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Association of common *JAK2* variants with body fat, insulin sensitivity and lipid profile

Dongliang Ge^{1,§}, Sakina B Gooljar^{2,*,†}, Theodosios Kyriakou², Laura J Collins², Ramasamyiyer Swaminathan³, Harold Snieder^{4,5,6}, Tim D Spector⁵, and Sandra D O'Dell^{2,§}

¹Center for Population Genomics and Pharmacogenetics, Duke University, Durham, NC, USA.

²Nutrition Food and Health Research Centre, King's College London, London, UK. ³Chemical Pathology, Guy's and St Thomas' Hospitals Trust, London, UK. ⁴Unit of Genetic Epidemiology and Bioinformatics, Department of Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands. ⁵Twin Research and Genetic Epidemiology Unit, King's College London, St Thomas' Campus, London, UK. ⁶Georgia Prevention Institute, Department of Pediatrics, Medical College of Georgia, Augusta, Georgia, USA .

Abstract

The leptin signal is transduced via the JAK2-STAT3 pathway at the leptin receptor. JAK2 also phosphorylates IRS, integral to insulin and leptin action and is required for optimum ABCA1-dependent transport of lipids from cells to apoA-I. We hypothesised that common variation in the *JAK2* gene may be associated with body fat, insulin sensitivity and modulation of the serum lipid profile in the general population. Ten tagging SNPs spanning the gene were genotyped in 2760 Caucasian female twin subjects (mean age 47.3±12.6 years) from the St Thomas' UK Adult Twin Registry (Twins UK). Minor allele frequencies were between 0.170 and 0.464. The major allele of rs7849191 was associated with higher central fat (P=0.030), % central fat (P=0.014) and waist circumference (P=0.027) and the major allele of rs3780378 with higher serum apoA (P=0.026), total cholesterol (P=0.014) and LDL cholesterol (P=0.012) and lower triglyceride (P=0.023). However, no associations were significant at a level which took account of multiple testing. Although JAK2 is a critical element in leptin and insulin signalling and has a role in cellular cholesterol transport, we failed to establish associations of common SNPs with relevant phenotypes in this human study.

Keywords

cholesterol; fat distribution; genetic susceptibility; lipoproteins; signal transduction

Janus kinase 2 (JAK2) is a cytoplasmic protein-tyrosine kinase recruited by receptors that lack intrinsic kinase activity, to initiate diverse signalling pathways [1]. Leptin signals adiposity levels to centres in the hypothalamus and is an important regulator of energy homeostasis through its inhibition of appetite and enhancement of energy expenditure [2]. On binding to receptors, leptin induces activation and tyrosine phosphorylation of JAK2 and subsequent tyrosine phosphorylation of specific residues on the receptor [3], which form high affinity binding sites for signalling proteins containing Src homology 2 and other

[§]Address correspondence to Dr Sandra O'Dell, Nutrition Food and Health Research Centre, King's College London, Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NH, UK. Email: sandra.o'dell@kcl.ac.uk..

[†]Present address: Department of Molecular Endocrinology, William Harvey Research Institute, Barts and the London, Queen Mary University of London.

[#]Joint first authorship

phosphotyrosine-binding domains. These include signal transducer and activator of transcription-3 (STAT3), which on tyrosine phosphorylation translocates to the nucleus to activate gene transcription [4], including that of suppressor of cytokine signalling (SOCS3) [3]. A different leptin receptor tyrosine residue phosphorylated by JAK2 recruits the Shc adaptor protein SHP2, which activates the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) pathway involved in the mitogenic response [3]. JAK2 is also involved in activating insulin receptor substrates 1 and 2, receptor docking proteins that mediate signalling of both insulin and leptin [5]. One of the targets of IRS is phosphatidylinositol 3-kinase (PI3K), involved in a range of metabolic functions initiated by leptin and insulin [6,7], with variation in the *PIK3R1* gene shown by us to be associated with leptin and body fat [8]. SOCS3 mediates feedback inhibition of signalling at both receptors through interfering with activation of the IRS proteins by JAK2 [9]. The ATP-binding cassette transporter A1 (ABCA1), located in the cell membrane, mediates transport of excess cholesterol and phospholipids out of cells to high density lipoprotein (HDL) apolipoproteins, such as apolipoprotein A-1 (apoA-I) [10]. Interaction of apoA-I with ABCA1 acutely stimulates the autophosphorylation of JAK2, which is required for binding of apoA-I to ABCA1 and removal of cellular lipids [11].

