Institution: Manchester Metropolitan University		
Unit of Assessment: C24 Sport and Exercise Sciences, Leisure and Tourism		
Title of case study: The genetics of sport: challenging international regulations and assumptions around genetic advantage		
Period when the underpinning research was undertaken: 2004-2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Alun Williams	Senior Lecturer, Reader	Jan 2003 – present
Georgina Stebbings	Lecturer, Senior Lecturer	Sep 2010 – present
Stephen Day	Principal Lecturer	Sep 2009 – Aug 2018
Period when the claimed impact occurred: 1 Aug 2013 – 31 December 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Manchester Metropolitan University's research on the genetics of human physiology and physical performance is at the forefront of major decisions regarding the regulation of sport. At the Caster Semenya v International Association of Athletics Federations (IAAF) (since renamed 'World Athletics') 'sporting trial of the century' in 2019, the judges agreed with Dr Alun Williams' research evidence that IAAF's proposed regulations were indeed discriminatory, but the majority verdict against Semenya deemed them also 'necessary' to protect the female category. The ruling directly affected the competition prospects of several national teams and the careers of champion runners; it also triggered truly global discourse around the role of genetics in sport and earned widespread condemnation, including from the United Nations Human Rights Council (UNHRC). This high-profile case followed years of media and public engagement by Williams, highlighting the ethics and evidence around genetic testing in sport. His research underpins the policy position on genetic testing by the Australian Institute of Sport and the DNAFit Code of Practice. At least three elite rugby clubs and two national governing bodies have also refused to adopt genetic testing programmes on the basis of Williams's research findings.

2. Underpinning research

Understanding genetic characteristics of elite athletes may, one day, improve selection, individualise training and personalise management of injury – all challenges faced by coaches and scientists in sport, and fitness professionals working with broad populations. Funded by The Royal Society, charities, the EU and a commercial sponsor (see Section 3), Williams leads sport genetics research into these challenges at Manchester Metropolitan University. The programme of research investigates the role of single and multiple genes and their variants on physical fitness, trainability, risk of injury and success in elite sport. The body of research is described in over 30 peer-reviewed journal papers.

A feature of the research has been studies on the combined effects of multiple genes. Williams pioneered methods for simultaneous analysis of multiple genetic variants alongside *in vivo* physiological characteristics to elucidate the roles of the *ACE*, *ACTN3* and related genes in physical performance. His team was first to show that possessing multiple specific genetic variants improves physical performance and hence the likelihood of success in sport. For example, an early study investigated the individual and combined effects of variants of *ACE* and the bradykinin receptor B2 (*BDKRB2*) on the efficiency of muscular contraction and running distance among Olympic standard track athletes. An *ACE* I with 'high kinin receptor activity' haplotype was significantly associated with endurance among athletes. The study provided the first evidence that at least part of the association of *ACE* and fitness phenotypes is through elevation of kinin activity **[1]**.

Similarly, using a range of physiological measures before and after resistance training in untrained men, the researchers discovered that participants carrying the *ACTN3* R577 allele had larger muscle volume, and greater power and strength compared to non-carriers, but training performance was unrelated to the *ACTN3* genotype. However, an 'optimal' genotype (*ACE* D allele combined with *ACTN3* R allele) gave greater isoinertial strength and maximum power, post training **[2]**.

Williams led the largest, international study of its kind that combined rare performance and genotype data from 698 elite athletes in six countries. The study design addressed the limitations of typical work in the field, such as small sample sizes from mixed sport disciplines

and a lack of quantitative measures of performance. Manchester Metropolitan provided six of the 25 authors (including joint lead and senior authors) and 83% of the data. The analysis showed that despite previous statistically significant associations, individual commonly tested genetic variants have, at best, a small effect on real-world performance in elite endurance running **[3]**.

This study also emphasised the translational value of a seminal, highly cited paper that demonstrated how multiple genetic factors combine in a complex, polygenic manner to regulate human physical performance. Modelling and analysing data on 23 genetic variants associated with human endurance performance with their frequencies in the general population, Williams found only a 0.0005% chance of a single individual in the world having the 'preferable' form of all 23 polymorphisms. Genetic predisposition to high endurance potential is genetically homogenous, with 99% of people differing by no more than seven genotypes from the typical profile **[4]**.

