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Sex-Specific and Sex-Independent Quantitative Trait Loci for Facets of the Metabolic Syndrome in WOKW Rats

Ingrid Klöting,[1] Peter Kovács, and Jens van den Brandt
Department of Laboratory Animal Science, Medical Faculty, University Greifswald, 17495 Karlsburg, Germany

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WOKW rats develop a complete metabolic syndrome closely resembling human disease. Since genetic studies using male (WOKW × DA)F2 progeny showed that several independent genetic factors were involved, a polygenic basis for the syndrome in WOKW was assumed. However, because the metabolic syndrome in human clearly demonstrates sex differences, we have extended our study to include both male and female (WOKW × DA)F2 progeny in a genome-wide scan. Male- or female-specific quantitative trait loci (QTLs) were mapped for body weight, body mass index, adiposity index and serum insulin on chromosomes 1 and 5, serum triglycerides on chromosomes 4, 7, 11, and 16, serum total and high density lipoprotein cholesterol on chromosomes 3, 4, 5, 10, and 17, and serum leptin on chromosomes 8 and 16 as well as blood glucose and glucose tolerance (AUC) on chromosomes 3, 4 and 17. QTLs for both, males and females were only found for body weight on chromosome 1 and for serum total cholesterol on chromosome 3 and 10. These findings clearly demonstrate that there are sex-specific and sex-independent QTLs for facets of the metabolic syndrome in WOKW rats. **© 2001 Academic Press**

Key Words: **genetics; chromosome; serum lipids; serum leptin; body weight.**

The metabolic syndrome involves a set of symptoms ranging from obesity, glucose intolerance, hyperinsulinemia and insulin resistance to dyslipidemia and hypertension (1). Much of our understanding of the etiopathogenesis of facets of the metabolic syndrome comes from studies using animal models. Most experimental studies have been carried out with models which develop either genetically determined obesity, hypertension or dyslipidemia (2–5). Studies with animal models developing a complete metabolic syndrome are rarely described. Recent studies, comparing several disease-prone and disease-resistant rat strains showed that the W(istar) O(ttaw) K(arlsburg)W (RT1^u) rat strain develops a nearly complete metabolic syndrome with obesity, moderate hypertension, dyslipidemia, hyperinsulinemia, and impaired glucose tolerance (6, 7). In addition, initial genetic studies to dissect the metabolic syndrome in the WOKW rat clearly demonstrated that several independent genetic factors influence quantitative traits of the syndrome (8). We conclude that the metabolic syndrome in WOKW rats is under polygenic control. However, the study was carried out only with male (WOKW × DA)F2 progeny. Because facets of the metabolic syndrome clearly show sex differences in human (1, 9) we extended the genetic analysis of the metabolic syndrome in WOKW rats to include female as well as male (WOKW × DA)F2 progeny. Therefore, female hybrids derived from the same cross of WOKW and DA rats were analysed for quantitative trait loci (QTLs) and compared with findings of male F2 hybrids to determine whether facets of metabolic syndrome might be sex specific.

MATERIALS AND METHODS

Experimental animals. Male and female WOKW were reciprocally crossed with DA/K (Dark Agouti/Karlsburg) rats (designated DA) to produce (WOKW × DA)F1 and (DA × WOKW)F1 hybrids, which were further intercrossed to generate F2 hybrid populations as described (8). No phenotypic differences were found between the two reciprocal F2 crosses for the traits studied. Therefore, 140 female F2 hybrids were analysed together and compared with findings of 150 male F2 hybrids (8). All hybrids were kept in the same animal unit under same environmental conditions as previously described (10).

