The influence of inheritance and genetics on physical performance.

- Variability in physical performance & Inheritance.
- Influence of specific genes? Angiotensin Converting Enzyme (ACE) \( \alpha \)-Actinin 3 (ACTN3)
- Role of multiple genes – The polygenic profile

Dr Jonathan Folland
School of Sport, Exercise & Health Sciences
Phenotypic Variation of Knee Extensor Strength

90 Young Men (18-30 years)

## Inheritance of Strength and Power

<table>
<thead>
<tr>
<th>Population</th>
<th>Phenotype</th>
<th>Heritability Estimate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys &amp; girls</td>
<td>Isometric Strength EF</td>
<td>74%</td>
<td>Maes et al., 1996</td>
</tr>
<tr>
<td>Boys</td>
<td>Isometric Strength EF</td>
<td>51-82 %</td>
<td>Peeters et al., 2005a</td>
</tr>
<tr>
<td>Boys</td>
<td>Vertical Jump Power</td>
<td>61-87%</td>
<td>Peeters et al., 2005b</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td>77-78%</td>
<td></td>
</tr>
<tr>
<td>Young men</td>
<td>Jump Power</td>
<td>90%</td>
<td>Kovar et al., 1976</td>
</tr>
<tr>
<td>Young men</td>
<td>Isoinertial Strength EF</td>
<td>77%</td>
<td>Thomis et al., 1998</td>
</tr>
<tr>
<td></td>
<td>Isometric Strength EF</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Young men</td>
<td>Cycling Power</td>
<td>74%</td>
<td>Calvo et al., 2002</td>
</tr>
<tr>
<td>Older men</td>
<td>Handgrip strength</td>
<td>48%</td>
<td>Reed et al., 1991</td>
</tr>
<tr>
<td>Older women</td>
<td>Isometric Strength KE Power</td>
<td>48%</td>
<td>Tianen et al., 2007</td>
</tr>
</tbody>
</table>

EF, Elbow Flexors. KE, Knee extensors.
Variation in the Individual Response to Strength Training [n=23].

Data from Folland et al., 1998. *J Physiol*, 506, 102P.
Genes for particular sports?

- **Sprinter – ACTN3**: Sprinters and power athletes are three times as likely to have this gene as other sportspeople, suggesting that alpha-actinin 3 is essential for fast-muscle-fibre function.

- **Mountaineer – ACE**: Two common variants exist. The II variant seems to predominate in endurance athletes and mountaineers, while the DD variant may predominate in sprint athletes.

- **Marathon runner – PPAR-delta**: Mice engineered to produce more PPAR-delta grow more slow-muscle fibres – used for endurance exercise – and can run almost twice as far as normal mice.

- **Cyclist – CKMM**: Different variants may affect an individual’s ability to improve their VO₂max – the rate at which they convert oxygen into energy – in response to training.

- **Weightlifter – myostatin**: A mutation in the gene which stops functional myostatin from being produced results in individuals with extremely large muscles.
Assessed the Angiotensin Converting Enzyme (ACE) Genotype of:

**Controls**: 1908 healthy British men

**Climbers**: 25 elite mountaineers who had ascended to \( \uparrow 7,000 \text{m} \) without the use of supplementary oxygen.

with each individual’s genotype either: II, ID or DD.
ACE Genotype & Elite Runners at different distances

Angiotensin Converting Enzyme (ACE) gene: Insertion / Deletion polymorphism

Chromosome 17q23

Angiotensin Converting Enzyme Gene:

5’  |  1 |  5 |  8 |  15 |  17 |  21 |  26 | 3’

 exons

5’  |  1 |  5 |  8 |  15 |  17 |  21 |  26 | 3’

287 Base Pairs

Insertion (I) or Deletion (D) of a 287 base pair fragment within Intron 16: I or D allele.

Individuals are either II, ID or DD ACE genotype.
Fibre type of 41 healthy young untrained Japanese.