These two studies, and others from the Manchester Metropolitan group, collectively confirm that a few common genetic variations can only account for a very small portion of the substantial genetic influence on physical performance. This overarching finding contradicts the marketing of genetic testing providers, and highlights the fact that meaningful interpretation of results from commercial tests is severely limited (see Section 4).

Recent work from the group has, uniquely, associated variants such as those in the *ACTN3*, *FTO* and *COL5A1* genes with the ability to attain elite competitive level in rugby union and the particular playing position that elite level players achieve **[5,6]**. This work has involved more elite athletes (tightly defined) from one professional sport than achieved by any other research group. Nevertheless, statistically significant associations in large well-controlled studies such as these do not (yet) translate to practical tools that can be used by coaches to identify talent and personalise training of individual athletes, due to the complex polygenic nature of effects as demonstrated by the other pioneering work described.

3. References to the research

Note: Citations, Web of Science (citations and expected citations) – December 2020.

1. **Williams** AG, Dhamrait SS, Wootton PTE, Day SH, Hawe E, Payne JR, Myerson SG, World M, Budgett R, Humphries SE, Montgomery HE, (2004). Bradykinin receptor gene variant and human physical performance. J Appl. Physiol. 96(3):938-942. DOI: 10.1152/japplphysiol.00865.2003. *Citations: 65 (expected: 45.67).*
2. Erskine RM, **Williams** AG, Jones DA, Stewart CE, Degens H, (2014). The individual and combined influence of ACE and ACTN3 genotypes on muscle phenotypes before and after strength training. Scand J. Med. Sci. Sports 24(4):642-648. DOI: 10.1111/sms.12055. *Citations: 36 (expected: 22.51).*
3. Papadimitriou ID, Lockey SJ, Voisin S, Herbert AJ, Garton F, Houweling PJ, Cieszczyk P, Maciejewska-Skrendo A, Sawczuk M, Massidda M, Calò CM, Astratenkova IV, Kouvatsi A, Druzhevskaya AM, Jacques M, Ahmetov II, **Stebbings** GK, Heffernan S, **Day** SH, Erskine R, Pedlar C, Kipps C, North KN, **Williams** AG, Eynon N, (2018). No association between ACTN3 R577X and ACE I/D polymorphisms and endurance running times in 698 Caucasian athletes. BMC Genomics 19(1):13. DOI: 10.1186/s12864-017-4412-0. *Citations: 24 (expected: 7.02).*
4. **Williams** AG, Folland JP, (2008). Similarity of polygenic profiles limits the potential for elite human physical performance. J. Physiol. 586(1):113-121. DOI: 10.1113/jphysiol.2007.141887. *Citations: 125 (expected: 56.80).*
5. Heffernan SM, **Stebbings** GK, Kilduff LP, Erskine RM, **Day** SH, Morse CI, McPhee JS, Cook CJ, Vance B, Ribbans WJ, Raleigh SM, Roberts C, Bennett MA, Wang G, Collins M, Pitsiladis YP, **Williams** AG, (2017). Fat mass and obesity associated (FTO) gene influences skeletal muscle phenotypes in non-resistance trained males and elite rugby playing position. BMC Genet. 18(1):4. DOI: 10.1186/s12863-017-0470-1. *Citations: 10 (expected: 7.91).*
6. Heffernan SM, Kilduff LP, Erskine RM, **Day** SH, **Stebbings** GK, Cook CJ, Raleigh SM, Bennett MA, Wang G, Collins M, Pitsiladis YP, **Williams** AG, (2017). COL5A1 gene variants previously associated with reduced soft tissue injury risk are associated with elite athlete status in rugby. BMC Genomics 18(Supp. 8):820. DOI: 10.1186/s12864-017-4187-3. *Citations: 5 (expected: 11.56).*