Phenotypic characterisation. Female hybrids were characterised as previously described for the males (8). Briefly, blood samples were obtained from 12 WOKW and 12 DA females as well as from 72 (WOKW × DA)F2 and 68 (DA × WOKW)F2 female progeny postprandialy three times by puncturing the ophthalmic venous plexus at 28, 30, and 32 weeks of age. The average of the three values for all measured parameters (28, 30, 32 weeks) was used for the linkage analysis. Serum triglycerides, HDL-cholesterol and total cholesterol were analysed using an automatic analyser (Roche Cobas Mira Plus, Roche, Switzerland). Serum leptin and insulin were determined using radio-immunoassay kits (Rat Insulin RIA Kit and Rat Leptin RIA Kit, Linco Research Inc., St. Charles, MO). Glucose tolerance was determined after i.p. glucose load of 2 g/kg body weight. Blood was

[1] To whom correspondence should be addressed. Fax: +49 3834 86 19 111. E-mail: kloeting@uni-greifswald.de.

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TABLE 1

Phenotypic Characteristics of Female WOKW and DA Rats as Well as Female and Male (WOKW × DA)F2 Hybrids

Phenotypic trait	Strain: Females (F)		(WOKW × DA)F2 hybrids		*P* values			
			Females (F)	Males (M)	Females			
	WOKW (n = 12)	DA (n = 12)	(n = 140)	(n = 150)	WOKW vs DA	WOKW vs F2	DA vs F2	F2 M vs F
Body weight (30 weeks) (g)	255 ± 9	199 ± 6	236 ± 19	414 ± 43	<0.0001	0.008	<0.0001	<0.0001
BMI (g/cm^2)	0.62 ± 0.02	0.51 ± 0.02	0.57 ± 0.03	0.76 ± 0.05	<0.0001	<0.0001	<0.0001	<0.0001
Adiposity index (%)	1.5 ± 0.31	0.6 ± 0.13	1.2 ± 0.38	2.0 ± 0.53	<0.0001	0.009	<0.0001	<0.0001
Serum triglycerides (mmol/l)	3.3 ± 0.5	0.5 ± 0.1	1.5 ± 0.7	1.9 ± 0.7	<0.0001	<0.0001	<0.0001	<0.0001
HDL-cholesterol (mmol/l)	1.5 ± 0.2	2.3 ± 0.4	2.6 ± 0.5	2.4 ± 0.4	<0.0001	<0.0001	0.05	0.014
Total cholesterol (mmol/l)	2.2 ± 0.2	3.0 ± 0.2	3.2 ± 0.7	3.2 ± 0.7	<0.0001	<0.0001	n.s.	n.s.
Serum leptin (ng/ml)	3.6 ± 0.6	1.8 ± 0.4	3.8 ± 1.6	10.8 ± 6.5	<0.0001	n.s.	<0.0001	<0.0001
Serum insulin (ng/ml)	2.2 ± 0.4	1.2 ± 0.5	1.7 ± 0.8	3.0 ± 1.2	<0.0001	0.03	0.03	<0.0001
Blood glucose (mg/dl)	91 ± 4	105 ± 7	97 ± 10	97 ± 8	<0.0001	0.04	0.008	n.s.
AUC (mmol × min)	612 ± 94	475 ± 90	607 ± 111	659 ± 89	0.001	n.s.	<0.0001	<0.0001

taken by tail vein incision at 0 (baseline), 10, 30, and 60 min after glucose load. Blood glucose was determined with a glucose analyser (Medingen ESAT 6660-2, Germany). The body weight of rats was determined at an age of 28, 30, and 32 weeks. Moreover, at 32 weeks the body length of animals was measured for calculating the body mass index (BMI). Rats were killed at 32 weeks by pentobarbital injection and left and right inquinal adipose pads were removed and weighed. The sum of adipose pads to body weight multiplied by 100 gave the adiposity index. Liver was dissected and used for isolation of high molecular DNA (Genomix Kit, Talent srl, Italy).

Genetic markers and genotyping. 126 microsatellite markers were used in a whole genome screen of F2 hybrids. Amplification programs and the PCR reactions were performed as described previously (11).