As JAK2 is involved in leptin, insulin and ABCA1 signalling pathways, we hypothesized that common variants in the *JAK2* gene may influence body fat mass, insulin sensitivity or serum lipid profile in humans. In this first gene-wide association study of *JAK2* variation in relation to metabolic variables, we have used tagging SNPs (tSNPs) to test associations with nine relevant phenotypes in 2759 Caucasian female twin subjects (mean age 47.3 ± 12.6 years). Characteristics of subjects in the Twins UK study sample are shown in Table 1. Seventy-five polymorphic SNPs with minor allele frequency (MAF) >0.05 in the selected 146.8 kb region, (which includes 2 kb upstream and downstream of the 142.75 kb *JAK2* gene) are listed on the HapMap database (HapMap Data Release #20/Phase II Jan 2006; <http://www.hapmap.org>).

tSNPs effectively capture information of most common variants by taking into account patterns of linkage disequilibrium (LD) across a gene [12]. *JAK2* lies in a region of strong LD on chromosome 9 and is therefore amenable to tagging. We used the *htSNP2* program developed by Chapman *et al.* [12] to select ten tSNPs: rs3808850, rs1887429, rs2274471, rs7849191, rs1536800, rs10974947, rs7857730, rs3780373, rs3780378 and rs3780379, all of which are in non-coding regions (Fig. 1). Online Table 1 shows pairwise linkage disequilibrium (LD) between selected tSNPs in the study sample. Online Table 2 shows the genotype and allele frequencies of the tSNPs, based on one monozygous (MZ) and both dizygous (DZ) twins genotyped for each pair.

We found no associations between any of the ten tSNPs and general obesity scores (see Methods) or insulin sensitivity indices HOMA or SiM, so individual variables were not tested further. An association for a 2 df overall genotypic test (i.e. a codominant model) showing borderline nominal significance ($P=0.03$) was found between tSNP rs7849191 and central obesity. We performed follow-up analyses to determine the best model for all central obesity related phenotypes and found dominant associations with central fat ($P=0.030$), % central fat ($P=0.014$) and waist circumference ($P=0.027$) in subjects with available data ($n=2660$) (Table 2). Subjects homozygous for the major allele had significantly higher waist or central fat measurements, in comparison to subjects homozygous or heterozygous for the minor allele, explaining 0.1-0.2% of variance. The only other associations for a codominant model showing borderline nominal significance ($P=0.03$ - 0.05) were found between tSNP rs3780378 and a number of serum lipid variables (Table 2). The major allele was associated with higher serum apoA ($P=0.026$), lower total cholesterol ($P=0.014$) and lower LDL cholesterol ($P=0.012$) based on an additive model, but there was no significant association

with HDL-cholesterol ($P=0.24$). Subjects homozygous for the major allele had lower levels of triglyceride ($P=0.023$) in comparison to subjects homozygous or heterozygous for the minor allele. However, no associations with either tSNP were significant at levels which took account of multiple testing of the 10 tSNP genotypes versus 19 phenotypes, pragmatically taken as $P<0.01$ (see Methods) [13].

Online Table 3 shows the distribution of the five tSNP haplotypes at frequencies $>5.0\%$ in the study sample, which cover 53.5% of the haplotype diversity. All phenotypes listed in Table 2 were tested in haplotypic analysis. Remaining haplotypes (online Table 3) were not analysed, as based on simulations, Lake *et al.* [14] suggest that haplotype frequencies of at least 5% are required to avoid biased regression parameters. Haplotype 2 was associated with an increase in serum apoA of 0.08 g/l compared to carriers of the common haplotype 1. Another, haplotype 5, was associated with 1.56 cm smaller waist measurement ($P=0.026$) compared to the most common haplotype. However, combined haplotypes accounted for less than 0.2% of the variance in either parameter (Table 3).

