207/689) with a mean BMI of 47.5 ± 7.6 kg/m^2 and a mean age of 45 ± 12 years.

The diabetic group was recruited by the Corbeil-Essonnes Hospital and by the CNRS-UMR8090. T2DM was defined as fasting plasma glucose ≥ 7.0 mmol/l and/or treatment by antidiabetic agents and age at onset of T2DM ≥ 45 years old. We selected 2,238 subjects (men/women 1,327/911, mean age of 59 ± 10 years, mean age at onset of T2DM 48 ± 10 years and mean BMI 30.2 ± 5.6 kg/m^2).

Tagging Procedure

We selected tagged SNPs in the chromosome 1 region defining the *FAAH* locus (chr1: 46,224,908_46,254,432), 5kb upstream and 5kb downstream flanking the gene. We used the Haploview program with the HapMap phase II database (October 2005) and selected SNPs with an $r^2 > 0.8$ and a minor allele frequency (MAF) > 0.05. Ten tagged SNPs that captured 100% of the haplotype representation within the 30 kb *FAAH* locus were chosen for the case control association study, including the previously observed associated SNP Pro129Thr amino acid change (fig. 1).

SNP Genotyping

Genotyping was performed using the Applied Biosystems SNPlex™ (Applied Biosystems, Foster City, CA, USA) technology based on the oligonucleotide ligation assay (OLA) combined with multiplex PCR target amplification. The chemistry of the assay relies on a set of universal core reagent kits and a set of SNP-specific ligation probes, allowing a multiplex genotyping of 48 SNPs simultaneously in a unique sample. Allelic discrimination is performed through capillary electrophoresis analysis using Applied Biosystems 3730xl DNA Analyzer and GeneMapper 3.7 software. The SNP rs913168 failed during the design process and was therefore genotyped using LightCycler™480 technology (Roche Diagnostics, Basel, Switzerland). The conditions are available upon request. The rs324420 was performed using the TaqMan® SNP Genotyping Assays on ABI 7900 (Applied Biosystems). The genotyping call rate was above 95% for the ten SNPs. As a standard laboratory quality control measure, a random 10% of DNA samples were systematically re-genotyped, and we recorded a concordance rate of 100% for each SNP.

Statistical Analysis

Genotypic distributions were in Hardy-Weinberg equilibrium for all SNPs in the control subjects ($p > 0.05$). Case control association tests were performed using logistic regression models to take into account the effect of co-variables such as gender, age, and BMI. Logistic regression adjusted for gender and age was used for childhood and adult class III obesity traits. Logistic regression adjusted for gender, age, and BMI were used for T2DM trait. We tested additive, dominant and recessive modes of inheritance. For statistical power calculation we used the program QUANTO [23]. Using spectral decomposition, we estimated the total number of tests at 8.18 to applied for multiple comparisons to Bonferroni correction (8.18 SNPs × 3 affection traits × 3 genetic models = 73.6; p corrected = 0.00068) [24].

We used linear regression models (corrected for gender and age) to assess the effect of SNP rs324420 on quantitative traits variation (BMI, fasting glucose and fasting insulin, waist circumference, triglycerides as well as HDL cholesterol and total cholesterol).

Table 1. Genotype distribution of *FAAH* tagged SNP in lean normoglycemic controls, obese children, class III obese adults and T2DM subjects[a]