Data analysis. Quantitative trait differences were assessed by two-tailed Student's test. The genetic linkage maps and the location of QTLs affecting quantitative traits were determined with the MAPMAKER (EXP 3.0b and QTL 1.1b) computer package (Whitehead Institute, Cambridge, MA) (12). Significant linkage was defined by the threshold of lod score (lod, likelihood of odds) ≥4.3. For suggestive linkage the threshold of lod score 2.8 was taken. In addition, cosegregation of phenotypes with alleles at marker loci was evaluated by comparing the values between different genotypes by one-way ANOVA using the SPSS computer program (SPSS Inc., Chicago, IL).

RESULTS

As shown in Table 1, female WOKW and DA rats differed significantly in all quantitative traits studied. Except HDL- and total cholesterol, higher values were mainly observed in WOKW females. Comparing the trait values between female WOKW, DA rats and in female (WOKW × DA)F2 hybrids, most traits showed values intermediate between those of WOKW and DA females. Dominant effect of WOKW was only seen in serum leptin and glucose tolerance (AUC) whereas DA dominance was found in HDL- and total cholesterol. As also demonstrated in Table 1, sex differences were found in 8 out of 10 traits studied in (WOKW × DA)F2 hybrids. Because of the study's aim, cosegregation analysis was carried out in female (WOKW × DA)F2 hybrids. The findings in females were compared with those of male F2 hybrids. As shown in Table 2, significant and suggestive linkage was found in (WOKW × DA)F2 females for body weight (chromosome 1), serum triglycerides (chromosomes 7, 11, 16), total cholesterol (chromosomes 3, 4, 10), fasting blood glucose (chromosome 4) and serum leptin (chromosome 16). No linkage was observed in F2 females on any chromosome for BMI, adiposity index, serum HDL-cholesterol, serum insulin and glucose tolerance (AUC).

Figure 1 shows the scans for lod scores for the placement of loci on chromosome 1 affecting body weight in females and males at an age of 30 weeks. Suggestive linkage was observed on chromosome 1 between markers *D1Mgh2* and *D1Mit9* with a maximum lod score of 4.19 in females. The body weight of male F2 hybrids showed also suggestive linkage at locus *D1Mgh2* (lod score 3.75), but significant linkage was found at the distal end of chromosome 1 between markers *Pbpc2* and *D1Mgh12* (lod score 4.49) where females did not show linkage.

Comparison of the body weight of females of genotypes WW, WD and DD suggests an intermediary inheritance. As demonstrated in Fig. 2, serum triglycerides showed significant and suggestive linkage to a region on chromosomes 7, 11, and 16 in female, but not in male F2 hybrids. Significant linkage was found on chromosome 16 spanning a large region of about 33 cM. The log likelihood surface reached its peak between *D16Wox7* and *D9Mgh1*with a maximum lod score of 5.00. In addition, suggestive linkage was found for serum triglycerides between *D7Mit2* and *D7Mgh4* (lod score 3.45) as well as between *D7Mgh6* and *D7Mgh7* (lod score 3.23) on chromosome 7 and between *Smst* and *D11Wox6* on chromosome 11 (lod score 3.06). Regarding inheritance, intermediary behaviour was ob-