The main strengths of this study lie in the large number of subjects with measures of body fat, regional fat distribution, serum lipids and insulin sensitivity and the comprehensive coverage of variation in this 142.75 kb gene using tSNPs. The test of association with obesity variables involving 2760 subjects (962 DZ pairs and 418 MZ pairs) provided power in excess of 80% (and $\alpha = 0.01$) to detect a locus effect of 0.75%. There were only slightly fewer subjects (2421-2594) available with serum lipid data and although there were fewer subjects than this available with insulin resistance measures, the current study had 80% ($\alpha = 0.01$) power to detect a locus effect explaining 1.25% of the variance in HOMA index ($n=1002$) and 1.7% of the variance in SiM ($n=735$). However, in tagging only common SNPs, we excluded the possibility of discovering any substantial effect associated with low frequency SNPs ($MAFs<0.05$), which could be functional.

We have found only suggestive associations between two tSNPs and phenotypes that could reflect the known involvement of JAK2 in the leptin signalling pathway (accumulation of central fat) and activation of the apoA1 transporter ABCA1 (level of serum apoA and total cholesterol). We did not however establish any association with serum leptin, so the association with central fat could originate elsewhere. Neither did we find any association with HDL-cholesterol, which would be expected if the association with apoA reflected an effect of JAK2 on ABCA1 activity. In conclusion, common *JAK2* variants were not strongly associated with body fat, insulin sensitivity or lipid profile in our sample of normal female twins.

Methods

Study design

The Twins UK Registry comprises unselected, Caucasian mostly female volunteers ascertained from the general population through national media campaigns in the UK [15]. The study sample comprised 2759 subjects (836 MZ, 1924 DZ) with available leptin data. The number of individuals in the study cohort with data on other phenotypic variables is shown in Table 1. Means and ranges of quantitative phenotypes in Twins UK are similar to an age-matched sample of the UK female population [16]. Informed consent was obtained from all participants before they entered the studies, which were approved by the local research ethics committee.

Zygosity, body composition and biochemical analyses

Zygosity was determined by standardised questionnaire and confirmed by DNA fingerprinting. Height was measured to the nearest 0.5 cm using a wall-mounted

stadiometer. Weight (light clothing only) was measured to the nearest 0.1 kg using digital scales. BMI was used as a measure of general adiposity and calculated as weight divided by height squared (kg/m^2). Waist circumference (cm) was measured at the level midway between the lower rib margin and the iliac crest. Body composition was measured by dual emission X-ray absorptiometry (Hologic QDR-2000, Vertec, Waltham, MA, USA). Serum leptin concentration was determined after an overnight fast using a radioimmunoassay (Linco Research, St Louis, MO, USA). Fasting insulin was measured by immunoassay (Abbott Laboratories Ltd., Maidenhead, UK) and glucose was measured on an Ektachem 700 multichannel analyser using an enzymatic colorimetric slide assay (Johnson and Johnson Clinical Diagnostic Systems, Amersham, UK). A random sub-sample of 738 subjects underwent an oral glucose tolerance test (OGTT) for which glucose and insulin levels were measured before and 2 h after a 75-g oral glucose load. Blood sample collection for determination of fasting lipids was drawn from most subjects after a minimum 8-h overnight fast. Serum was stored at -45°C until analyzed using a Cobas Fara machine (Roche Diagnostics, Lewes, UK). A colourimetric enzymatic method was used to determine total cholesterol, triglycerides and HDL cholesterol levels. The latter was measured after precipitation from chylomicron, LDL and VLDL particles by magnesium and dextran sulphate. Apolipoproteins A1 and B were assayed by an immunoturbidimetric method. The Friedewald equation was used to calculate LDL cholesterol levels in subjects with triglycerides $< 4.52 \text{ mmol.L}^{-1}$.

Selection of tSNPs

Seventy-five polymorphic SNPs with $\text{MAF} < 0.05$ in the region Chr 9: 4975242..5117996 are listed on the HapMap database (HapMap Data Release #20/Phase II Jan 2006; <http://www.hapmap.org>). Genotypes of 90 CEU parent-offspring trio subjects were downloaded from HapMap and the package *htSNP2* was used to select a tSNP set that predicts remaining SNPs with a minimum R_L^2 of 0.8. This approach selects an optimal set of tSNPs in such a way that the allele frequencies of the remaining (non tSNPs) can be predicted well. A series of regression equations are calculated for which the predictive efficiency is assessed in terms of R_L^2 , which measures the proportion of variance of each remaining SNP explained by regression on the tSNP alleles (locus-based scoring).

tSNP genotyping

The tSNPs were genotyped by Pyrosequencing, (Biotage, Uppsala, Sweden). Genotyping accuracy as assessed by inclusion of duplicates (50 pairs of monozygous (MZ) twins) in the arrays was approx. 98% and negative controls (water blanks) were included on each plate. Two SNPs refractory to genotyping by Pyrosequencing, rs1536800 and rs3780378, were genotyped by KBiosciences, Hoddesdon, Herts., UK, using the KASPar system. This is a fluorescence-based allele-specific PCR with improved robustness and discriminating power over conventional ARMS, (<http://www.kbioscience.co.uk/chemistry/chemistry-intro.htm>). Genotyping success rates varied between 79.43% and 91.94%. Primers and PCR conditions for tSNP genotyping by pyrosequencing are given in online Table 4.

