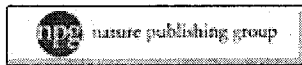


Mol Psychiatry. 2006 May;11(5):505-13.

[Related Articles](#), [Links](#)



## The brain-derived neurotrophic factor Val66Met

polymorphism is associated with age-related change in reasoning skills.

[Harris SE](#), [Fox H](#), [Wright AF](#), [Hayward C](#), [Starr JM](#), [Whalley LJ](#), [Deary IJ](#).

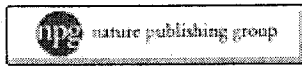
Department of Psychology, University of Edinburgh, Edinburgh, UK.  
Sarah.Harris@hgu.mrc.ac.uk

A polymorphism (Val66Met) in the gene encoding brain-derived neurotrophic factor (BDNF) has previously been associated with impaired hippocampal function and scores on the Logical Memory subtest of the Wechsler Memory Scale-Revised (WMS-R). Despite its widespread expression in the brain, there have been few studies examining the role of BDNF on cognitive domains, other than memory. We examined the association between BDNF Val66Met genotype and non-verbal reasoning, as measured by Raven's standard progressive matrices (Raven), in two cohorts of relatively healthy older people, one aged 79 (LBC1921) and the other aged 64 (ABC1936) years. LBC1921 and ABC1936 subjects had reasoning measured at age 11 years, using the Moray House Test (MHT), in the Scottish Mental Surveys of 1932 and 1947, respectively. BDNF genotype was significantly associated with later life Raven scores, controlling for sex, age 11 MHT score and cohort ( $P = 0.001$ ). MHT, Verbal Fluency and Logical Memory scores were available, in later life, for LBC1921 only. BDNF genotype was significantly associated with age 79 MHT score, controlling for sex and age 11 MHT score ( $P = 0.016$ ). In both significant associations, Met homozygotes scored significantly higher than heterozygotes and Val homozygotes. This study indicates that BDNF genotype contributes to age-related changes in reasoning skills, which are closely related to general intelligence.

Publication Types:

- [Comparative Study](#)
- [Research Support, Non-U.S. Gov't](#)

PMID: 16446742 [PubMed - indexed for MEDLINE]



The SNAP-25 gene is associated with cognitive ability:  
evidence from a family-based study in two independent Dutch  
cohorts.

Gosso MF, de Geus EJ, van Belzen MJ, Polderman TJ, Heutink P,  
Boomsma DI, Posthuma D.

Department of Biological Psychology, Vrije Universiteit, Amsterdam,  
The Netherlands. mf.gosso@vumc.nl

The synaptosomal-associated protein of 25 kDa (SNAP-25) gene plays an integral role in synaptic transmission, and is differentially expressed in the mammalian brain in the neocortex, hippocampus, anterior thalamic nuclei, substantia nigra and cerebellar granular cells. Recent studies have suggested a possible involvement of SNAP-25 in learning and memory, both of which are key components of human intelligence. In addition, the SNAP-25 gene lies in a linkage area implicated previously in human intelligence. In two independent family-based Dutch samples of 391 (mean age 12.4 years) and 276 (mean age 37.3 years) subjects, respectively, we genotyped 12 single-nucleotide polymorphisms (SNPs) in the SNAP-25 gene on 20p12-20p11.2. From all individuals, standardized intelligence measures were available. Using a family-based association test, a strong association was found between three SNPs in the SNAP-25 gene and intelligence, two of which showed association in both independent samples. The strongest, replicated association was found between SNP rs363050 and performance IQ (PIQ), where the A allele was associated with an increase of 2.84 PIQ points ( $P=0.0002$ ). Variance in this SNP accounts for 3.4% of the phenotypic variance in PIQ.

Publication Types:

- Research Support, Non-U.S. Gov't
- Twin Study

- Comparative Study
- Research Support, N. I. H., Intramural
- Research Support, Non-U. S. Gov' t

PMID: 17202556 [PubMed - indexed for MEDLINE]

2、

Am J Psychiatry. 2004 Jan;161(1):125-32.

Related Articles, Links



**Genetic and neurochemical modulation of prefrontal  
cognitive functions in children.**

Diamond A, Briand L, Fossella J, Gehlbach L.

