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ORIGINAL ARTICLE

Genome-wide linkage analysis for circulating levels of adipokines and C-reactive protein in the Quebec family study (QFS)

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Abstract Adipose tissue synthesizes and secretes a wide range of biologically active molecules considered as inflammatory markers whose dysregulation in obesity plays a role in the development of insulin resistance and vascular disorders. Thus, finding genes that influence circulating levels of inflammatory biomarkers may provide insights into the genetic determinants of obesity-related metabolic diseases. We performed linkage analyses for fasting plasma levels of adiponectin, C-reactive protein (CRP), interleukin-6 (IL-6) and tumor-necrosis factor-alpha (TNF-α) in 764 subjects enrolled in the Quebec family study (QFS). A maximum of 393 pairs of siblings from 211 nuclear families were available for analyses. A total of 443 markers spanning the 22 autosomal chromosomes with an average inter-marker distance of 6.24 Mb were genotyped. Linkage was tested using both allele-sharing (SIBPAL) and variance component linkage methods (MERLIN). We showed suggestive evidence of linkage for plasma adiponectin levels on chromosome 15q21.1 [D15S659; logarithm of the odds (LOD) score = 2.23], 3q13.33 (D3S3023; LOD = 2.09), 20q13.2 (D20S197; LOD = 1.96) and 14q32.2 (D14S1426; LOD = 1.79). Evidence of linkage (SIBPAL) was also found for CRP on 12p11.23 (P = 0.001) and 12q15 (P = 0.0005) and for IL-6 on 14q12 (P = 0.002). None of these linkages remained significant after adjustment for body mass index. No evidence of linkage was found for TNF-α plasma levels. These results suggest that several QTLs can influence plasma levels of adiponectin and CRP, partly via their effects on adiposity.

Keywords Linkage analysis · Adiponectin · C-reactive protein · Interleukin-6 · Tumor-necrosis factor-alpha

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Introduction

The concept of inflammation in relation to metabolic conditions such as obesity and insulin resistance was first proposed by Hotamisligil et al. in 1993. They demonstrated that adipocytes constitutively express the pro-inflammatory cytokine tumour necrosis factor-α (TNF-α) and that TNF-α expression in adipocytes of obese animals (ob/ob mouse, db/db mouse and fa/fa Zucker rat) was markedly increased (Hotamisligil et al. 1993). Further work in the area of obesity and insulin resistance in animals and humans has confirmed that inflammation is a key feature of obesity and type 2 diabetes mellitus (T2DM) (Wellen and Hotamisligil 2005). The fact that obesity, a major risk factor for T2DM, and T2DM itself are inflammatory conditions led to investigations exploring whether inflammatory mediators predicted the development of T2DM in humans.

Interleukin-6 (IL-6) and C-reactive protein (CRP) plasma levels were found to be positively correlated with obesity-related anthropometric variables, but negatively with insulin sensitivity (Lemieux et al. 2001; Park et al. 2005; Piché et al. 2005; Yudkin et al. 1999). In addition, results from the Atherosclerosis Risk in Communities Study (ARIC) (Duncan et al. 2003) and the Women's Health Initiative Study (Liu et al. 2007) showed that elevated plasma concentrations of IL-6 and CRP predicted T2DM development. Data on correlations between plasma levels of TNF-α and obesity or T2DM are less consistent, although adipose tissue expression of the adipokine has been reported to be increased in obesity and insulin resistance (Hotamisligil et al. 1995; Kern et al. 2001). In contrast, plasma concentrations of adiponectin were found to be lower in overweight, obese and diabetic subjects (Arita et al. 1999; Hotta et al. 2000), and low adiponectin plasma levels have been reported to predict T2DM development (Choi et al. 2004; Lindsay et al. 2002; Spranger et al. 2003).