Statistical analyses

Factor analysis was used to combine strongly correlated indices of obesity into two measures: one for general obesity (serum leptin, BMI, weight, total fat mass and % total fat) and one for central obesity (waist circumference, central fat mass and % central fat). Insulin-resistance measures HOMA and SiM described previously [17] were available for subsets of subjects with leptin data. Serum lipids were total-, LDL- and HDL-cholesterol, triglycerides and apolipoproteins A1 and B. Phenotypes significantly ($P < 0.05$) deviating from normal were log transformed to obtain normal distributions prior to analysis.

Preliminary association analyses were performed using STATA 8 (StataCorp, College Station, Texas). To reduce the likelihood of generating false positive associations through multiple testing, single variables characterizing obesity were analysed only if initial tests with the general and central obesity scores yielded a positive association for at least one of these combined variables. This strategy was also used for HOMA and SiM.

For related individuals, conventional statistical analyses lead to inflated significance. Dependency of the observations within pairs was accounted for by use of the Generalized Estimating Equations (GEE) procedure [18] in which both monozygous (MZ) and dizygous (DZ) twins can be used in tests of association. The approach accounts for dependency of the observations within pairs and yields unbiased standard errors and P-values. Association analyses in the full cohort included both twin subjects from each pair.

Analyses were done separately for each of the SNPs and followed up by haplotype analyses. For individual SNP association analyses, we first performed a 2-df overall test of genotypic association. Additive, dominant and recessive models (all 1-df) were further tested to find the best mode of inheritance. In adjusting the P-value to account for multiple testing we follow the recommendations of van den Oord and Sullivan [13]. The adjustment depends on ρ_0 , the number of markers for which there is no true effect (i.e., the null hypothesis is true), which is generally unknown in candidate gene studies. For a range of plausible ρ_0 values for candidate gene studies, a significance level of $P=0.01$ will on average control the false discovery rate at 0.10. Lower false discovery rates generally resulted in sharp increases in sample size, i.e., loss of power. Thus, the significance level of this study was pragmatically taken as $P<0.01$.

Age and menopausal status were included as covariates in all models. BMI was included as an additional covariate in models testing lipids and insulin sensitivity variables. Details of our approach to test the association of statistically inferred haplotypes with continuous traits have been described previously [19]. The probabilities of haplotype pairs were estimated by PHASE 2.0 software [20]. Individual SNP and haplotype association analyses were performed using STATA 8 (StataCorp, College Station, Texas). Where needed, phenotypic variables were log transformed to obtain better approximations of the normal distribution prior to analysis. Hardy-Weinberg equilibrium was tested by a χ^2 test with 1 df in one twin of each pair chosen at random to prevent inflated significance. Assuming a sibling correlation of 0.3, a sample of 840 DZ pairs is adequate to detect a locus effect of 0.75% with 80% power (and $\alpha = 0.01$). The current study of 962 DZ pairs with additionally 418 MZ pairs provided even greater power.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

JAK2 gene map showing selected tSNPs

Genotype data for SNPs of MAF>0.05 in the region Chr 9: 4,975,242-5,117,996 in 90 CEU subjects were downloaded from <http://www.hapmap.org> (Phase II HapMap Release January 2006). The 10 tSNPs selected using the method of Chapman *et al.* [12] are shown. Numbers refer to exons, with coding exons shown as solid boxes and untranslated exons as open boxes.