ACE I/D Genotype and Muscle Function in Young & Older Men

<table>
<thead>
<tr>
<th>Young Men, n=78</th>
<th>Older Men, n=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy UK Caucasian Men</td>
<td></td>
</tr>
<tr>
<td>Low-moderate physical activity level (&lt; 4 x per week).</td>
<td></td>
</tr>
</tbody>
</table>

20 ± 2 years 65 ± 3 years

Genetics:
ACE I/D Genotype: II 17, ID 40, DD 22  II 25, ID 48, DD 27

Knee Extensor Muscle Function
ACE I/D Genotype and Muscle Function in Young & Older Men

- Strength at a range of velocities:

- Contractile response:
Strength and the Torque-Velocity relationship for different ACE Genotypes

Young Men (n=78)

ACE I/D genotype:
- II
- ID
- DD

Older Men (n=100)

ACE I/D genotype:
- II
- ID
- DD

Contractile Properties of the Knee Extensors for different ACE Genotypes

Young Men (n=78)

Older Men (n=100)

ACE Genotype: Case–Control studies of Athletes

Different genotype distribution in Athletes vs Controls?

Endurance Athletes


YES


NO

Sprint Athletes


↑ proportion of DDs amongst short distance athletes.


NO
ACE Genotype and the Response to Strength Training

[Mean ± SEM; \( n_{II}=6, n_{ID}=17, n_{DD}=9 \)].

ACE genotype and the Gain in Isometric Strength after Training [Mean ± SD, \( n_{II} = 16 \), \( n_{ID} = 17 \), \( n_{DD} = 11 \)].

Conclusions so far

Variability in physical performance:
- There is considerable variability in physical performance & the response to training.
- Inheritance accounts for >50% variability between individuals.

Angiotensin Converting Enzyme (ACE) Genotype:
- May confer a slight advantage to elite performance - mixed evidence as may depend on ethnicity and event - but is not deterministic.
- Within the normal population any effect on baseline performance or the response to training is unclear.
Human DNA Testing

You are here: Home > Human DNA Testing > Sports Performance

Sports Performance

ACTN3 Sports Gene Test®

A fast, simple and painless genetic test can identify whether you may be naturally geared toward sprint/power events, or towards endurance sporting ability.

Regardless of whether you are an accomplished athlete, or a beginner, your ACTN3 Sports Gene Test® result could assist you in optimising your training to make the most of your natural ability within a wide range of sports.

The scientific evidence to date suggests that knowing the results of your ACTN3 Sports Gene Test® could help you to determine the types of sports or events in which you may be most likely to succeed.

This will assist in tailoring training.
BOULDER, Colo. — When Donna Campiglia learned recently that a genetic test might be able to determine which sports suit the talents of her 2 ½-year-old son, Noah, she instantly said, “Where can I get it and how much does it cost?”
\(\alpha\)-Actinin 3 (ACTN3) genotype in Athletes

ACTN3 genotype of Australian athletes and controls:

### ACTN-3 Genotype: Case–Control studies of Athletes

Different genotype distribution in Athletes vs Controls?

#### Endurance Athletes

|-----|---------------------------------------------------------|

#### Strength & Power Athletes

|-----|---------------------------------------------------------|


↑ proportion of RR genotype
α-Actinin 3 (ACTN3) R/X Polymorphism

Replacement of an arginine (R) with a stop codon X at amino acid 577.

- Chromosome 11, region q14
- Genotype of: RR, RX or XX.

- X codon (& XX genotype) results in deficiency of the α-Actinin 3 protein that forms part of the z-disk of Type II fibres.
ACTN3 Genotype and Sprint Performance

40-m sprint times in 507 Greek adolescents

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
<th>Mean</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>172</td>
<td>5.92</td>
<td>P=0.003</td>
</tr>
<tr>
<td>RX</td>
<td>242</td>
<td>6.00</td>
<td></td>
</tr>
<tr>
<td>XX</td>
<td>93</td>
<td>6.13</td>
<td>V=2.3%</td>
</tr>
</tbody>
</table>

There's currently no evidence that ACTN3 offers improved predictive power over physical talent ID tests. ACTN3 doesn't tell you whether or not your child will be a super-athlete. ACTN3 may explain 2-3% of the variation in muscle function. The thoughts of Daniel MacArthur (2008):
Humans have ~20,000 genes.

Complex phenotypes or characteristics are unlikely to depend on just one gene.

To date > 25 genes associated with endurance performance.