Center for Developmental Cognitive Neuroscience, Eunice Kennedy Shriver Center Campus, University of Massachusetts Medical School, Waltham 02452, USA. [adele.diamond@umassmed.edu](mailto:adele.diamond@umassmed.edu)

**OBJECTIVE:** The catechol O-methyltransferase (COMT) gene affects how long dopamine acts in the prefrontal cortex. The Methionine polymorphism, which results in a slower breakdown of prefrontal dopamine, is associated with better adult prefrontal cortex function. The authors investigated the relation between the COMT gene polymorphism and cognitive performance in children. **METHOD:** Children were tested on cognitive tasks that depend on the dorsolateral prefrontal cortex and seem to be sensitive to the level of dopamine there (dots-mixed task), depend on that neural region but appear insensitive to its dopamine content (self-ordered pointing), and depend on other neural systems (recall memory and mental rotation). After data collection, cheek swabs were obtained from all children. DNA was extracted and genotyped for the COMT gene with polymerase chain reaction. **RESULTS:** Children who were homozygous for the Methionine polymorphism performed significantly better on the dots-mixed task but not on others. **CONCLUSIONS:** The findings provide an existence proof that genotypic differences can relate to differences in cognitive performance in typically developing children. The authors achieved a level of specificity

executive functions have been described in adults and prepubescent children, but there is a paucity of research assessing these relations in adolescent samples. METHODS: In this study, 70 children aged 9-17 were genotyped for COMT and completed measures of working memory, attention, fine motor coordination, and motor speed. RESULTS: COMT genotype modulated all but the motor speed measures. The Val-Met genotype was optimal for performance in this adolescent sample. CONCLUSIONS: Results are discussed within the context of developmental changes in the dopaminergic system during adolescence.

Publication Types:

- Research Support, N. I. H., Extramural
- Research Support, Non-U. S. Gov't

PMID: 17014828 [PubMed - indexed for MEDLINE]

1: Genes Brain Behav. 2006 Nov;5(8):577-84.

## Association between the *CHRM2* gene and intelligence in a sample of 304 Dutch families

Authors: Gosso; van Belzen, ; de Geus, ; Polderman<sup>1</sup>; Heutink; Boomsma; Posthuma

Source: Genes, Brain & Behavior, Volume 5, Number 8, November 2006, pp. 577-584(8)

Publisher: Blackwell Publishing

Abstract:

The *CHRM2* gene is thought to be involved in neuronal excitability, synaptic plasticity and feedback regulation of acetylcholine release and has previously been implicated in higher cognitive processing. In a sample of 667 individuals from 304 families, we genotyped three single-nucleotide polymorphisms (SNPs) in the *CHRM2* gene on 7q31-35. From all individuals, standardized intelligence measures were available.

Methods: The genotypes were determined with polymerase chain reaction and allele-specific restriction enzyme analysis. Patients suffering from depression (n=184) and sex and age-matched controls (n=158) were compared in this study.

Results: The frequencies of 5-HTTLPR SS and GN[beta]3 825TT genotypes and 5-HTTLPR S and GN[beta]3 825T alleles in patients suffering from depression were significantly higher than those in the controls (P<0.01). Combined genotype analysis showed that individuals with both 5-HTTLPR S and GN[beta]3 825T alleles (odds ratio=3.25, P=0.002) had a risk of depressive disorder higher than those with 5-HTTLPR S (odds ratio=1.817, P=0.01) or GN[beta]3 825T alleles (odds ratio=2.214, P=0.001) alone.

Conclusions: These results indicated that the etiology of depressive disorder is associated with 5-HTTLPR and GN[beta]3 825T polymorphisms. Our data also suggests that an interaction effect may exist between the 5-HTTLPR S allele and GN[beta]3 825T allele in increasing the risk of depressive disorder.

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PMID: 17621167 [PubMed - indexed for MEDLINE]

1: Arch Gen Psychiatry. 2005 Jan;62(1):85-94.

## **2. Influence of the Serotonin Transporter Promoter Gene and Shyness on Children's Cerebral Responses to Facial Expressions**

Marco Battaglia, MD; Anna Ogliari, MD; Annalisa Zanoni, MSc; Alessandra Citterio, MSc; Uberto Pozzoli, PhD; Roberto Giorda, PhD; Cesare Maffei, MD; Cecilia Marino, MD, PhD

*Arch Gen Psychiatry*. 2005;62:85-94.

**Background** Childhood shyness can predate social anxiety disorder and may be associated with biased discrimination of facial expressions of emotions.