Large inter-individual variations have been observed for adiponectin, CRP, IL-6 and TNF-α plasma levels. Genetic factors have been reported to explain part of these variations. Depending on the ethnic group and the statistical adjustment for co-variables, the additive genetic heritability was estimated to be between 39 and 70% for adiponectin levels (Chuang et al. 2004; Comuzzie et al. 2001; Guo et al. 2006; Lindsay et al. 2003; Pollin et al. 2005), 17–69% for IL-6 (de Maat et al. 2004; Dupuis et al. 2005; Grunnet et al. 2006; Pantsulaia et al. 2002), 26–68% for TNF-α (de Maat et al. 2004; Pantsulaia et al. 2002) and 30–40% for CRP (de Maat et al. 2004; Dupuis et al. 2005; Keenan et al. 2008; Lakka et al. 2006; Pankow et al. 2001).

Genome-wide linkage analyses have been performed for plasma levels of adiponectin (six studies) and CRP (four studies), but not for IL-6 and TNF-α. The first genome scan for plasma adiponectin levels measured in 1,100 adults from 170 families of Northern European ancestry (Comuzzie et al. 2001) revealed significant evidence of linkage on chromosomes 5 (LOD = 4.1, close to D5S817) and 14q12-q13.1 (LOD = 3.2, between D14S608 and D14S599) with secondary signals on chromosomes 2, 3, 10 and 17. A second study in 517 non-diabetic Pima Indians from 162 families reported a QTL for adiponectin on chromosome 9 (LOD = 3.0 between D9S168 and D9S925) with other putative loci on chromosomes 2, 3 and 10 (Lindsay et al. 2003). A third study undertaken in 1,007 siblings from 360 Chinese families and 352 siblings from 147 Japanese families reported a maximal LOD score of 3.2 on chromosome 15q21.1 in the Chinese families and a LOD score of 2.4 on chromosome 18p11.22 in the Japanese families (Chuang et al. 2004). A fourth study undertaken in 569 non-diabetic participants from the Amish Family Diabetes Study reported a QTL for adiponectin on chromosome 3q27 between markers D3S1602 and D3S1580 (LOD = 2.13; $P = 0.009$) flanking the adiponectin structural gene with other regions of suggestive linkage on chromosomes 7q11–12, 9q34, 10p12–14 and 16p13 (Pollin et al. 2005). Results from the Insulin Resistance Atherosclerosis Study Family (IRAS) revealed evidence of linkage for plasma adiponectin levels on chromosome 3q27 (LOD = 5.8 between markers D3S2418 and MFD427 outside the adiponectin gene locus) and on chromosome 2q33.3 (LOD = 1.8 between D2S1384 and D2S2944) with other suggestive evidence of linkage on chromosomes 10, 12 and 16 (Guo et al. 2006). Finally, a sixth study undertaken in populations of African descent revealed evidence of linkage on chromosomes 2, 4 and 11 (Hicks et al. 2007).

The first genome-wide scan for plasma CRP was performed in the Framingham Heart Study (Dupuis et al. 2005) and revealed a QTL on chromosome 14q31.1 LOD = 1.7 near marker D14S610). A second study based on data from the HERITAGE Family Study (Lakka et al. 2006) reported evidence of linkage for plasma CRP levels on chromosomes 20q13 ($2.07 < \text{LOD} < 2.87$) and 5p13 (D5S1470, LOD = 2.23). In a third study, results from two independent Caucasian populations revealed a QTL for CRP levels on chromosome 10 (at 141 cM) with LOD scores of 3.2 and 2.7 (Broeckel et al. 2007) with other putative QTLs on chromosomes 5 (at 150 cM), 2 (10 cM) and 16 (at 30 cM). Finally, evidence of linkage on chromosome 5p15 (LOD = 3.41) was found in a fourth study (Keenan et al. 2008).

The exploration of genetic pathways regulating plasma levels of inflammatory markers is important in terms of expanding our knowledge about obesity and T2DM pathophysiology. We thus performed a genome-wide linkage scan for plasma levels of adiponectin, CRP, IL-6 and TNF-α measured in subjects participating in the Quebec Family Study (QFS).