TABLE 2

Cosegregation Analysis Results in Female and Male (WOKW × DA)F2 Rats

Chromosome	Marker	Sex	Genotype WW	Genotype WD	Genotype DD	Lod score	*P* (one-way ANOVA)
			Body weight 30 weeks (g)				
1	*D1Mit9*	F	245 ± 19 (37)	236 ± 19 (70)	226 ± 16 (33)	3.79	<0.0001
	D1Mgh2	M	434 ± 43 (40)	413 ± 42 (78)	393 ± 33 (32)	3.75	<0.0001
			Serum triglycerides (mmol/l)				
7	*D7Mit2*	F	1.77 ± 0.68 (34)	1.57 ± 0.64 (78)	1.14 ± 0.43 (28)	3.45	<0.0001
11	*D11Wox6*	F	1.43 ± 0.67 (30)	1.69 ± 0.67 (72)	1.30 ± 0.50 (38)	2.96	0.006
16	*D16Mit4*	F	1.91 ± 0.71 (35)	1.50 ± 0.57 (68)	1.24 ± 0.55 (37)	4.63	<0.0001
			Serum cholesterol (mmol/l)				
3	*D3Mit10*	F	2.86 ± 0.50 (30)	3.15 ± 0.68 (73)	3.57 ± 0.65 (37)	4.29	<0.0001
		M	3.13 ± 0.66 (45)	3.19 ± 0.65 (70)	3.48 ± 0.57 (35)	1.54	0.034
		M/F	3.02 ± 0.61 (75)	3.17 ± 0.67 (143)	3.53 ± 0.61 (72)	5.25	<0.0001
4	*Npy*	F	3.28 ± 0.65 (39)	3.34 ± 0.69 (70)	2.79 ± 0.55 (31)	3.50	<0.0001
		M	3.29 ± 0.75 (38)	3.24 ± 0.69 (71)	3.20 ± 0.55 (31)	0.08	n.s.
		M/F	3.28 ± 0.69 (77)	3.29 ± 0.63 (151)	3.00 ± 0.65 (62)	2.11	0.008
10	*D10Mit4*	F	3.25 ± 0.68 (35)	3.35 ± 0.66 (70)	2.85 ± 0.62 (35)	2.89	0.001
	D10Mgh7	M	3.48 ± 0.67 (45)	3.22 ± 0.66 (66)	3.01 ± 0.52 (39)	2.49	0.004
	Aep	M/F	3.44 ± 0.69 (68)	3.22 ± 0.56 (159)	3.00 ± 0.56 (63)	3.35	<0.0001
			Fasting blood glucose (mg/dl)				
4	*D4Mgh14*	F	76 ± 7 (33)	70 ± 7 (81)	72 ± 8 (26)	3.28	0.001
		M	74 ± 8 (41)	74 ± 8 (76)	73 ± 8 (33)	0.17	n.s.
		M/F	75 ± 8 (74)	72 ± 8 (157)	73 ± 8 (59)	1.26	n.s.
			Serum leptin (ng/ml)				
16	*D16Mgh3*	F	4.59 ± 1.63 (33)	3.71 ± 1.42 (71)	3.14 ± 1.47 (36)	3.49	<0.0001

Note. Values are means ± SD; number of rats is given in parentheses. W, allele of the WOKW rat; D, allele of the DA rat.

served for triglycerides on chromosomes 7, 11, and 16 (cf. Table 2). Although no sex differences were observed in serum total cholesterol, there was suggestive linkage in females on chromosomes 3, 4, and 10 as demonstrated in Fig. 3. On chromosomes 3 and 10 only females but not males showed linkage, an additive effect of females and males was seen in total serum cholesterol with a maximum lod score of 5.25 around the marker *D3Mit10* on chromosome 3 and of 4.99 on chromosome 10 in a region of about 25 cM flanked by *Aep* and *D10Mgh7*. On chromosome 4 suggestive linkage was only found in female F2 hybrids around the *Npy* locus (lod score 3.50) and between *D4Mgh17* and *D4Mgh6* (lod score 3.35). Comparing pheno- and genotypes, we see intermediary inheritance for total cholesterol on chromosomes 3 and 10 whereas the comparable cholesterol values at the *Npy* locus for WOKW homozygotes (WW) and WOKW-DA heterozygotes (WD) on chromosome 4 suggest dominant inheritance of WOKW (cf. Table 2).

Although there were no sex differences in fasting and non-fasting blood glucose, suggestive linkage was found in F2 females, but not in males on chromosome 4 with a peak at locus *D4Mgh14* (lod score 3.28) (Fig. 4). In addition, suggestive linkage was observed for serum leptin on chromosome 16 between *D16Mgh3* and *D16Mit4* (lod score 3.91) in female, but not in male F2 hybrids (Fig. 4). In this case we see a dominant effect of DA for fasting blood glucose on chromosome 4 and there is intermediary inheritance for serum leptin on chromosome 16 (cf. Table 2).