“What is the chance of an individual possessing the optimal polygenic profile for performance?”
# The Optimal Polygenic Profile for Endurance

<table>
<thead>
<tr>
<th>Number of polymorphisms influencing endurance performance</th>
<th>New gene included at each stage</th>
<th>Typical frequency of optimal genotype (%)</th>
<th>Probability of possessing a ‘perfect’ profile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% chance</td>
</tr>
<tr>
<td>1</td>
<td>ACE</td>
<td>21</td>
<td>21.0</td>
</tr>
<tr>
<td>2</td>
<td>ACTN3</td>
<td>18</td>
<td>3.78</td>
</tr>
<tr>
<td>3</td>
<td>ADRA2</td>
<td>62</td>
<td>2.34</td>
</tr>
<tr>
<td>4</td>
<td>ADRB2</td>
<td>35</td>
<td>0.82</td>
</tr>
<tr>
<td>5</td>
<td>AMPD1</td>
<td>80</td>
<td>0.66</td>
</tr>
<tr>
<td>6</td>
<td>APOE</td>
<td>24</td>
<td>0.16</td>
</tr>
<tr>
<td>7</td>
<td>ATP1A2*</td>
<td>81</td>
<td>0.13</td>
</tr>
<tr>
<td>8</td>
<td>ATP1A2</td>
<td>5</td>
<td>6.4 x 10^{-3}</td>
</tr>
<tr>
<td>9</td>
<td>BDKRB2</td>
<td>15</td>
<td>9.6 x 10^{-4}</td>
</tr>
<tr>
<td>10</td>
<td>CKM</td>
<td>49</td>
<td>4.7 x 10^{-4}</td>
</tr>
<tr>
<td>11</td>
<td>EPAS1*</td>
<td>33</td>
<td>1.5 x 10^{-4}</td>
</tr>
<tr>
<td>12</td>
<td>EPAS1</td>
<td>19</td>
<td>2.9 x 10^{-5}</td>
</tr>
<tr>
<td>13</td>
<td>HFE</td>
<td>4</td>
<td>1.2 x 10^{-6}</td>
</tr>
<tr>
<td>14</td>
<td>HIF1A</td>
<td>77</td>
<td>9.1 x 10^{-7}</td>
</tr>
<tr>
<td>15</td>
<td>HLA-A</td>
<td>2</td>
<td>1.8 x 10^{-8}</td>
</tr>
<tr>
<td>16</td>
<td>MT-ND5*</td>
<td>93</td>
<td>1.7 x 10^{-8}</td>
</tr>
<tr>
<td>17</td>
<td>MT-ND5</td>
<td>7</td>
<td>1.2 x 10^{-9}</td>
</tr>
<tr>
<td>18</td>
<td>MT-ND5</td>
<td>7</td>
<td>8.3 x 10^{-11}</td>
</tr>
<tr>
<td>19</td>
<td>MT-TT</td>
<td>7</td>
<td>5.8 x 10^{-12}</td>
</tr>
<tr>
<td>20</td>
<td>PPARA</td>
<td>70</td>
<td>4.0 x 10^{-12}</td>
</tr>
<tr>
<td>21</td>
<td>PPARGC1A</td>
<td>40</td>
<td>1.6 x 10^{-12}</td>
</tr>
<tr>
<td>22</td>
<td>UCP2</td>
<td>17</td>
<td>2.7 x 10^{-13}</td>
</tr>
<tr>
<td>23</td>
<td>VEGFA</td>
<td>30</td>
<td>8.2 x 10^{-14}</td>
</tr>
</tbody>
</table>

*Approximate odds ratio*

- 1 : 5
- 1 : 25
- 1 : 40
- 1 : 120
- 1 : 150
- 1 : 600
- 1 : 800
- 1 : 16 000
- 1 : 100 000
- 1 : 200 000
- 1 : 600 000
- 1 : 3 million
- 1 : 85 million
- 1 : 110 million
- 1 : 5.5 billion
- 1 : 6 billion
- 1 : 85 billion
- 1 : 1.2 trillion
- 1 : 17 trillion
- 1 : 25 trillion
- 1 : 62 trillion
- 1 : 364 trillion
- 1 : 1212 trillion

1,000,000 hypothetical individuals, with a randomly generated genetic profile. A score (3= ideal, 2= neutral, 1 = poor) was assigned to each of the genotypes within each gene polymorphism. Total genotype score was the sum of the 23 polymorphisms, scaled to 100.

Polygenic Profile of Elite Endurance Athletes

Considered 7 gene variants and calculated a total genotype score.