**Objective** To determine whether childhood shyness, or the serotonin transporter promoter polymorphism genotype, can predict participants' visual event-related potentials in response to expressions of children of similar ages.

## **Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking**

Richard P. Ebstein<sup>1,3,4</sup>, Olga Novick<sup>2</sup>, Roberto Umansky<sup>2</sup>, Beatrice Priel<sup>2</sup>, Yamima Osher<sup>2</sup>, Darren Blaine<sup>1</sup>, Estelle R. Bennett<sup>1</sup>, Lubov Nemanov<sup>1</sup>, Miri Katz<sup>1</sup> & Robert H. Belmaker<sup>2</sup>

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<sup>4</sup>Correspondence should be addressed to R. P. E.

PMID: 8528256

Human personality traits which can be reliably measured by any of a number of rating scales, show a considerable heritable component<sup>1,2</sup>. The tridimensional personality questionnaire (TPQ) is one such instrument and was designed by Cloninger to measure four distinct domains of temperament — Novelty Seeking, Harm Avoidance, Reward Dependence and Persistence — that are hypothesized to be based on distinct neurochemical and genetic substrates. Cloninger proposed that individual variations in the Novelty Seeking trait are mediated by genetic variability in dopamine transmission<sup>2</sup>. Individuals who score higher than average on the TPQ Novelty Seeking scale are characterized as impulsive, exploratory, fickle, excitable, quick-tempered and extravagant, whereas those who score lower than average tend to be reflective, rigid, loyal, stoic, slow-tempered and frugal. We now show that higher than average Novelty Seeking test scores in a group of 124 unrelated Israeli subjects are significantly associated with a particular exonic polymorphism, the 7 repeat allele in the locus for the D4 dopamine receptor gene (D4DR). The association of high Novelty Seeking and the 7-repeat allele was independent of ethnicity, sex or age of the subjects. This work,

<sup>1</sup>Faculty of Health Sciences, Ben Gurion University of the Negev, Israel

<sup>2</sup>Research Laboratory, S Herzog Memorial Hospital, Israel

Correspondence to: Professor R P Ebstein, Research Laboratory, S Herzog Memorial Hospital, PO Box 35300, Jerusalem 91351, Israel. E-mail: ebstein@netmedia.net.il

## Abstract

Dopamine D4 receptor (DRD4), serotonin transporter promoter regulatory region (5-HTTLPR) and catechol O-methyltransferase (COMT) polymorphisms were examined for association with TPQ personality factors in 455 subjects. Significant interactions were observed by multivariate analysis, (COMT × 5-HTTLPR: Hotelling's Trace = 2.3,  $P = 0.02$ ) and by subsequent univariate 3-way ANOVA when Novelty Seeking (NS) was the dependent variable: 5-HTTLPR × D4DR ( $F = 6.18$ ,  $P = 0.03$ ) and COMT × 5-HTTLPR ( $F = 4.42$ ,  $P = 0.03$ ). In the absence of the short 5-HTTLPR allele and in the presence of the high enzyme activity COMT val/val genotype, NS scores are higher in the presence of the DRD4 seven-repeat allele. The effect of these three polymorphisms on NS was also examined using a within-families design. Siblings who shared identical genotype groups for all three polymorphisms (COMT, DRD4 and 5-HTTLPR) had significantly correlated NS scores (intraclass coefficient = 0.39,  $F = 2.26$ ,  $P = 0.008$ ,  $n = 49$ ) whereas sibs with dissimilar genotypes in at least one polymorphism showed no significant correlation for NS scores (intraclass coefficient = 0.177,  $F = 1.43$ ,  $P = 0.09$ ,  $n = 110$ ). Similar interactions were also observed between these three polymorphisms and Novelty Seeking when the 150 independently recruited and non-related subjects were analyzed. The current results are consistent with two earlier reports in which we demonstrated an interaction between the 5-HTTLPR and DRD4 polymorphisms in 2-week-old neonates, in the same children assessed again at 2 months of age and in adults. *Molecular Psychiatry* (2000) 5, 96–100.

PMID: 10673775 [PubMed - indexed for MEDLINE]

## I.

*Neuropsychopharmacology* (2008) 33, 425–430; doi:10.1038/sj.npp.1301417; published online 11 April 2007

aggression, as well as for how *MAOA* genotype may influence aggressive behavior in human males.