DISCUSSION

It is well-recognised that the metabolic syndrome including obesity, glucose intolerance, hyperinsulinemia and insulin resistance, dyslipidemia and hypertension has a major genetic component (1, 9). However, the search for candidate genes has been very difficult since each facet of the syndrome is complex, heterogeneous, and multifactorial resulting both from genetic susceptibility and environmental risk factors. Therefore, the availability of inbred animal models closely

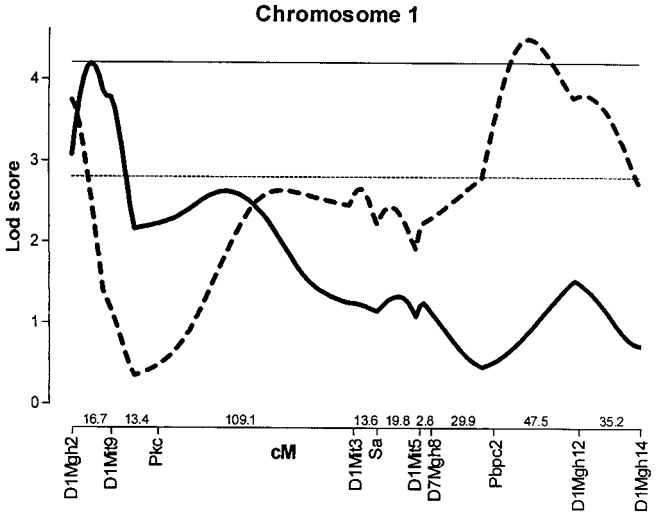

FIG. 1. Scans for lod scores for the placement of loci affecting body weight at an age of 30 weeks in female (—) and male (– –) F2 hybrids. Lod score plots were computed by MAPMAKER/QTL program. Distances between markers are in cM (centiMorgans). The horizontal lines represent the threshold for significant (—) or suggestive (- - -) linkage.

resembling the human disease will be an essential component of genetic investigations in this field. Animal models are mostly genetically homozygous and it is possible to direct mating for optimal crosses and to control environmental factors. Despite this advantage our findings suggest that each facet of the metabolic syndrome in inbred WOKW rat kept in a controlled environment is complex. Significant and suggestive linkage was found for several traits of the metabolic syndrome which differ not only in genetic localisation but also between sexes. The results of male and female (WOKW × DA)F2 hybrids are summarised in Table 3. QTLs were mapped with sex specificity for body weight, BMI, adiposity index and serum insulin on chromosomes 1 and 5, serum triglycerides on chromosomes 4, 7, 11, and 16, total and HDL-cholesterol on chromosomes 3, 4, 5, 10, and 17, serum leptin on chromosomes 8 and 16 as well as blood glucose and glucose tolerance (AUC) on chromosomes 3, 4 and 17. These QTLs were designated as Q1MS1, Q1MS2,Q3MS1 etc. whereby Q means QTL, followed by chromosome number, disease M(etabolic) S(yndrome) and locus numbered as described in Table 3.

There was only one QTL for body weight at an age of 30 weeks which showed suggestive linkage on chromosome 1 in both, males and females. However, significant linkage for body weight was found in males, though not in females, more than 150 cM distant from the region on chromosome 1. This finding suggest that there are different QTLs on chromosome 1 of the WOKW rat affecting body weight in females and/or males. This is consistent with previously published data suggesting a male specific QTL which was confirmed by use of congenic BB.SHR rats (13, 14). Sex specificity was also demonstrated for serum triglycerides. Significant linkage was found on chromosome 16 and suggestive linkage on chromosomes 7 and 11 in females. In male F2 hybrids significant linkage was seen only for serum triglycerides on chromosome 4 between *Il6* and *D4Mit4*, a region in which suggestive linkage was found for fasting blood glucose in F2 females. In contrast to the QTL for the serum triglycerides in male (WOKW × DA)F2 hybrids which was confirmed in another cross (15), the sex-specific QTLs