Methods

Subjects

The Quebec Family Study (QFS) cohort is composed of nuclear families of French Canadian descent from the greater Quebec City area (Bouchard 1994). Briefly, QFS was initiated in 1978. In the first phase of QFS (1979–1981), families were randomly ascertained from the population at large, and 1,628 subjects from 373 families agreed to participate. In the second phase (1989–1997), about 100 families from phase I were re-measured, and obese families with a minimum of one obese subject ($\geq$30 kg/m^2) were recruited and incorporated in the cohort.

In the third phase, members of the phase II cohort were re-measured, and other obese families were recruited. In the present study, the subjects were participants from phases II and III. Written consent was obtained from all participants, and the Medical Ethics Committee of Laval University approved all procedures.

Phenotypes

Fasting plasma levels of adiponectin, CRP, IL-6 and TNF-α were available for 764 subjects (393 sib-pairs) from 211 nuclear families. The subjects with hs-CRP plasma levels ≥10 mg/l were excluded from all analyses because such elevated hs-CRP levels suggest a major infection or trauma (Ridker et al. 2004). Fasting plasma levels of the inflammatory markers were log10 transformed and adjusted initially for age and sex, and then for age, sex and body mass index (BMI). Fasting plasma adiponectin, TNF-α and IL-6 concentrations were determined by high-sensitivity enzyme-linked immunosorbant assay (ELISA) using a commercial kit (B-Bridge International, Inc., San Jose, CA, and R&D Systems Inc., Minneapolis, MN). Fasting plasma hs-CRP levels were measured using the Behring latex-enhanced high-sensitivity assay on a Behring BN-100 nephelometer (Dade Behring) according to the methods described by the manufacturer (Ledue et al. 1998). Concentrations of all adipokines were assessed from frozen plasma samples (−80°C).

Genotyping

A total of 443 markers spanning the 22 autosomal chromosomes with an average inter-marker distance of 6.24 Mb were genotyped as described previously (Chagnon et al. 2000). These marker included 337 microsatellite markers (dinucleotide, trinucleotide and tetranucleotide repeats) and 106 polymorphisms in 65 candidate genes. The results were stored in a local dBase IV database, GENEMARK, and Mendelian inheritance incompatibilities within nuclear families and extended pedigrees were verified using the Pedcheck software (O'Connell and Weeks 1998).

Linkage analysis

Maximum heritability was estimated using the variance components method as implemented in the QTDT programme of MERLIN (Abecasis et al. 2000). Total phenotypic variance was broken into genetic, environmental and residual variance, and the maximum heritability was calculated as the proportion of the total variance explained by the genetic component. We conducted quantitative trait linkage analysis using the Haseman–Elston regression-based method (Elston et al. 2000), and both singlepoint and multipoint linkage analyses were performed with the sib-pair linkage procedure as implemented in the SIBPAL software from the Statistical Analysis for Genetic Epidemiology (SAGE 5.11) (SAGE 2002). Briefly, if there is a linkage between a marker locus and a putative gene influencing a phenotype, sibs sharing a greater proportion of alleles identical-by-descent (IBD) at the marker locus will also exhibit a greater resemblance in the phenotype. Phenotypic resemblance of the sibs, modelled as a weighted combination of squared trait difference and squared mean-corrected trait sum is linearly regressed on the estimated proportion of alleles that the sib-pair shares IBD at each marker locus. Both singlepoint and multipoint estimates of alleles sharing IBD were generated using the GENIBD programme of SAGE. Empirical *P* values were derived from a maximum of 500,000 permutations. For each replicate, the allele sharing among the sibling pairs was permutated, the test statistic was recalculated, and the proportion of the replicate that is equal to or greater than the statistic calculated from the original observations was determined. Due to the multiple statistical tests performed in a genome-wide linkage scan, the traditional alpha level of 0.05 would be too liberal. Therefore, we used a LOD score of ≥3.0 (P value ≤ 0.0001) to indicate adequate evidence of linkage and a LOD threshold of ≥1.75 (P value ≤ 0.0023) as suggestive (Rao and Province 2000).