Grants and funding

- Polygenic profiles of elite Russian strength athletes (part of GENESIS). The Royal Society, International Joint Project, 2010-12. PI: Williams. GBP12,000.
- Genetic characteristics of elite rugby athletes (part of RugbyGene). Dream It Believe It Achieve It (charity), 2013-2014. PI: Dr Alun Williams. GBP36,000.
- Genetics of sarcopenia. Funded through the MOVE-AGE EU Erasmus Mundus Joint Doctoral Program, 2014-17. PI: Dr Chris Morse. Total award: GBP108,703.
- Biomarkers of concussion – pilot work. Holos Life Sciences, 2018 (Project ID: 158249). PI: Dr Alun Williams. Total award: GBP5,000.
- Biomarkers of concussion. Holos Life Sciences, 2019-2021 (Project ID: 152771). PI: Dr Alun Williams. Total award: GBP231,123.

Additional indicators of quality

- Publication metrics for [1-4] indicate higher than expected citations, suggesting they have made a significant contribution to the academic field. Metrics for [1-3] also indicate high Altmetric attention percentiles.
- Williams led expert consensus statements on sport genetics in 2007, 2012 and 2015 for the British Association of Sport and Exercise Sciences (BASES) and the International Federation of Sports Medicine (FIMS, see Section 4).
- The international GENESIS and RugbyGene collaborations are led by Manchester Metropolitan University.
- Williams is a member of the Steering Committee of the International Athlome Consortium (GENESIS is a major component). Stebbings is Convenor of the BASES Molecular Exercise Physiology Special Interest group, succeeding Williams.
- Stebbings and Williams, with colleagues at Birmingham City University, Swansea University, University of Colorado Boulder and World Rugby, received an Expert Statement Grant from BASES in 2020 to prepare expert statements on sex testing in sport (*in prep.*). These grants are awarded according to the importance, impact and interest of the topic, relevance to sport and exercise, and expertise of the team.

4. Details of the impact

This body of work on the genetics of human physiology and physical performance in sport has been at the forefront of global public discourse and major controversial decisions on sports regulations and practices, which have had significant repercussions for individual athletes and national teams.

Informing the high-profile Caster Semenya legal case

In February 2019, Williams provided scientific evidence on sports genetics as an expert witness in the controversial hearing of two-time Olympic women's 800m champion Caster Semenya *versus* IAAF at the Court of Arbitration for Sport (CAS). CAS is the highest authority for dispute resolution in sport. Semenya challenged IAAF on its proposal that all women – notably those like Semenya with differences of sex development (DSD) – must ensure their natural genetics and testosterone levels meet defined criteria, including testosterone below 5ng/ml, to compete internationally in specified women's running distances **[A]**. The UK's Guardian newspaper described the hearing *as "the sporting trial of the century"* **[B]**.

The selection of Williams as a witness is evidence of the significance of his research findings to the case. Semenya's lawyers selected him from the worldwide pool of experts in the field; he was one of only nine expert witnesses for Semenya and the only one with expertise in sport genetics. Semenya's lawyers remarked that: *"this case has become widely recognized as one of the most significant and complex sport disputes in history,"* adding that Williams' published research was directly relevant to this issue and that his testimony and insights *"were impressive and very valuable to the CAS as it grappled with the issues before it"* **[A]**.

Williams submitted an 80-page report and delivered an oral deposition with cross-examination. His confidential report cited more than 30 Manchester Metropolitan University publications (including [1-6], see Section 3) to evidence the complex nature and uncertainties of genetic associations with physical performance **[A]**. Based on his extensive research, he told the CAS arbitrators *"the mutations found in DSD athletes are not exceptional and arguably should not be treated differently by special regulations"* **[A,B,C]**.

Significance and reach of the verdict

CAS gave a divided ruling of 2:1 against Semenya on 1 May 2019. The arbitrators acknowledged the regulations were indeed "discriminatory" (as argued by Williams), but also "necessary" to protect the female category. The unprecedented publication of the hearing's transcript by CAS indicates the global significance of the verdict and its likely impact across all international sport (not just athletics) **[C]**. The transcript placed Williams' evidence into the public domain, helping to inform the ensuing public discourse and debate (see next section).