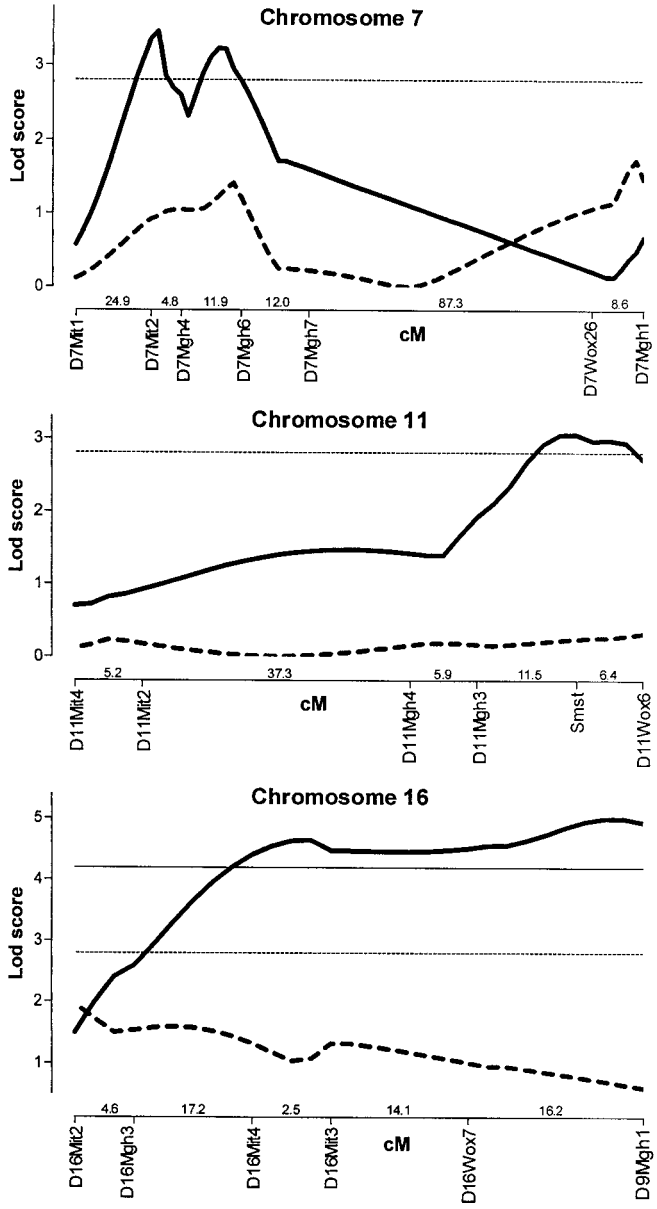

FIG. 2. Scans for lod scores for the placement of loci affecting serum triglycerides in female (—) and male (– –)F2 hybrids. See Fig. 1.