The multipoint linkage analyses were also performed by variance component (VC) linkage with the MERLIN programme (Abecasis et al. 2002). VC analysis partitions the variance into components attributable to an additive major gene, an additive polygenic effect and non-shared environmental effects at genomic positions where multipoint IBD sharing has been estimated. MERLIN calculates exact IBD sharing probabilities using the Lander–Green algorithm with sparse gene flow tress and can handle pedigrees up to about 20 individuals for multipoint analysis.

Results

The characteristics of the subjects in the four sex-by-generation groups (fathers, mothers, sons and daughters) are reported in Table 1. The maximum heritabilities reached 61.5% for adiponectin, 20.82% for CRP, 13.7% for IL-6 and 28.4% for TNF-α.

A summary of linkage results is presented in Table 2. We showed suggestive evidence of linkage for plasma adiponectin levels on chromosomes 15q21.1 (D15S659; LOD = 2.23), 3q13.33 (D3S3023; LOD = 2.09), 20q13.2 (D20S197; LOD = 1.96) and 14q32.2 (D14S1426; LOD = 1.79). Evidence of linkage based on the sibpair linkage

Table 1 Characteristics of participants by gender and generation groups

	Fathers (n = 157)	Mothers (n = 194)	Sons (n = 185)	Daughters (n = 227)
Age (years)	55.24 ± 9.29	52.84 ± 9.39	27.82 ± 10.27	28.84 ± 10.26
BMI (kg/m^2)	28.94 ± 6.08	28.80 ± 7.77	26.75 ± 7.06	26.49 ± 7.04
Waist circumference (cm)	99.39 ± 14.49	87.85 ± 17.26	89.85 ± 18.05	80.75 ± 15.71
Adiponectin (μg/ml)	5.38 ± 2.78	7.43 ± 4.00	5.34 ± 2.26	6.45 ± 2.75
CRP (mg/ml)	2.23 ± 2.08	3.02 ± 2.64	1.39 ± 1.88	2.21 ± 2.44
IL-6 (pg/ml)	1.98 ± 1.16	1.76 ± 0.72	1.75 ± 0.67	1.68 ± 0.73
TNF-α (pg/ml)	2.42 ± 3.00	3.75 ± 14.45	1.47 ± 1.08	3.52 ± 21.86

Data are presented as mean ± SD

Table 2 Summary of empirical P values ≤0.01 from the multipoint allele-sharing method (SIBPAL) or LOD scores ≥1.75 for the variance component linkage (MERLIN)

Phenotype	Chromosome	Distance (Mb)	Marker[a]	Multipoint P value	LOD score (VC)
Adiponectin	1p36.3	3.5	D1S468	**0.0021997**	0.21
	3q13.12	111.3	D3S3045	0.0034996	1.43
	3q13.33	124.5	**D3S3023**	**0.0021997**	**2.09**
	6q16.3	116.6	D6S1021	**0.0005999**	0.69
	9q31.3	100.2	D9S1835	**0.0002999**	0.76
	9q34.3	127.4	D9S158	**0.0005999**	0.28
	14q32.12	86.0	D14S617	0.0028997	1.45
	14q32.2	94.4	**D14S1426**	**0.0007999**	**1.79**
	15q21.1	44.1	**D15S659**	**0.0010998**	**2.23**
	20q13.2	45.9	D20S197	0.0644699	**1.96**
CRP	12p11.23	27.7	D12S1042	**0.0009999**	1.22
	12q15	68.7	D12S375	**0.0004999**	1.62
IL-6	5q32	145.8	D5S436	0.0045995	0.91
	5q33.1	150.6	D5S640	0.0053994	1.24
	11p13	35.3	D11S1392	0.0033996	0.12
	14q12	20.4	D14S1280	**0.0021997**	0.18
	17q11.2	30.3	D17S1294	0.0067993	0.39
TNF-α	3p24.1	32.8	D3S2432	0.0097829	0.96

P values ≤0.01 from the multipoint allele-sharing method or LOD scores ≥1.75 for the variance component linkage are shown in boldface

[a] Markers showing promising evidence of linkage with the two linkage methods used are shown in boldface (P values of ≤0.0023 from the multipoint allele-sharing method and LOD scores ≥1.75 for the variance component linkage)

method was also found for CRP plasma levels on chromosomes 12p11.23 (D12S1042, P = 0.001) and 12q15 (D12S375, P = 0.0005) and for IL-6 on chromosome 14q12 (D14S1280, P = 0.002). After adjustment for BMI, none of the linkages described above remained significant. No evidence of linkage was found for plasma levels of TNF-α.