The significance of the ruling is evidenced by its direct impact on individual athletes and national teams. Semenya refused to comply with the regulations and will now be unable to defend her Olympic title for South Africa. She is attempting to qualify for the Tokyo 2021 Olympics in the 200m. She is also preparing to overturn the CAS ruling through the European Court of Human Rights **[D]**. Several champion athletes have declared their DSD status and been deselected, affecting their wellbeing and the medal prospects of their teams. Kenya's deselected Olympic 800m bronze medallist Margaret Wambui said: *"That was my career, my talent… That's how I was earning a living. And all of a sudden, this was blocked. It affected me a lot"* **[D]**.

The IAAF regulations triggered international condemnation. The World Medical Association (WMA) urged members not to implement the IAAF rules **[E]**. The UN High Commissioner for Human Rights led an inquiry and published a report that concluded countries should outlaw sporting regulations that pressurise athletes to undergo "unnecessary" medical interventions **[E]**.

Other than World Athletics, no other sport federation has regulations for the eligibility of DSD women. Nevertheless, two federations – UCI (cycling) and World Rugby – have followed the precedent set by CAS to implement regulation(s) in other domains, specifically transgender participation, while the International Olympic Committee (IOC) notably failed to reach a decision on transgender participation, citing a lack of insufficient evidence **[F]**. Responding to this flurry of controversial regulatory activity, the IOC recently announced creation of a human rights unit to *"ensure fairness, safety and non-discrimination of athletes on the basis of gender identity and sex characteristics."* The move shows a high-level attempt to develop more inclusive, evidence-based regulations in alignment with current research **[F]**.

Global public discourse

The CAS verdict by no means ended debate or discourse: rather, it fuelled huge volumes of news and opinion in global media, reaching almost all news consumers worldwide (at least 6,000 headlines in 40 languages and 130 countries) **[G]**. Among the top ten press articles in terms of reach, reiterating Williams' arguments and his CAS evidence during this period, was an Associated Press column '*Welcome to the world of performance-reducing drugs'* (republished in 117 outlets across nine countries), and The Washington Post's '*We celebrated Michael Phelps's genetic differences. Why punish Caster Semenya for hers?*' (reach: 56,583,222), which triggered 141,445 Facebook reactions worldwide **[G]**. Almost a quarter of the 1,689,536 Facebook reactions about the CAS verdict were linked to articles discussing the genetic angle of the case. An analysis in South Africa's Daily Maverick (reach: 1,052,179) summed up the main argument (and Williams' position) succinctly, i.e. that IAAF *"might have won on a technicality – not because its science is sound"* **[G]**.

Williams added his own voice and research findings to the discourse, with a personal piece published in The Independent (readership: 11,362,292), which was directly referenced by The Telegraph (readership: 458,487). Immediately following the verdict, he provided scientific expertise to discourse on UK national TV news (BBC1, ITV; viewers: 8,968,166); national radio in the UK, USA and Canada (BBC 5 Live; BBC Radio 4; BBC local radio, CBC Radio One (Canada); US local radio); and a podcast by Sigma Nutrition (13,911 downloads) **[G]**.

The BBC Radio 4 flagship programme, *Inside Science* (1,900,000 listeners) dedicated most of an episode to discussion with Williams about the case. Evidence of the significance of this contribution is indicated by the selection of the interview for two re-broadcasts as *Inside Science Shorts*. A post-broadcast discussion on Twitter recorded 83,000 views. The show's presenter says the episode received: *"a well-above average volume of correspondence"* and that *"many expressed the view that we dealt with this topic sensitively, and [Dr Williams's] contribution as an expert in both genetics and sport was welcome in a potentially fractious subject"* **[G]**.