Figure 1. Frequency distribution of total genotype scores from a model sample of 50,000 randomly selected Spanish individuals, 46 elite athletes and 123 non-athletes (controls).

Polygenic Profile of Elite Power Athletes

Considered 6 gene variants and calculated a total genotype score.

Conclusions

- Individual genes seem to have at best a small influence on physical performance in the normal population.

- However some genes appear to confer an advantage at the very highest levels of competition in some events, as specific genotypes are more common amongst elite athletes.

- As many genes influence complex phenotypes (strength, endurance etc.) it is an individual’s profile across many genes which is likely to be important.

- This field of science is still in its infancy and is far from predictive of individual talent or potential.
Acknowledgements

Tracey Mc Cauley,
Nottingham University

Dr Sarabjit Mastana
Loughborough University

Dr Alun Williams
Manchester Metropolitan University

Professor Hugh Montgomery
University College London
## ACE genotype and Responses to Strength Training

10 weeks of strength training the elbow flexors:

<table>
<thead>
<tr>
<th>% Changes:</th>
<th>II (n=146)</th>
<th>ID (n=291)</th>
<th>DD (n=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isometric Strength</td>
<td>22.8 ± 1.7</td>
<td>22.0 ± 1.3</td>
<td>16.8 ± 1.6**</td>
</tr>
<tr>
<td>1-RM</td>
<td>51.6 ± 2.5</td>
<td>50.9 ± 1.8</td>
<td>51.2 ± 2.3</td>
</tr>
<tr>
<td>CSA</td>
<td>18.1 ± 0.9</td>
<td>19.1 ± 0.6</td>
<td>19.9 ± 0.8</td>
</tr>
</tbody>
</table>

▶ For Isometric Strength gains 1.5% variance was explained by ACE genotype.

Variation in the response to Endurance Training.

Response to a 20 weeks of a standardised training in previously untrained.

Fig. 2. Distribution of the 481 subjects by classes of increase (delta) in $\Delta VO_2_{\text{max}}$ from baseline levels.

Bouchard et al., JAP 87:1003-8.
Polygenic Profile of Elite Endurance Athletes

1,132 Controls and 1,423 Athletes. 10 metabolic gene variants. How many with a high number (>9/20) endurance alleles?

Athletes stratified for:
- Power, short/middle/long endurance, mixed events
- Elite, sub-elite, non-elite standard

Hum Gen
126:751-761.
The Systemic Renin-Angiotensin System

Angiotensinogen → Renin → Angiotensin I → Angiotensin II → ACE → Kinin

Water retention vasoconstriction → BP↑
Rigat et al., (1990)
Gene Athlete study – 192 Endurance athletes with VO$_2$max of >75 ml.kg$^{-1}$.min$^{-1}$

## ACTN3 Genotype and Sprint Performance

284 healthy Spanish adults:

<table>
<thead>
<tr>
<th></th>
<th>RR (n = 90)</th>
<th>RX (n = 141)</th>
<th>XX (n = 52)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vertical jump tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SJ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flight time (s)</td>
<td>546.6 (5.1)</td>
<td>545.0 (4.1)</td>
<td>540.3 (6.6)</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td>Vertical displacement of CG (cm)</td>
<td>36.9 (0.7)</td>
<td>36.7 (0.5)</td>
<td>36.1 (0.9)</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td>RR (n = 90)</td>
<td>RX (n = 141)</td>
<td>XX (n = 52)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Vertical displacement of CG (cm)</td>
<td>38.1 (0.7)</td>
<td>37.9 (0.6)</td>
<td>38.2 (0.9)</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td><strong>Sprint tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 m running start</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time at 15 m (s) (A)</td>
<td>2.00 (0.02)</td>
<td>2.01 (0.19)</td>
<td>1.98 (0.02)</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td>Time at 30 m (s) (B)</td>
<td>3.91 (0.04)</td>
<td>3.93 (0.03)</td>
<td>3.89 (0.05)</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td>30 m standing start</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time at 15 m (s) (C)</td>
<td>2.61 (0.02)</td>
<td>2.61 (0.02)</td>
<td>2.61 (0.02)</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td>Time at 30 m (s) (D)</td>
<td>4.54 (0.04)</td>
<td>4.56 (0.03)</td>
<td>4.57 (0.04)</td>
<td>&gt; 0.1</td>
</tr>
</tbody>
</table>

Santiago et al. (2009). *SJMSS* in press.
ACE I/D Genotype and Muscle Function in Young & Older Men

Healthy UK Caucasian Men
Low-moderate physical activity level (< 4 sessions per week).