Foley DL, Eaves LJ, Wormley B, Silberg JL, Maes HH, Kuhn J *et al* (2004). Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder. *Arch Gen Psychiatry* 61: 738–744.

Kim-Cohen J, Caspi A, Taylor A, Williams B, Newcombe R, Craig IW *et al* (2006). MAOA, maltreatment, and gene-environment interaction predicting children's mental health: new evidence and a meta-analysis. *Mol Psychiatry* 11: 903–913.

PMID: 17429405

2.




## Association between monoamine oxidase A (MAOA) and personality traits in Japanese individuals

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Received 4 May 2008;

revised 17 September 2008;

## **Abstract**

Epidemiological studies provided a large body of evidence that personality dimensions are influenced by genetic factors and that the genetic component is highly complex, polygenic, and epistatic. However, consistent findings on the genetic basis of personality have yet remained sparse. In recent years, molecular genetics has begun to identify specific genes coding in particular for components of the serotonergic and dopaminergic neurotransmitter systems representing quantitative trait loci (QTLs) for behavioral traits. The QTL concept suggests that complex traits are not attributable to single genes. According to this polygenic model, the genetic basis of personality and behavior and its pathological variations thus results from additive or nonadditive interactions of various genes. As the number of suitable candidate genes constantly increases, the QTL model provides a reasonable explanation for the genetic basis of personality and its disorders. In this review, the current knowledge on the impact of a large number of candidate gene polymorphisms (e.g. variations in serotonin and dopamine receptor and serotonin transporter genes) on personality and temperament is summarized. Additionally, investigations of gene-gene and gene-environment interactions in humans and animals, which currently intensify the identification of genes that underlie behavioral variations, are examined. The findings converge on the notion that a probabilistic rather than deterministic impact of genes on the expression of behavior will contribute to the demystification of behavioral disorders.

**Author Keywords:** Behavioral genetics; Candidate genes; Serotonin transporter; 5-HTT; Dopamine receptor; DRD4; Polymorphism; Quantitative trait loci

## **Article Outline**

### 1. Introduction

### 2. Personality disorders: distinct categories or dimensions of human behavior?

### 3. The genetic dissection of personality

### 4. Candidate genes for personality

#### 4.1. The serotonergic system

##### 4.1.1. Serotonin metabolism

##### 4.1.2. Tryptophan hydroxylase

##### 4.1.3. 5HT receptors

##### 4.1.4. 5HT transporter

##### 4.1.5. Gene-environment interactions

#### 4.2. Dopaminergic gene pathway

(ADHD) and the 10-repeat allele of the dopamine transporter gene (DAT1) has been reported in independent clinical samples using a categorical clinical definition of ADHD. The present study adopts a quantitative trait loci (QTL) approach to examine the association between DAT1 and a continuous measure of ADHD behaviours in a general-population sample, as well as to explore whether there is an independent association between DAT1 and performance on neuropsychological tests of attention, response inhibition, and working memory. From an epidemiological sample of 872 boys aged 6-11 years, we recruited 58 boys scoring above the 90th percentile for teacher reported ADHD symptoms (SWAN ADHD scale) and 68 boys scoring below 10th percentile for genotyping and neuropsychological testing. A significant association was found between the DAT1 homozygous 10/10-repeat genotype and high-scoring boys ( $\chi^2(2)=4.6$ ,  $P<0.03$ ; odds ratio=2.4, 95% CI 1.1-5.0). Using hierarchical linear regression, a significant independent association was found between the DAT1 10/10-repeat genotype and measures of selective attention and response inhibition after adjusting for age, IQ, and ADHD symptoms. There was no association between DAT1 and any component of working memory. Furthermore, performance on tasks of selective attention although associated with DAT1 was not associated with SWAN ADHD high scores after controlling for age and IQ. In contrast, impairment on tasks that tapped sustained attention and the central executive component of working memory were found in high-scoring boys after adjusting for age and IQ. The results suggest that DAT1 is a QTL for continuously distributed ADHD behaviours in the general population and the cognitive endophenotype of response inhibition.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 15809660 [PubMed - indexed for MEDLINE]

Correspondence to: J L Kennedy MD, Head, Neurogenetics Section, Centre for Addiction and Mental Health (CAMH), Clarke Division, 250 College St, R-31 Toronto, Ontario, Canada M5T 1R8. E-mail: james\_kennedy@camh.net