Table 1

Characteristics of subjects

<i>Variable</i>	<i>n</i>	<i>Mean (SD)</i>
Age, years *	2760	47.3(12.6)
Postmenopausal, %	2439	47.5
Obesity-related variables:		
Leptin, ng/ml	2760	16.5(12.0)
BMI, kg/m ²	2743	24.8(4.4)
Weight, kg	2744	65.4(11.8)
Waist, cm	2692	78.4(10.2)
Total fat, kg	2703	23.4(8.8)
Total fat, %	2662	35.6(8.0)
Central fat, kg	2660	1.33(0.73)
Central fat, %	2660	31.1(11.5)
Lipid profile:		
ApoA, g/l	2421	1.70(0.34)
ApoB, g/l	2439	1.17(0.36)
Triglyceride, mmol/l	2473	1.27(0.80)
Total cholesterol, mmol/l	2585	5.56(1.25)
LDL cholesterol, mmol/l	2443	3.46(1.15)
HDL cholesterol, mmol/l	2594	1.55(0.39)
Insulin sensitivity: ‡		
Fasting glucose, mmol/L	1002	4.39(0.45)
Fasting insulin, µIU/mL	1002	6.27(4.41)
2-h glucose, mmol/L	735	5.19(1.10)
2-h insulin, µIU/mL	735	34.3(25.5)
HOMA	1002	1.24(0.89)
SiM [‡] , 10 ⁸ ·µ ⁻¹ ·mmol ⁻¹ ·L	735	88.5(69.0)

* Number of subjects (836 MZ, 1924 DZ) with leptin data and genotype data on at least 1 SNP

‡ Non-fasting subjects, patients with either type 1 or type 2 diabetes, patients on any anti-diabetic drugs, and subjects with fasting glucose>7.8mmol/L or 2h-glucose>11.1mmol/L were all excluded.

‡ SiM was calculated according to the following formulae: SiM=(0.137*SiB+SiH2)/2, where SiB=10⁸/(fasting insulin*fasting glucose*VD); SiH2=10⁸/(2h insulin*2h glucose*VD) and VD=150ml/kg*body weight.

Table 2Association of *JAK2* tSNPs with obesity-related phenotypes and lipids profile.

<i>t</i> SNP	<i>Phenotypes</i>	<i>No.</i> 11/12/22	<i>Mean (SD)</i>			<i>Genetic</i>		<i>P</i>	
			11	12	22	<i>Model</i>	<i>Var.</i>	<i>GEE</i>	
rs7849191	Central fat, kg	851/1148/ 349	1.34(0.75)	1.30(0.70)	1.35(0.73)	Dominant	0.2%	0.030	
	Central fat, %	851/1148/ 349	31.4(11.3)	30.5(11.6)	31.8(11.7)	Dominant	0.1%	0.014	
	Waist, cm	846/ 1166/ 352	78.7(10.9)	77.9(9.6)	78.4(10.4)	Dominant	0.2%	0.027	
rs3780378	ApoA, g/l	582/ 1077/ 459	1.71(0.36)	1.70(0.35)	1.66(0.32)	Additive	0.2%	0.026	
	Total cholesterol, mmol/l	623/ 1141/ 489	5.47(1.21)	5.59(1.27)	5.64(1.27)	Additive	0.2%	0.014	
	LDL cholesterol, mmol/l	583/ 1084/ 464	3.39(1.11)	3.48(1.17)	3.55(1.16)	Additive	0.2%	0.012	
	Triglyceride, mmol/l	590/ 1094/ 472	1.21(0.70)	1.31(0.79)	1.28(0.85)	Dominant	0.3%	0.023	

Table 3

Association of *JAK2* haplotypes (freq. > 5%) with phenotypes.

<i>Haplotype</i>	<i>Freq. (SE) (%)</i>	<i>ApoA</i>			<i>Waist</i>		
		<i>β (SE)</i>	<i>P</i>	<i>Variance explained (%)</i>	<i>β (SE)</i>	<i>P</i>	<i>Variance explained (%)</i>
1. 2112112121 [*]	18.2 (0.3)	...	...	...	...	...	...
2. 1111211211	15.1 (0.3)	.08(.04)	0.042	0.19	-.48(.66)	NS	0.1
3. 1221121112	7.9 (0.3)	.09(.05)	NS	...	-.36(.84)	NS	...
4. 2112112111	7.0 (0.3)	.05(.06)	NS	...	-2.11(.88)	NS	...
5. 1111211221	5.3 (0.3)	.09(.06)	NS	...	-1.56(.97)	0.026	...
			NS [†]			NS [†]	

* The most common haplotype with which the others were compared.

[†]The P value for the overall haplotypic effects.