Taggeds SNP	Subjetcs	Genotypes			Adjusted odds ratio					
		11	12	22	additive model		recessive model		dominant model	
					p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)
rs913168	controls	431 (34.0)	613 (48.3)	225 (17.7)						
A>G	obese children	228 (37.4)	280 (45.9)	102 (16.7)	0.24	0.92 (0.80–1.06)	0.65	0.94 (0.73–1.22)	0.18	0.87 (0.71–1.06)
	obese adults	278 (31.6)	432 (49)	171 (19.4)	0.09	1.12 (0.98–1.27)	0.31	1.13 (0.90–1.42)	0.10	1.18 (0.97–1.43)
	T2DM subjects	737 (34.1)	1,042 (48.2)	384 (17.8)	0.90	0.99 (0.82–1.19)	0.94	0.99 (0.71–1.38)	0.90	0.98 (0.75–1.29)
rs17361950	controls	671 (51.2)	528 (40.3)	112 (8.5)						
C>T	obese children	315 (50.0)	265 (42.1)	50 (7.9)	0.79	1.02 (0.88–1.18)	0.70	0.93 (0.66–1.32)	0.57	1.06 (0.87–1.28)
	obese adults	432 (49.9)	365 (42.2)	68 (7.9)	0.74	1.02 (0.89–1.18)	0.53	0.90 (0.65–1.25)	0.44	1.07 (0.90–1.29)
	T2DM subjects	1,131 (52.1)	833 (38.4)	206 (9.5)	0.97	1.00(0.82–1.22)	0.67	1.10 (0.70–1.72)	0.84	0.97 (0.75–1.26)
rs6429600	controls	736 (56.5)	487 (37.4)	79 (6.1)						
A>G	obese children	349 (57.0)	221 (36.1)	42 (6.9)	0.76	1.02 (0.87–1.20)	0.48	1.15 (0.78–1.70)	0.98	1.00 (0.82–1.22)
	obese adults	535 (61.7)	294 (33.9)	38 (4.4)	*0.001*	*0.78 (0.67–0.91)*	0.08	0.69 (0.45–1.04)	*0.002*	*0.75 (0.62–0.90)*
	T2DM subjects	1,273 (58.3)	792 (36.3)	118 (5.4)	0.79	1.03 (0.83–1.27)	0.57	0.85 (0.50–1.46)	0.54	1.08 (0.84–1.40)
rs324420	controls	836 (63.3)	432 (32.7)	52 (3.9)						
C>A	obese children	407 (64.8)	193 (30.7)	28 (4.5)	0.83	0.98 (0.83–1.16)	0.67	1.11 (0.69–1.78)	0.66	0.96 (0.78–1.17)
	obese adults	602 (67.7)	262 (29.5)	25 (2.8)	*0.005*	*0.79 (0.67–0.93)*	0.20	0.72 (0.43–1.19)	*0.005*	*0.76 (0.63–0.92)*
	T2DM subjects	1,404 (64.3)	696 (31.9)	84 (3.8)	0.72	1.04 (0.83–1.30)	0.65	0.86 (0.45–1.65)	0.54	1.09 (0.83–1.41)
rs324419	controls	920 (70)	365 (27.8)	29 (2.2)						
G>A	obese children	466 (74.1)	150 (23.8)	13 (2.1)	0.13	0.86 (0.71–1.04)	0.84	0.93 (0.48–1.81)	0.10	0.83 (0.67–1.04)
	obese adults	613 (70.5)	222 (25.5)	34 (3.9)	0.46	1.07 (0.90–1.26)	*0.01*	*1.99 (1.17–3.39)*	0.93	0.99 (0.81–1.21)
	T2DM subjects	1,555 (71.7)	556 (25.6)	57 (2.6)	0.92	0.99 (0.77–1.27)	0.85	1.08 (0.47–2.51)	0.87	0.98 (0.74–1.29)
rs324418	controls	800 (61)	453 (34.5)	59 (4.5)						
T>C	obese children	383 (61.1)	206 (32.9)	38 (6.1)	0.53	1.05 (0.90–1.24)	0.19	1.32 (0.87–2.02)	0.86	1.02 (0.84–1.24)
	obese adults	561 (64.4)	276 (31.7)	34 (3.9)	*0.04*	*0.85 (0.72–0.99)*	0.72	0.92 (0.58–1.45)	*0.02*	*0.80 (0.67–0.97)*
	T2DM subjects	1,333 (61.5)	739 (34.1)	97 (4.5)	0.54	1.07 (0.86–1.33)	0.82	0.93 (0.51–1.69)	0.40	1.12 (0.86–1.45)
rs2295633	controls	526 (40.6)	606 (46.8)	163 (12.6)						
C>T	obese children	280 (46.0)	259 (42.5)	70 (11.5)	0.09	0.88 (0.76–1.02)	0.56	0.91(0.68–1.23)	0.55	0.83 (0.68–1.00)
	obese adults	378 (44.7)	375 (44.4)	92 (10.9)	*0.02*	*0.86 (0.74–0.98)*	0.18	0.82 (0.62–1.09)	*0.03*	*0.82 (0.68–0.98)*
	T2DM subjects	916 (43.4)	937 (44.3)	260 (12.3)	0.92	0.99 (0.82–1.20)	0.80	0.95 (0.65–1.40)	0.97	1.00 (0.77–1.30)
rs11576941	controls	606 (46.3)	571 (43.6)	133 (10.2)						
G>T	obese children	285 (45.2)	280 (44.4)	66 (10.5)	0.93	1.01 (0.87–1.16)	0.95	1.01 (0.74–1.38)	0.94	1.01 (0.83–1.22)
	obese adults	391 (45.1)	388 (44.8)	88 (10.1)	0.58	1.04 (0.91–1.19)	0.86	0.97 (0.72–1.31)	0.41	1.08 (0.90–1.29)
	T2DM subjects	973 (45.0)	959 (44.3)	232 (10.7)	0.60	0.95 (0.79–1.15)	0.96	1.01 (0.67–1.52)	0.46	0.91 (0.70–1.17)
rs324425	controls	1,199 (91.5)	108 (8.2)	3 (0.2)						
G>A	obese children	570 (90.9)	52 (8.3)	5 (0.8)	0.31	1.17 (0.86–1.60)	0.10	3.34 (0.78–14.21)	0.49	1.12 (0.80–1.58)
	obese adults	807 (92.4)	63 (7.2)	3 (0.3)	0.36	0.86 (0.63–1.18)	0.54	1.66 (0.32–8.58)	0.28	0.83 (0.59–1.16)
	T2DM subjects	2,009 (92.0)	172 (7.9)	2 (0.1)	0.80	1.06 (0.67–1.69)	0.74	0.55 (0.02–18.65)	0.76	1.08 (0.67–1.75)
rs7520850	controls	1,010 (77.5)	280 (21.5)	14 (1.1)						
G>A	obese children	488 (80.8)	111 (18.4)	5 (0.8)	0.12	0.84 (0.67–1.05)	0.70	0.82 (0.29–2.30)	0.12	0.82 (0.65–1.05)
	obese adults	662 (77.1)	175 (20.4)	22 (2.6)	0.19	1.14 (0.94–1.38)	*0.005*	*2.79 (1.37–5.69)*	0.56	1.06 (0.86–1.32)
	T2DM subjects	1,662 (76.8)	473 (21.9)	28 (1.3)	0.77	1.04 (0.79–1.38)	0.52	0.64 (0.16–2.54)	0.65	1.07 (0.79–1.45)