## Abstract

A recent study demonstrated that treatment of hyperactive mice with psychostimulants and serotonergic agents produced a calming effect that was dependent on serotonergic neurotransmission and was not associated with any changes in extracellular dopamine levels.<sup>1</sup> The complex interaction between the serotonergic and dopaminergic neurotransmitter systems suggests that a balance between the two systems may be necessary for mediating hyperactive behaviour. Defects in serotonin system genes, therefore, may disrupt normal brain serotonin function causing an imbalance between these neurotransmitter systems leading to the development of attention deficit hyperactivity disorder (ADHD). Using the transmission disequilibrium test (TDT), the current study assesses for linkage disequilibrium between polymorphisms in the serotonin HTR2A receptor gene and ADHD. One hundred and fifteen families with a total of 143 children diagnosed with ADHD (DSM-IV) were genotyped for the His<sup>452</sup>Tyr and the T102C polymorphisms in the serotonin HTR2A receptor gene. TDT analysis revealed a preferential transmission of the <sup>452</sup>Tyr allele to the affected offspring ( $P = 0.03$ ), suggesting linkage disequilibrium of this polymorphism with ADHD. This may open a new door in ADHD molecular genetics research, expanding the existing view of a catecholaminergic hypothesis to include a serotonergic hypothesis and should help elucidate the complex interplay among the neurotransmitter systems in the etiology of ADHD. *Molecular Psychiatry* (2000) 5, 537–541.

PMID: 11032388

Genes Brain Behav. 2007 Jul;6(5):444–52. Epub 2006 Sep 8.

Related Articles, Links



Association of the glutamate receptor subunit gene GRIN2B  
with attention-deficit/hyperactivity disorder.

Dorval KM, Wigg KG, Crosbie J, Tannock R, Kennedy JL, Ickowicz A,  
Pathare T, Malone M, Schachar R, Barr CL.

Cell and Molecular Biology Division, Toronto Western Research



[《中国运动医学杂志》](#)

2000年第19卷第3期

[论文发表保发快发（点击进入）](#)

**摘 要:**

为探讨血管紧张素 I 转化酶 (ACE) 基因 I / D 多态性与运动能力的关系, 并力求相关的遗传标志, 应用 PCR-AFLP (扩增片段长度多态性) 方法检测了优秀力量运动员和普通人群的 ACE 基因型。结果显示, 优秀运动员组 ACE 等位基因频率  $D = 0.375$ ,  $I = 0.635$ , I 等位基因频率高于普通人群组 ( $I = 0.450$ ), 差异有显著性 ( $P < 0.05$ )。提示 ACE 基因 I / D 多态性可能与运动能力相关联, 考虑将其遗传标志用

(共 3 页)

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**关键词:**

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## 2、

Sci Prog. 2000;83(Pt 4):317-36. [Links](#)

## Endurance and the ACE I/D polymorphism.

**Woods DR, Brull D, Montgomery HE.**

Department Cardiovascular Genetics, University College London, 3rd floor, Rayne Institute, 5, University Street, London WC1E 6JJ.  
rmhadwo@ucl.ac.uk

*J Appl Physiol* 90: 1205-1210, 2001;

8750-7587/01 \$5.00

Vol. 90, Issue 4, 1205-1210, April 2001

PMID: 10688186

1: *J Appl Physiol*, 2001 Apr;90(4):1205-10. free

## **CNTF genotype is associated with muscular strength and quality in humans across the adult age span**

Stephen M. Roth<sup>1,2</sup>, Matthew A. Schrager<sup>1,3</sup>, Robert E. Ferrell<sup>2</sup>, Steven E. Riechman<sup>2</sup>, E. Jeffrey Metter<sup>3</sup>, Nicole A. Lynch<sup>4</sup>, Rosemary S. Lindle<sup>1</sup>, and Ben F. Hurley<sup>1</sup>