Discussion

The identification of genes influencing circulating levels of key inflammatory markers is important to increase our understanding of the genetic determinants of obesity-related metabolic diseases. In the present study, we performed a genome-wide linkage analysis of plasma levels of adiponectin, CRP, IL-6 and TNF-α measured from the same plasma sample in subjects from the Quebec Family Study. The strongest evidence of linkage was found for adiponectin levels on chromosomes 15q21.1, 3q13.33, 20q13.2 and 14q32.2. Weaker evidence of linkage was found for CRP on chromosomes 12p11.23 and 12q15 and for IL-6 on 14q12. After adjustment for BMI, in addition to age and sex, these linkages became non-significant, suggesting that the effects of these loci on the circulating levels of these inflammatory markers are mediated by adiposity.

Linkage analyses of adiponectin levels have been performed previously in several populations, but the results varied across different ethnic groups, perhaps indicating genetic heterogeneity in the determination of plasma concentrations of adiponectin. In the present study, the peak linkage (LOD = 2.23) was found for adiponectin on chromosome 15q21.1 (marker D15S659). To the best of our knowledge, only one study reported evidence of linkage for adiponectin on 15q21.1 (near marker GATA63A03, or D15S659), and it was in a Chinese population (Chuang et al. 2004). Adiponectin, a protein secreted by the adipose tissue, has been shown to play a role in adipogenesis and in

the pathogenesis of the metabolic syndrome (Lara-Castro et al. 2007). Interestingly, a recent genome-wide linkage analysis derived from factor analysis of eight metabolic syndrome-related phenotypes assessed in subjects from QFS revealed that the first factor, loading on all phenotypes of the metabolic syndrome, was linked to a QTL (LOD = 3.1; marker D15S171) located on chromosome 15q25 (Bosse et al. 2007). This region of chromosome 15q has previously been shown to be linked to obesity-related phenotypes such as age at adiposity rebound, (Meyre et al. 2004), BMI (Feitosa et al. 2002) and plasma levels of acylation-stimulating protein (ASP), which, like adiponectin, is an adipose-derived protein influencing lipid metabolism, obesity and glucose level (Cianflone et al. 2003). This suggests that this region of chromosome 15q may harbour genes with pleiotropic effects on several traits associated with the metabolic syndrome. An interesting potential candidate gene for the linkage with adiponectin on 15q21.1 is the cytochrome P450, family 19, subfamily A, polypeptide 1 gene (CYP19A1), which is located about 5 cM from the peak linkage. CYP19A1 encodes the aromatase, which catalyses the conversion of androgens to oestrogens. Variations in the CYP19A1 have been reported to contribute to female syndromes of androgen excess, such as polycystic ovarian syndrome (PCOS) (Petry et al. 2005). Women with PCOS exhibit an adverse cardiovascular risk profile characteristic of the metabolic syndrome (Cho et al. 2007), such as hypoadiponectinemia (Sieminska et al. 2004), supporting a role of CYP19A1 in adiponectin plasma levels.