[a]Odds ratios and 95% CIs were calculated using logistic regression model adjusted for gender and age for childhood and adult class III obesity traits. Logistic regression model adjusted for gender, age and BMI were used for T2DM trait.

Results

Ten tagged SNPs in the *FAAH* locus were successfully genotyped in 1,340 lean normoglycemic adults, 635 obese children, 896 class III obese adults and 2,238 T2DM subjects. Results of the case control study under both additive, dominant and recessive modes of inheritance are given in table 1. There was no significant association between *FAAH* SNPs and risk for childhood obesity or T2DM. Nominal evidences of association were observed for rs6429600 ($OR_{additive}$ = 0.78 (95% CI

Table 2. Study of metabolic traits according to the *FAAH* rs324420 (Pro129Thr) polymorphism[a]

rs324420 (Pro129Thr)	CC			AC			AA			p value		
	number	mean	S.D.	number	mean	S.D.	number	mean	S.D.	additive	dominant	recessive
BMI, kg/m^2	836	21.6	1.7	432	21.6	1.7	52	21.6	1.5	0.38	0.30	0.98
Fasting glucose, mmol/l	836	5.04	0.42	431	5.01	0.44	52	5.03	0.45	0.40	0.38	0.81
Fasting insulin, mU/l	816	31.6	16.6	426	31.0	15.1	52	33.7	16.6	0.96	0.69	0.26
Waist circumference, cm	813	74.7	7.5	424	73.6	7.7	50	75.6	7.2	0.58	0.31	0.35
HDL cholesterol, mmol/l	775	1.74	0.45	401	1.78	0.41	50	1.86	0.41	0.02	0.06	0.03
Total cholesterol, mmol/l	775	5.58	0.94	401	5.55	0.91	50	5.84	1.01	0.26	0.59	0.05
Triglycerides, mmol/l	775	0.89	0.46	401	0.85	0.40	50	0.86	0.38	0.64	0.59	0.98

[a]p values were corrected for gender and age.