### ► **ABSTRACT**

The relationship between ciliary neurotrophic factor (CNTF) genotype and muscle strength was examined in 494 healthy men and women across the entire adult age span (20–90 yr). Concentric (Con) and eccentric (Ecc) peak torque were assessed using a Kin-Com isokinetic dynamometer for the knee extensors (KE) and knee flexors (KF) at slow (0.52 rad/s) and faster (3.14 rad/s) velocities. The results were covaried for age, gender, and body mass or fat-free mass (FFM). Individuals heterozygous for the CNTF null (A allele) mutation (G/A) exhibited significantly higher Con peak torque of the KE and KF at 3.14 rad/s than G/G homozygotes when age, gender, and body mass were covaried ( $P < 0.05$ ). When the dominant leg FFM (estimated muscle mass) was used in place of body mass as a covariate, Con peak torque of the KE at 3.14 rad/s was also significantly greater in the G/A individuals ( $P < 0.05$ ). In addition, muscle quality of the KE (peak torque at 3.14 rad  $\cdot$  s<sup>-1</sup>  $\cdot$  leg muscle mass<sup>-1</sup>) was significantly greater in the G/A heterozygotes ( $P < 0.05$ ). Similar results were seen in a subanalysis of subjects 60 yr and older, as well as in Caucasian subjects. In contrast, A/A homozygotes demonstrated significantly lower Ecc peak torque at 0.52 rad/s for both KE and KF compared with G/G and G/A groups ( $P < 0.05$ ). No significant relationships were observed at 0.52 rad/s between genotype and Con peak torque. These data indicate that individuals exhibiting the G/A genotype possess significantly greater muscular strength and muscle quality at relatively fast contraction speeds than do G/G individuals. Because of high positive correlations between fast-velocity peak torque and muscular power, these findings



## A gene for speed: contractile properties of isolated whole EDL muscle from an $\alpha$ -actinin-3 knockout mouse.

Chan S, Seto JT, Macarthur DG, Yang N, North K, Head S.

Institute for Neuromuscular Research, The Children's Hospital at Westmead, Sydney, 2145 NSW, Australia; and (see.

The actin-binding protein  $\alpha$ -actinin-3 is one of the two isoforms of  $\alpha$ -actinin that are found in the Z-discs of skeletal muscle.  $\alpha$ -Actinin-3 is exclusively expressed in fast glycolytic muscle fibers. Homozygosity for a common polymorphism in the ACTN3 gene results in complete deficiency of  $\alpha$ -actinin-3 in about 1 billion individuals worldwide. Recent genetic studies suggest that the absence of  $\alpha$ -actinin-3 is detrimental to sprint and power performance in elite athletes and in the general population. In contrast,  $\alpha$ -actinin-3 deficiency appears to be beneficial for endurance athletes. To determine the effect of  $\alpha$ -actinin-3 deficiency on the contractile properties of skeletal muscle, we studied isolated extensor digitorum longus (fast-twitch) muscles from a specially developed  $\alpha$ -actinin-3 knockout (KO) mouse.  $\alpha$ -Actinin-3-deficient muscles showed similar levels of damage to wild-type (WT) muscles following lengthening contractions of 20% strain, suggesting that the presence or absence of  $\alpha$ -actinin-3 does not significantly influence the mechanical stability of the sarcomere in the mouse.  $\alpha$ -Actinin-3 deficiency does not result in any change in myosin heavy chain expression. However, compared with  $\alpha$ -actinin-3-positive muscles,  $\alpha$ -actinin-3-deficient muscles displayed longer twitch half-relaxation times, better recovery from fatigue, smaller cross-sectional areas and lower twitch-to-tetanus ratios. We conclude that  $\alpha$ -actinin-3 deficiency results in fast-twitch, glycolytic fibers developing slower-twitch, more oxidative pCitius and longius (faster and longer) with no  $\alpha$ -actinin-3 in skeletal muscles?

2: Br J Sports Med. 2007 Sep;41(9):616-7. Epub 2007 Feb 8

Lucia A, Oliván J, Gómez-Gallego F, Santiago C, Montil M, Foster C.

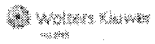
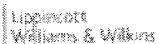
Department of Physiology, Universidad Europea de Madrid, Villaviciosa de Odón, Madrid, Spain. alejandro.lucia@uem.es

The muscle protein alpha-actinin-3 (ACTN3) is normally thought to be expressed in type II muscle fibres and to be necessary for high-power, high-velocity muscle contractions, such as those typically seen in speed/power athletes. The authors report the case of a Spanish elite long jumper (two times Olympian, personal best of 8.26 m) whose genotype for the ACTN3 gene is 577XX (ACTN3 deficient). These data suggest that there might be notable exceptions to the concept that ACTN3 is the "gene for speed".

PMID: 17289854 [PubMed - indexed for MEDLINE]

roperties. These changes in the contractile properties of fast-twitch skeletal muscle from alpha-actinin-3-deficient individuals would be detrimental to optimal sprint and power performance, but beneficial for endurance performance. Key words: alpha-actinin-3, extensor digitorum longus.