We also found evidence of linkage for adiponectin on 3q13.33 (LOD = 2.09 at 124.5 Mb) in a region located outside the structural gene for adiponectin (APM1), which is located on 3q27 (188.0 Mb). Strong evidence of linkage (LOD = 5.25) for adiponectin on 3q27 near the APM1 gene has been reported in Hispanic-Americans (Guo et al. 2006), while suggestive evidence of linkage was also reported in Hispanic children (Tejero et al. 2007), Pima Indians (Lindsay et al. 2003) and Amish (Pollin et al. 2005). These findings suggest that variations in APM1 may be an important determinant of circulating adiponectin levels in some populations, but not others. In our study, it is unlikely that APM1 accounts for our linkage on 3q13.33 as it lies at approximately 64 Mb cM from the marker D3S3023. A potential candidate gene for the QTL on 3q13.33 could be the glycogen synthase kinase-3 (GSK-3), located at 1.08 cM from the linkage peak. GSK-3 is the rate-limiting enzyme in glycogen synthase and has been shown to be implicated in both insulin action and adipogenesis in human. Furthermore, it has been demonstrated that GSK-3 can regulate PPAR-γ, a master gene required for adipogenesis (Farmer 2005), and which regulates target genes involved in energy homeostasis, glucose and lipid metabolism (Guo and Tabrizchi 2006, for a review). The QTL for adiponectin found on chromosome 20q13.2 (LOD = 1.96) lies in a region that previously showed linkage with obesity-related phenotypes in both human and animal studies (Lee et al. 1999; Lembertas et al. 1997). Recently, a bivariate genome-wide linkage analysis for phenotypes related to the metabolic syndrome revealed the presence of a QTL in this region of chromosome 20 (20q13) for most of the pairs of traits included in the metabolic syndrome (Chiu et al. 2007). An interesting potential candidate gene, located exactly at the marker locus, is the nuclear receptor co-activator 3 (NCOA3), or oncogenic steroid receptor coactivator 3 (SRC3). SRC3 is known to play an important role in many biological processes and has been reported to be a critical regulator of adipocyte development (Louet et al. 2006). A potential candidate gene for our last adiponectin QTL on chromosome 14q32 is the preadipocyte factor 1 (PREF1), encoded in humans by the gene DLK1, which is located at 0.58 cM from the peak linkage. PREF1 is a regulator of adipocyte differentiation and inhibits adipogenesis in vivo (Wang et al. 2006).

Our linkage analysis also revealed the presence of two QTLs for CRP on chromosomes 12p11.23 and 12q15 and one QTL for IL-6 on 14q12. The 12q15 and 14q12 regions harbour genes involved in asthma susceptibility (interleukin-1 receptor-associated kinase 3 and chymase 1), an inflammatory condition that has been associated with circulating CRP and IL-6 (Arif et al. 2007; Butland et al. 2008; Yokoyama et al. 1997). Interestingly, asthma and obesity are common conditions that are strongly associated, and this association has been found to be caused by shared genetic factors (Hallstrand et al. 2005), reinforcing the role of inflammation in obesity.

The fact that the linkages reported in the present study were no longer significant when analyses were repeated on data adjusted for BMI in addition to age and sex suggests that the effects of the underlying genes on circulating levels of inflammatory markers are mediated by adiposity. However, we cannot conclude that the adiponectin QTLs identified in our study are necessarily linked to obesity. Indeed, adiponectin levels are correlated to adiposity, and it has been shown that the two traits are also genetically correlated (Comuzzie et al. 2007), which indicates that their covariance could be partly attributable to common genetic factors, i.e., genetic pleiotropy. The presence of a genetic correlation between the two traits implies that by doing an adjustment for BMI, we remove some of the genetic variance in adiponectin levels, which therefore reduces the power to detect QTLs. This is probably one of the main factors explaining why our linkages become non-significant after adjustment for BMI.

In summary, we conducted linkage analyses for fasting plasma levels of adiponectin, CRP, IL-6 and TNF-α. We found no evidence of linkage for TNF-α and marginal evidence of linkage for CRP (12p11.23, 12q15) and IL-6 (14q12). We identified novel chromosomal regions linked with circulating adiponectin levels on chromosome 3q13.33, 11p13, 14q32.2, 15q21.1 and 20q13.2. The linkage on chromosome 15q21.1 replicates findings in a Chinese population. The QTLs identified for adiponectin suggest, for the majority, the implication of genes involved in adipogenesis. Further fine mapping of the QTLs identified in the present study will allow the identification of genetic polymorphisms that influence plasma levels of key inflammatory markers involved in the pathogenesis of obesity-related diseases.

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