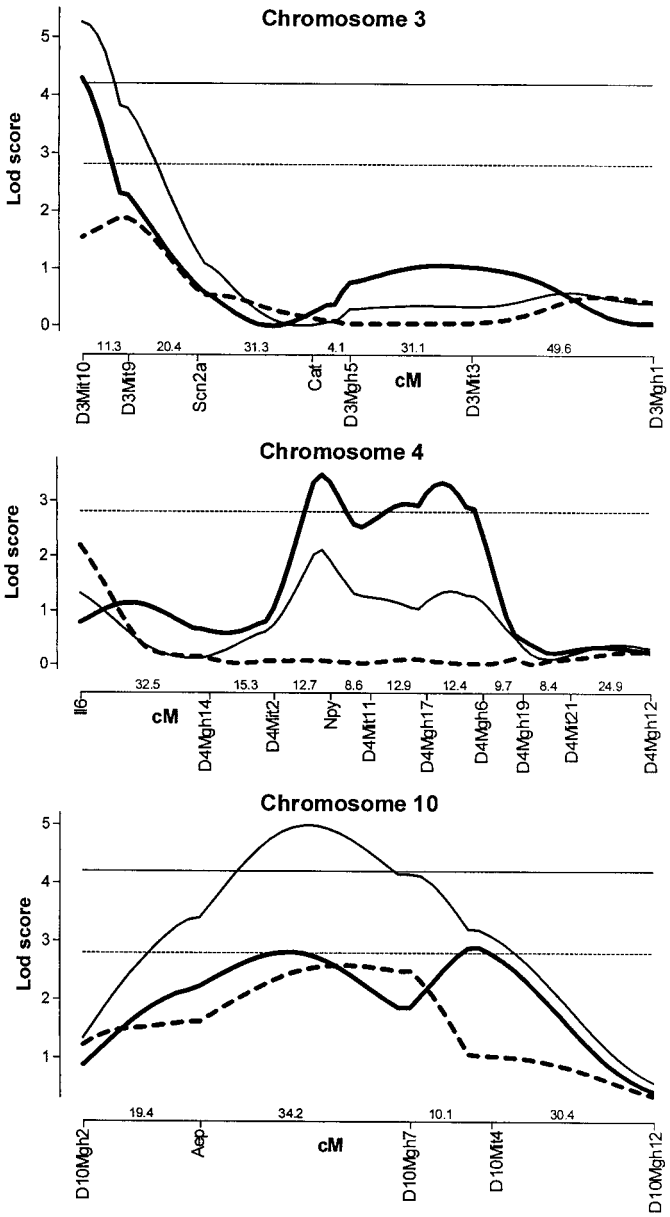

FIG. 3. Scans for lod scores for the placement of loci affecting serum total cholesterol in female (—), male (– –) and both, male and female (—) F2 hybrids. See Fig. 1.

for triglycerides on chromosomes 7, 11, and 16 in females new. The fact that sex-specific QTLs are rarely described is usually attributed to the analysis of male cross-hybrids only or—where males and females are studied together—sex differences may be obscured by statistical correction on pooled data. Studies in which QTLs are mapped using male and female cross-hybrids separately are the exception until now (16–18).

Although sex-specific QTLs for traits with well-known sex differences like body weight, serum triglycerides or leptin are imaginable, location differences between males and females in traits without sex differences seem inexplicable. In our study the serum total cholesterol values were comparable between male and female F2 hybrids. Nevertheless suggestive linkage for total cholesterol was found in females, but not in males on chromosomes 3, 4 and 10. Analysing male and female F2 hybrids together the cholesterol QTLs on chromosomes 3 and 10 were confirmed at a significant level by additive effects and the putative QTL on chromosome 4 was confirmed as sex-specific. Had we only analysed male F2 hybrids as done before (8) these QTLs for serum cholesterol and most others described in our study would not have been detected.

Our findings clearly illustrate that both sex-specific and sex-independent QTLs contribute to facets of the metabolic syndrome. It will clearly be important to map these QTLs in greater detail and to