PMID: 18650267 [PubMed - as supplied by publisher]

3: Exerc Sport Sci Rev. 2007 Jan;35(1):30-4.   [Links](#)

## ACTN3: A genetic influence on muscle function and athletic performance.


MacArthur DG, North KN.

Institute for Neuromuscular Research, Children's Hospital at Westmead, Westmead NSW, Australia.

A common variant of the ACTN3 gene, R577X, results in complete deficiency of the alpha-actinin-3 protein in the fast skeletal muscle fibers of more than a billion humans worldwide. We review the evidence that this genetic variant is strongly associated with

elite athlete status and with normal variation in human muscle strength and sprinting speed.

PMID: 17211191 [PubMed - indexed for MEDLINE]

4: Bioessays. 2004 Jul;26(7):786-95.  [Links](#)

## A gene for speed? The evolution and function of alpha-actinin-3.

MacArthur DG, North KN.

The Children's Hospital at Westmead, Westmead, Sydney, Australia.

The alpha-actinins are an ancient family of actin-binding proteins that play structural and regulatory roles in cytoskeletal organisation and muscle contraction. alpha-actinin-3 is the most-highly specialised of the four mammalian alpha-actinins, with its expression restricted largely to fast glycolytic fibres in skeletal muscle. Intriguingly, a significant proportion (approximately 18%) of the human population is totally deficient in alpha-actinin-3 due to homozygosity for a premature stop codon polymorphism (R577X) in the ACTN3 gene. Recent work in our laboratory has revealed a strong association between R577X genotype and performance in a variety of athletic endeavours. We are currently exploring the function and evolutionary history of the ACTN3 gene and other alpha-actinin family members. The alpha-actinin family provides a fascinating case study in molecular evolution, illustrating phenomena such as functional redundancy in duplicate genes, the evolution of protein function, and the action of natural selection during recent human evolution. Copyright 2004 Wiley Periodicals, Inc.

PMID: 15221860 [PubMed - indexed for MEDLINE]

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ACTN3 genotype is associated with human elite athletic performance.

Yang N, MacArthur DG, Gulbin JP, Hahn AG, Beggs AH, Easteal S, North K.

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There is increasing evidence for strong genetic influences on athletic performance and for an evolutionary "trade-off" between performance traits for speed and endurance activities. We have recently demonstrated that the skeletal-muscle actin-binding protein alpha-actinin-3 is absent in 18% of healthy white individuals because of homozygosity for a common stop-codon polymorphism in the ACTN3 gene, R577X. alpha-Actinin-3 is specifically expressed in fast-twitch myofibers responsible for generating force at high velocity. The absence of a disease phenotype secondary to alpha-actinin-3 deficiency is likely due to compensation by the homologous protein, alpha-actinin-2. However, the high degree of evolutionary conservation of ACTN3 suggests function(s) independent of ACTN2. Here, we demonstrate highly significant associations between ACTN3 genotype and athletic performance. Both male and female elite sprint athletes have significantly higher frequencies of the 577R allele than do controls. This suggests that the presence of alpha-actinin-3 has a beneficial effect on the function of skeletal muscle in generating forceful contractions at high velocity, and provides an evolutionary advantage because of increased sprint performance. There is also a genotype effect in female sprint and endurance athletes, with higher than expected numbers of 577RX heterozygotes among sprint athletes and lower than expected numbers among endurance athletes. The lack of a similar effect in males suggests that the ACTN3 genotype affects athletic performance differently in males and females. The differential effects in sprint and endurance athletes suggests that the R577X polymorphism may have been maintained in the human population by balancing natural selection.

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## Unique among unique. Is it genetically determined?

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The cross-country World championship is one of the best models to study characteristics needed to achieve top-level endurance athletic capacity. We report the genotype combination of a recent cross-country champion (12km race) in polymorphisms of seven genes that are candidates to influence endurance phenotype traits (ACTN3, ACE, PPARGC1A, AMPD1, CKMM, GDF8 (myostatin) and HFE). His data were compared with those of eight other runners (World class but not World champions). The only athlete with the theoretically more suited genotype for attaining World-class endurance running performance was the case study subject. A favourable genetic endowment, together with exceptional environmental factors (years of altitude living and training in this case) seems to be necessary to attain the highest possible level of running endurance performance.

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