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High penetrance, overweight, and glucocorticoid receptor variant: case-control study

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A possible link between the glucocorticoid receptor gene (*GRL*, 5q31-q32) and overweight has been suggested in a study of 42 families with morbid obesity.[1] Data from another small study—of pairs of siblings—although not significant, showed a trend towards similar body mass index (weight(kg)/(height(m)^2); difference = 2.4) for 20 pairs sharing similar alleles compared with 19 pairs having discordant alleles (difference = 3.5).[2] An Asn363Ser variant, caused by a single nucleotide difference (A1218G) in exon 2 of *GRL* has since shown an association with increased sensitivity to glucocorticoids.[3] Because of the predisposition to a rise in body mass index that this increased sensitivity should cause, we tested this variant for association with overweight in two groups of non-diabetic white subjects of British descent.

Methods and results

All participants lived in or near Sydney and had responded to requests to take part in a study that involved DNA testing. Because of the interaction between obesity and hypertension we selected subjects on the basis of a positive or negative family history of hypertension and tested them separately. Group 1 was recruited from donors at the Sydney Blood Bank and comprised 195 subjects who were normotensive offspring of two normotensive parents. Group 2 comprised 124 subjects recruited by public advertising for people with essential hypertension whose parents also had hypertension. Mean body mass index was 26 (SD 4) in group 1 and 26 (SD 5) in group 2; mean age was 48 (SD 10) years and 52 (SD 12) years respectively; percentage of male participants was 57% and 49% respectively; and blood pressure was 120 (SD 11)/73 (SD 8) mm Hg and 173 (SD 24)/110 (SD 17) mm Hg respectively.

Each group was divided into two subgroups: lean (body mass index ≤ 25) and overweight (> 25). Genotyping was performed on leucocyte DNA using polymerase chain reaction primers described previously[4] and *Tsp*509I digestion of polymerase chain reaction products, which gave a band of 134 base pairs for the Asn363 variant and 153 base pairs for the Ser363 variant, together with a band of 95 base pairs for both.

The frequency of the Ser363 variant (number of Ser363 alleles divided by total number of alleles) in each group was similar (7.4% (95% confidence interval 4.8% to 10.0%) in group 1 *v* 6.0% (3.1% to 9.0%) in group 2), with 12.3% (7.7% to 16.9%) in group 1 being carriers (that is, they had one or two alleles) and 10.5% (5.1% to 15.9%) in group 2. In participants with body mass index ≤ 25 the Ser363 allele was rare (1.8% in group 1 and 0% in group 2). All Ser/Ser homozygotes were overweight, as were all Asn/Ser heterozygotes in group 2 and 80% of Asn/Ser heterozygotes in group 1 (table). Association with overweight was highly significant (table), with overall penetrance in participants with the Ser363 variant being 83% in group 1 and 100% in group 2. Consistent with this, the higher the body mass index, the more likely the subject was to have the Ser363 variant (table).

Comment

We found that the Ser363 variant of the glucocorticoid receptor confers a virtually absolute likelihood of being overweight—unlike most markers

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Association of Ser363 allele of *GRL* gene with overweight and body mass index

	Genotype			
	Asn/Asn	Asn/Ser	Ser/Ser	Significance
Frequency of genotype				
Group 1:				
Body mass index ≤25	107	4	0	χ^2=18.8 (P=0.0001)
Body mass index >25	64	15	5	
Group 2:				
Body mass index ≤25	63	0	0	χ^2=15.0 (P<0.0001)
Body mass index >25	48	11	2	
Mean (SD) body mass index				
Group 1	25.7 (4.3); n=171	27.6 (4.0); n=19	28.2 (3.2); n=5	F=2.5* (P=0.082)
Group 2	25.6 (4.1); n=111	29.9 (2.4); n=11	38.0 (11); n=2	F=13.9* (P<0.0001)

*By one way analysis of variance.

of overweight, which confer only a slight increase in likelihood. The allele is relatively common. Given the difference in response to various modalities of intervention according to genetic propensity to increased body mass index for a variant in another gene,[5] our finding of almost complete penetrance of Ser363 genotypes to an overweight phenotype suggests that use of this marker could be important in clinical management.

Contributors: RCYL performed the genotyping, WYSW provided guidance with study design and performed statistical analyses, and BJM conceived the idea for the project and directed the research. All authors contributed to the drafting of the paper. BJM will act as guarantor.

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Does time spent in hospital in the final 15 years of life increase with age at death? A population based study

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The use of health services rises substantially with increasing age.[1] Although this is commonly assumed to be a consequence of longevity, the chief determinants of lifetime use of health services, irrespective of age at death, may be the antecedents of death,[2] and increased use by elderly people may result from their being closer to death than young people. We studied time in hospital in the final 15 years of life (as a proxy for major morbidity) and related this to age at death.

Subjects, methods, and results

We used data from the Oxford record linkage study, which includes death certificates and statistical records of NHS hospital admissions for part of southern England (population 1.9 million).[3] We chose 1991 as the base year because the data provided a retrospective period of 15 years and because from 1992, the system of providing mortality data to the record linkage study changed. We included all NHS admissions in the 15 years before death, of residents of the region who died in 1991 at 45 years and over (excluding those in the specialties of psychiatry and obstetrics). The data were grouped separately by sex and by age at death at 45-59 years and in five year age groups thereafter to 90-94 (too few deaths occurred at ≥95 years for worthwhile analysis). We analysed time in hospital for these age groups in each of the 15 years before death and calculated centile distributions of "heaviness" of hospital use in each group.

There were 18 524 deaths (men, 9156; women, 9368). Time in hospital in the 15 years before death rose with increasing age—median days in hospital rose in men from 11 days at age 45-59 at death to 26 days at age 90-94 at death and in women from 18 days at age 45-59 to 32 days at age 90-94. These increases in the median represent an extra half day in hospital in the 15 years before death for each additional year of life beyond age 60.

Time in hospital did not accumulate uniformly over the 15 years before death. Generally, hospital admissions either occurred in the years immediately before death and increased in the final year of life or were confined to that last year. The total time spent in