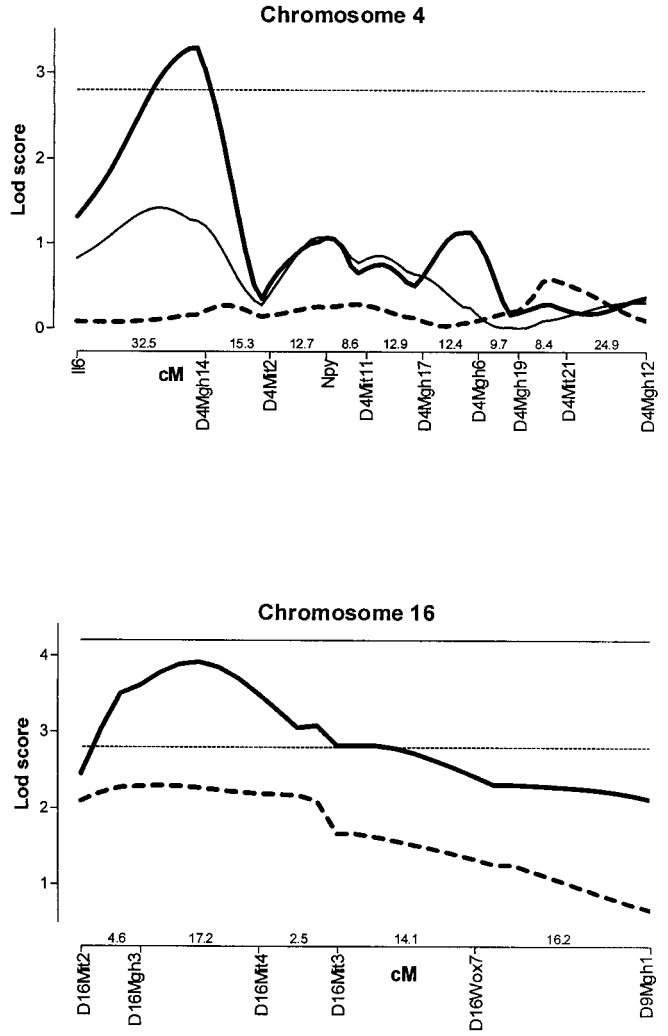

FIG. 4. Scans for lod scores for the placement of loci affecting fasting blood glucose (top) and serum leptin (bottom) in female (—), male (– –) and both, male and female (—) F2 hybrids. See Fig. 1.

TABLE 3

Summary of Cosegregation Analysis Results in Female (F) and Male (M) (WOKW × DA)F2 Rats Considering Significant (lod ≥ 4.3) and Suggestive Linkage (lod ≥ 2.8)

Phenotypic traits	Chromosome	QTL markers and regions	Locus	Maximum lod scores		
				M	F	M/F
Body weight (30 weeks) (g)	1	*Pbpc2-D1Mgh12*	*Q1MS1*	4.87		
	1	*D1Mgh2-D1Mit9*	*Q1MS2*	3.75	4.19	
	5	*D5Mgh6-D5Mit5*	*Q5MS1*	4.19		
BMI (g/cm^2)	1	*Pbpc2-D1Mgh12*	*Q1MS1*	3.05		
	5	*D5Mgh6-D5Mit5*	*Q5MS1*	4.47		
Adiposity index (%)	1	*D1Mgh2*	*Q1MS2*	4.05		
Serum triglycerides (mmol/l)	4	*Il6-D4Mit2*	*Q4MS1*	5.15		
	7	*D7Mit2-D7Mgh4*	*Q7MS1*		3.45	
	7	*D7Mgh4-D7Mgh6*	*Q7MS2*		3.23	
	11	*D11Wox6-Smst*	*Q11MS1*		3.06	
	16	*D9Mgh1-D16Wox7*	*Q16MS1*		5.00	
HDL-cholesterol (mmol/l)	5	*D5Mgh14-D5Mgh15*	*Q5MS2*	3.34		
	17	*D17Mit2*	*Q17MS1*	4.36		
Total cholesterol (mmol/l)	3	*D3Mit10*	*Q3MS1*		4.29	5.25
	4	*Npy*	*Q4MS2*		3.50	
	4	*D4Mgh17-D4Mgh6*	*Q4MS3*		3.35	
	5	*D5Mgh14-D5Mgh15*	*Q5MS2*	3.13		
	10	*Aep-D10Mgh7*	*Q10MS1*		2.89	3.35
Serum leptin (ng/ml)	8	*D8Mit4-D8Mit6*	*Q8MS1*	3.43		
	16	*D16Mit4-D16Mgh3*	*Q16MS2*		3.91	
Serum insulin (ng/ml)	1	*D1Mit5*	*Q1MS3*	3.25		
Blood glucose (mg/dl)	4	*D4Mgh14*	*Q4MS4*		3.28	1.26
	17	*D17Mit5*	*Q17MS2*	4.79		
AUC (mmol × min)	3	*D3Mit3*	*Q3MS2*	5.01		

identify candidate genes so that human genes can be identified.

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