0.67–0.91), p = 0.001; $OR_{dominant}$ = 0.75 (95% CI 0.62–0.90), p = 0.002), rs324419 ($OR_{recessive}$ = 1.99 (95% CI 1.17–3.39), p = 0.01), rs324418 ($OR_{additive}$ = 0.85 (95%CI 0.72–0.99), p = 0.04; $OR_{dominant}$ = 0.80 (95%CI 0.67–0.97), p = 0.02), rs2295633 ($OR_{additive}$ = 0.86 (95% CI 0.74–0.98), p = 0.02; $OR_{dominant}$ = 0.82 (95% CI 0.68–0.98), p = 0.03), rs7520850 ($OR_{recessive}$ = 2.79 (95% CI 1.37–5.69), p = 0.005) and risk for class III obesity. The rs324420 (Pro129Thr) SNP was associated neither with childhood obesity nor with T2DM in our study. However, we found a nominally significant association between Pro129Thr polymorphism and class III adult obesity ($OR_{additive}$ = 0.79 (95% CI 0.67–0.93), p = 0.005; $OR_{dominant}$ = 0.76 (95% CI 0.63–0.92), p = 0.005), Pro129 being the obesity risk allele. These associations did not remain significant after multiple testing correction.

We then studied the effect of the SNP rs324420 (Pro129Thr) on metabolic traits in 1,340 lean normoglycemic adults (table 2). The lowest significance was observed between the rs324420 SNP and HDL cholesterol (nominal p = 0.02) but is no more significant after Bonferroni correction (1 SNP × 3 genetic models × 7 traits = 21; p corrected = 0.0024).

Discussion

Our study is the first to cover the whole *FAAH* gene haplotype structure in a large data set (n = 5,109). Our results suggest that the *FAAH* Pro129Thr functional polymorphism [17] may modestly contribute to class III adult obesity, but not to childhood obesity or to T2DM in the French population. The full coverage of the *FAAH* locus using a tagged SNP approach did not reveal any additional gene variation significantly associated with the same affection traits. Our study was designed to detect an effect size of 1.35, 1.30 and 1.25 with a statistical power of 80% (MAF 0.1, p = 0.05) for childhood obesity, adult class III obesity and T2DM risk, respectively.

Regarding the Pro129Thr non-synonymous SNP, we were unable to confirm the initial association between Thr129 and obesity [18]. Indeed we found significant evidence of association between this polymorphism and class III adult obesity, but in opposite direction of the one reported by Sipe et al. [18] (obesity risk allele Pro129 in our design). Interestingly, Jensen et al. [19] found a nominal association of the Pro129 allele with risk of overweight/obesity in a large Danish population (n = 5,801). This highlights the need for multiple replication to fully validate new disease susceptibility genes, as recently shown for the *INSIG2* story [25–29]. It remains possible that severe familial forms of obesity may harbor a different genetic architecture than moderate forms of common obesity as studied by Sipe et al. [18]. However, Jensen et al. [19] were unable to replicate this association in a population-based Danish cohort.

A recent report has provided evidence that the hyperglycemic status could modulate FAAH mRNA level in subcutaneous abdominal adipose tissue of lean patients [20]. From these results, we hypothesized that *FAAH* gene variation could be involved in the etiology of T2DM. Our results based on 1,340 lean normoglycemic and 2,238 T2DM subjects exclude a major effect of *FAAH* SNPs in the risk for T2DM.

In conclusion, a tagging SNP approach in the *FAAH* locus combined with a case control study of 635 obese children cases, 896 class III obese adults cases, 2,238 T2DM cases, and 1,340 controls suggest that *FAAH* Pro129Thr polymorphism may modestly contribute to class III adult obesity in the French population. Further validation is needed to precise the role of this gene variant in the obesity susceptibility background.

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Disclosure

The authors declared no conflict of interest.

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