Limiting uptake of direct-to-consumer (DTC) genetic testing

The CAS hearing was a culmination of Williams' long-running public advocacy for ethical and evidence-based use of genetic testing in sport. Since 2014 his work has featured in more than 30 media articles, videos (e.g. BBC Radio 1 DNA+Fitness series, approximately 50,000 viewers)

and TV appearances (e.g. BBC Watchdog, 3,000,000 viewers). He has thus cautioned millions of people against DTC testing, reaching broad groups through TV and radio, and relevant amateur sports participants (e.g. runners, cyclists and rugby players) **[G]**.

In 2015, Williams was corresponding author on a consensus statement that drew on his research (citing [3-4], see Section 3) to conclude that DTC testing had "*little or no role to play in talent identification or individualised prescription of training*", including in children **[H]**. The statement has gained significant attention: 23,388 full article views, 8,060 downloads and 492 tweets (60% from non-experts and reaching up to 1,531,149 followers). Altmetric places it in the 99th percentile of over 16,000,000 research outputs tracked (attention score: 428) **[H]**. Global media helped to raise awareness among parents and sport participants, citing Williams and/or the consensus statement in at least 46 articles in nine countries (approximate reach: 271,000,000) **[G]**.

This statement directly underpins policy positions and codes of practice. Most notably, a Position Statement from the Australian Institute of Sport (AIS), which leads Australia's high performance system, references the consensus statement and concludes that: "*use of genetic testing as an absolute predictor of athletic prowess or sport selection is unscientific and unethical"* **[I]**. DTC testing company DNAFit reacted directly to the statement by publishing a code of practice, including no DTC testing for talent identification or of children. The company called on the DTC sector to adopt the code as best practice **[I]**.

During the course of their research with elite players, Manchester Metropolitan researchers have used every opportunity to educate players, clubs and national governing body staff on the limitations of genetic testing. They have presented to national bodies in five countries, 11 professional rugby clubs and three Premier League football clubs. At least three elite clubs, plus the UK Rugby Football Union (RFU) and the Rugby Union of Russia (RUR) have consequently resisted DTC genetic testing **[J]**. The current Head of Physical Performance at RUR says that as a result of input from Williams *"at Ospreys, Bristol, and the RFU and in Russia, we have not paid any genetic testing companies to work with our players… had we devoted precious resources to genetic testing instead of other more effective biomedical science applications, we would probably not have achieved the success we did*" **[J]**.

A recent survey shows only 13% of UK elite athletes had undergone some form of genetic testing. This low level suggests that athletes are still reluctant to use genetic testing in the absence of clear benefits. It appears that the caution advocated by the consensus statement and policies, like the AIS position statement, are being heeded **[J]**.

5. Sources to corroborate the impact

A. Statement from Tyr LLP, lawyers for Caster Semenya at the CAS hearing, *provides evidence of the significant contribution of Dr Williams' research to the hearing.*
B. "Caster Semenya v IAAF: the inside story of sporting trial of the century" (The Guardian, 1 May 2019) *refers to Dr Williams' evidence as part of the Semenya's case*.
C. Redacted hearing transcript released by CAS *is evidence of the global significance of the hearing. It also provides detailed evidence of Dr Williams' contribution to the hearing.*
D. Compilation of press items provides *evidence of the significant impact of the CAS decision on Semenya, the deselection of other champion female runners, and Semenya's preparation to take the case to the European Court of Human Rights.*
E. *World Medical Association* press statement and UNHRC report *provide evidence of high level, international outrage and resistance to the IAAF regulations.*
F. News items about: *adoption of transgender regulations by UCI and World Rugby; disagreement on transgender regulation in the IOC; the new IOC human rights unit.*
G. Analysis of media coverage and statements from CEO, Sigma Nutrition and Presenter of BBC Radio 4 *Inside Science provide evidence of the media reach of discourse about genetics in sport, DTC testing and Dr Williams' significant contribution to discussion.*
H. Copy of Consensus Statement with *metrics indicating high levels of reach and engagement.*
I. Copy of AIS Position Statement and DNAFit Code of Practice *are evidence of change in elite sport policy and industry practice influenced by the consensus statement.*
J. Testimonials from practitioners and a peer-reviewed survey of elite athletes *provide evidence that elite clubs, national governing bodies and athletes are cautious about adopting genetic testing.*