

Human gene for physical performance

A specific genetic factor that strongly influences human physical performance has not so far been reported, but here we show that a polymorphism in the gene encoding angiotensin-converting enzyme does just that. An 'insertion' allele of the gene is associated with elite endurance performance among high-altitude mountaineers. Also, after physical training, repetitive weight-lifting is improved eleven-fold in individuals homozygous for the 'insertion' allele compared with those homozygous for the 'deletion' allele.

The endocrine renin-angiotensin system is important in controlling the circulatory system. Angiotensin-converting enzyme (ACE, or kinase II) degrades vasodilator kinins, and converts angiotensin I (ATI) to the vasoconstrictor angiotensin II (ATII). In addition, local renin-angiotensin systems may influence tissue growth¹. A polymorphism of the human ACE gene has been described in which the deletion (*D*) rather than insertion (*I*) allele is associated with higher activity by tissue ACE².

There is evidence for a skeletal muscle renin-angiotensin system³, suggesting that muscle growth, and thus physical performance, might be positively associated with the *D* allele. However, our initial studies suggested that the *I* allele was associated with improved endurance performance. We investigated this association in two parallel experiments.

High-altitude mountaineers perform extreme-endurance exercise. Thirty-three elite unrelated male British mountaineers, with a history of ascending beyond 7,000 metres without using supplementary oxygen, were identified by the British Mountaineering Council. DNA was extracted from a mouthwash sample of the 25 male respondents, and ACE genotype was determined using a three-primer polymerase chain reaction amplification⁴.

Genotype distribution was compared with that of 1,906 British males free from clinical cardiovascular disease⁵. Mean age was 40.6 ± 6.5 years in the 25 subjects, and 55.6 ± 3.2 years for the controls. Both groups were in Hardy-Weinberg equilibrium. Both genotype distribution and allele frequency differed significantly between climbers and controls (Fig. 1a; P was 0.02 and 0.003 respectively (χ^2 test)), with a relative excess of *II* genotype and deficiency of *DD* genotype found in the climbers.

Among the 15 climbers who had ascended beyond 8,000 m without oxygen, none was homozygous for *D* (6 *II* and 9 *ID*: *I* allele frequency = 0.65). Further, ranked by number of ascents above 8,000 m without oxygen, the top performer was homozygous

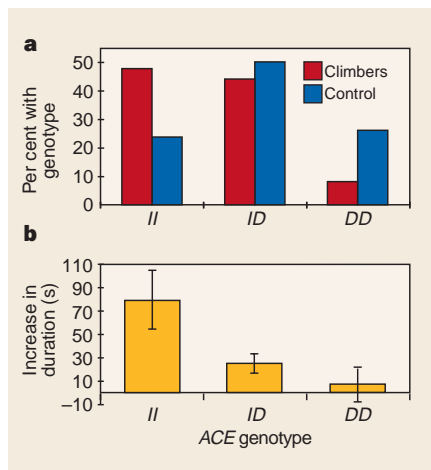


Figure 1 Association of ACE alleles with performance. **a**, Distribution of ACE *II/D* genotypes in 25 elite British mountaineers and 1,906 healthy British men. **b**, Mean (\pm s.e.m.) of individual improvement in duration of repetitive elbow flexion after 10 weeks of physical training among British army recruits. An initial cycle frequency of 0.3 Hz was strictly regulated by an electronic metronome and was increased by 0.05 Hz every minute. Performance was independent of skill or variation in technique. For each individual, the absolute difference between pre- and post-training data was obtained, and the mean of these differences calculated. Pre-training and post-training data were compared using two-tailed paired *t*-tests. Means were compared by generalized linear modelling with Statistical Analysis Software¹³. Data were adjusted by including baseline values as a covariate in the statistical model.

for *I* (5 ascents, compared with a mean of 2.4 ± 0.3 ascents, or 1.44 ± 0.3), as were the top two in this group for number of additional 7,000-m ascents (> 100 and 18, compared with a mean of 10.3 ± 6.5 ascents).

In a second study, ACE genotype was determined in 123 Caucasian males recruited to the UK army consecutively. Seventy-eight completed an identical 10-week general physical training programme (age, 19.0 ± 0.2 years; height, 176.6 ± 0.7 cm; body mass index, 22.2 ± 0.2 kg m²). Their ACE genotype (20 (25.6%) *II*, 46 (59.0%) *ID*, 12 (15.4%) *DD*) matched that of those who failed training, as did their physical characteristics (neck, chest and waist circumference, elbow diameter and armspan), and all characteristics were independent of genotype.

The maximum duration (in seconds) for which they could perform repetitive elbow flexion while holding a 15-kg barbell was assessed both before and after the training period. Pre-training performance was independent of genotype (mean, 119.8 ± 6.2 s). Duration of exercise improved significantly for those (66 individuals) of *II* and *ID* geno-

type (79.4 ± 25.2 and 24.7 ± 8.8 s: P was 0.005 and 0.007 respectively) but not for the 12 of *DD* genotype (7.1 ± 14.9 s: $P = 0.642$) (Fig 1b). Improvement was thus eleven-fold greater ($P = 0.001$) for those of *II* than for those of *DD* genotype.

Genotype-dependent improvements were unlikely to be due to changes in individual muscle fibre size and strength (which need more than three months of specific strength-training to occur) or altered co-ordination, neural firing pattern or recruitment of fast motor units (given the lack of specific training for the test task)⁶⁻⁸. Increased performance is therefore most likely to be due to an improvement in the endurance characteristics of the tested muscles.

The association of the *I* allele with improved endurance might derive from variable increases in substrate delivery due to increases in cardiac output and muscle capillary density; from changes in the nature of substrate used, due to a differential shift to stored fatty acids as fuel⁹, or in the efficiency of substrate utilization relating to altered muscle fibre type; from altered mitochondrial density, or from raised muscle myoglobin content^{10,11}. Elevated catecholamine, cortisol and growth hormone concentrations may all increase the availability of oxidative fuel¹².

Further work will be needed to determine whether this correlation holds beyond the limited group studied here and to explore the mechanisms underlying these observations.

H. E. Montgomery, R. Marshall, H. Hemingway, S. Myerson

University College London Centre for Cardiovascular Research, Rayne Institute, University Street, London WC1E 6JJ, UK

P. Clarkson, C. Dollery, M. Hayward

University College London Hospital, London WC1E 6DB, UK

D. E. Holliman

Centre for Human Sciences, DERA Farnborough GU14 0LX, UK

M. Jubbs, M. World

Royal Defence Medical College, HMS Dolphin, Gosport, Hampshire PO12 2AB, UK

E. L. Thomas, A. E. Brynes, N. Saeed,

M. Barnard, J. D. Bell

Imperial College School of Medicine MRI Unit, London W12 0HS, UK

K. Prasad

St George's Hospital, Department of Cardiovascular Sciences, London SW17 0RE, UK

M. Rayson

Optimal Performance, Farnham GU9 7EB, UK

P. J. Talmud, S. E. Humphries

University College London Centre for Cardiovascular Genetics, Rayne Institute, University Street, London WC1E 6JJ, UK