Young Men, n=78
Older Men, n=100

20 ± 2 years
65 ± 3 years

♦ Genetics:
ACTN3 R/X Genotype: RR 27, RX 37, XX 15
RR 43, RX 41, XX 16

♦ Knee Extensor Muscle Function:
Strength at different velocities
Contractile Properties
Strength and the Torque-Velocity relationship for different ACTN3 Genotypes

Young Men (n=78)

ACTN3 R/X genotype:
- RR
- RX
- XX

Older Men (n=100)

ACTN3 R/X genotype:
- RR
- RX
- XX

McCauley et al. *EJAP in press.*
Contractile Properties of the Knee Extensors for different ACTN3 Genotypes

Young Men (n=78)

Older Men (n=100)

McCauley et al. EJAP in press.
ACTN-3 Genotype and Physical Performance

Changes in cycling efficiency after 11 weeks of basic military training.

Fibre type of 41 healthy young untrained Japanese.

The Systemic Renin-Angiotensin System

Angiotensinogen → Renin → Angiotensin I → ACE → Angiotensin II → Kinin → BP↑

Water retention vasoconstriction
ACTN3 genotype and Muscle Composition?

<table>
<thead>
<tr>
<th>ACTN3 genotype</th>
<th>577 RR</th>
<th>577 RX</th>
<th>577 XX</th>
<th>Statistics (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Men (n=16)</td>
<td>Women (n=7)</td>
<td>Men (n=9)</td>
<td>Women (n=8)</td>
</tr>
<tr>
<td></td>
<td>Men (49 ±17)</td>
<td>Women (66 ± 7)</td>
<td>Men (54 ±10)</td>
<td>Women (62 ±13)</td>
</tr>
<tr>
<td></td>
<td>Men (12 ±13)</td>
<td>Women (8 ± 5)</td>
<td>Men (9 ± 5)</td>
<td>Women (7 ± 6)</td>
</tr>
</tbody>
</table>

Possible effect of Angiotensin II (& perhaps the ACE gene) on performance

Effects of Angiotensin II on Muscle Performance

Angiotensin II

Nervous System
Enhanced nor-adrenalin release from CNS and SNS.

Vascular
Increased capillary density in skeletal muscle tissue via AT1 receptors.

Smooth Muscle
Alter skeletal VSMC tone via:

↑ VSMC growth
↑ Stimulation of:
  - FGF
  - TGF-β
  - PDGF

Skeletal Muscle
Direct hypertrophic effect on skeletal muscle
Redirection of blood flow to type 2 fibres
↑ O₂ consumption
↑ Contraction tension

Fig. 1. Illustration of the mechanisms of angiotensin II on muscle performance.
α-Actinin 3 (ACTN3)

ACTN3 genotype of 301 Australian athletes and controls:

ACTN-3 Genotype and Physical Performance

Isometric Strength in relation to ACE genotype
[Mean ± SEM; II, n=11; ID, n=33; DD, n=16].

![Graph showing isometric strength (N) in relation to ACE genotype (II, ID, DD).](image-url)
Circulating ACE activity and Isokinetic Strength at 1.05 rad.s\(^{-1}\) \((n = 81)\).

\[
r = 0.375, \quad P < 0.01
\]
Circulating ACE activity and Isokinetic Strength at 1.05 rad.s\(^{-1}\) (\(n = 81\)).

\[ r = 0.375, \ P < 0.01 \]
Circulating ACE activity and Isometric Strength at 1.57 rad $[n = 81]$. $r = 0.253, P = 0.013$.
Vitamin D Receptor Genotype & Muscle strength of 175 Swedish women.

ACE genotype and Muscular Strength
[Mean ± SEM, n = 81].

ACE Genotype

Isometric strength (N)

Isokinetic strength (N m)

- Isometric at 1.05 rad
- Isometric at 1.57 rad
- Isokinetic at 1.05 rad.s\(^{-1}\)
ACE Genotype & Elite Runners at different distances

ACE Genotype: Association Studies
Affect on Strength in the normal population?

Young Men


Older

Fredericksen et al. ?