The Dawning Age of Genetic Testing for Sports Injuries

Gabrielle T. Goodlin, BAS, Thomas R. Roos, MS,† Andrew K. Roos, MS,† and Stuart K. Kim, PhD**

The regular demands of training and competition make professional, collegiate, and recreational athletes highly susceptible to injury. The incidence rate of injuries among National Collegiate Athletic Association (NCAA) athletes is approximately 15.47 per 1000 athlete exposures.[1] Recreational distance running causes high numbers of injuries, with incidence rates estimated between 30% and 75% per person per year.[2,3] Similarly, up to 75% of age-group triathletes who participate in Ironman-distance races are injured at least once each training season.[4,5] Treatment of sports injuries costs at least $160 billion per year in the United States, and Major League Baseball lost $1.6 billion in payroll between 2008 and 2013 because of injuries to players.[6,7] Avoiding injuries and remaining healthy is key to the success of a team or an individual athlete.[8]

The potential to use genetic testing to reduce sports injuries is rapidly increasing. The *COL1A1* gene, for example, encodes the alpha chain of type I collagen, the major protein component of all tendons and ligaments.[9,10] There is a DNA single-nucleotide polymorphism (SNP), rs1800012, in the upstream region of this gene that affects its level of expression. The majority of people carry a G nucleotide at this polymorphic position, and approximately 20% carry a T nucleotide.[11] The T allele leads to increased expression of type I collagen alpha polypeptides compared with the G nucleotide, which may increase the tensile strength of tendons and ligaments.[12–14] About 4% of athletes carry 2 copies of the T allele.[11,14] These TT athletes show significantly decreased risk for anterior cruciate ligament (ACL) rupture and Achilles tendinopathy.[14–16] Besides this polymorphism in *COL1A1*, there are additional DNA variants associated not only with ACL rupture and Achilles tendinopathy but also with other athletic injuries (eg, shoulder dislocations and muscle strain severity).[14,17–21] There are separate studies concerning genetic polymorphisms associated with athletic performance, such as muscle contractility and $\dot{V}O_2$max.[22,23]

Genetic information of this sort has recently been used to prevent injuries and maximize athletic performance (Table 1). A professional soccer team in the English Premier League, for example, tested athletes for genetic loci associated with sports performance, and the English Institute of Sport expressed interest in providing genetic testing to Britain's Olympic athletes in 2012.[34,36] Uzbekistan is introducing genetic testing into its Olympic-talent identification program, Australian National Rugby League players use DNA testing to tailor workouts for sprinting or explosive power-lifting, and 2 English Premier League soccer teams have introduced genetic testing for their players.[35,37,38] In the United States, the NCAA currently requires blood draws for all NCAA collegiate athletes to test for the presence of the sickle cell trait, which is genetically determined.[39]

Several direct-to-consumer genomic companies offer genetic testing to a wide range of athletes (Table 2).[40] Some companies offer genetic tests that indicate risk for sports injuries, such as soft-tissue injuries and concussions. Others provide information about sports performance, muscle fiber type, and $\dot{V}O_2$max. DNAFit (DNAFit Ltd, London, United Kingdom)

From the *Departments of Developmental Biology and Genetics, Stanford University Medical Center, Stanford, California; and †Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California.

The authors report no conflicts of interest.

Corresponding Author: Stuart K. Kim, PhD, Stanford University School of Medicine, Developmental Biology, 279 Campus Dr, Beckman Center B300, Stanford, CA 94305 (stuartkm@stanford.edu).

provides a service to recreational athletes, elite athletes, professional sports teams, and individuals interested in weight loss.[41] 23andMe (23andMe, Inc, Mountain View, California) and Pathway Genomics (Pathway Genomics, San Diego, California) include information on athletic markers as part of a wider range of genetic services.[42,43] This genetic information is then used in the development of injury prevention programs tailored for each individual.[44] Most direct-to-consumer companies offer information on how to alter athletic training based on an individual's genetic results. For example, DNAFit provides its customers access to a network of personal trainers, and the Stanford Sports Genetics Program provides a 60-minute consultation to each participant.[41,45]

The DNA polymorphisms currently used in sports were identified in studies that test a small number of candidate genes using relatively small athlete populations (typically several hundred). There is a large and rich source of additional genetic information that could be used by athletes based on genome-wide association studies (GWAS) that examine health risks in the general population. Genomic-wide association studies can test over 1 million different polymorphisms and often include tens of thousands of subjects. Therefore, the statistical power of discovering significant genetic variants that contribute to complex phenotypes is very high.[46] The results from these health studies in the general population can also provide key information to athletes about their risk for injury or nutritional needs. Low bone mineral density, for example, affects both older individuals (osteoporosis and skeletal fracture) and athletes (stress fracture).[47–50] A large meta-analysis assessing bone mineral density integrated the results of 17 GWAS that screened approximately 1 million SNPs in a total of 32 961 elderly individuals.[51] Sixty-three SNPs associated with bone mineral density at genome-wide significance were identified. The weighted contributions of each of these 63 SNPs were combined into 1 genetic score. Elderly individuals in the highest risk category have 1.56 increased odds for osteoporosis and 1.60 increased odds for fracture. Conversely, elderly individuals in the lowest category are protected against osteoporosis and fracture (0.62 and 0.46 decreased odds, respectively).[51] Genetic variants related to osteoporosis in elderly women may very well have prognostic application regarding stress fractures in young athletes. First, bone mineral density is a major determinant for stress fractures, especially among endurance athletes.[47–50] Second, higher rates of osteoporosis in older women and higher rates of stress fractures in young, active women tend to appear together in the same family.[52–54] Thus, the genetic score developed for low bone mineral density in the elderly could also be a powerful tool for athletes, especially endurance athletes. The sports genetics program at Stanford University uses genetic variants associated with bone mineral density—as well as other pathological or predisposing states such as osteoporosis, asthma, vitamin and mineral levels, red blood cell phenotypes, caffeine metabolism, and disc degeneration—that can be used to reduce injury risk.[45,55] By incorporating results from GWAS, the Stanford Sports Genetics Program has greatly expanded the set of DNA polymorphisms that can be used to reduce sports injury risk from approximately 13 previously known polymorphisms to 195 polymorphisms now currently in use.[45]

It is too early to measure the effect of genetic testing on reducing the incidence of injuries or inducing behavioral changes that will promote health and/or prevent injury. It is clear that there are many genetic polymorphisms that provide information about risk for sports-related injuries and performance-related conditions. Athletes, coaches, and medical practitioners can use this information to generate personalized training regimens for athletes. It is too early, however, to gauge the effectiveness of these personalized regimens at reducing injury incidence compared with standard training. Nevertheless, any additional information about performance might be useful to help reduce injuries and maximize performance among elite athletes, who are typically early adopters of many medical treatments designed to speed recovery from injury and/or reduce pain so that they can return to play as soon as possible.[56–58] For recreational athletes, the benefits of genetic testing may be small when compared with the results of increased participation in standard approaches to training.[59] Besides prompting athletes to include new modifications in their training or diet, genetic knowledge may also increase compliance with currently prescribed "prehabilitation" strategies.[60]

As genetic testing in sports gains momentum, it is important to develop best practices to protect the legal, ethical, and social rights of the athlete. The existing

TABLE 1. General Timeline of Genetic Testing in Sports

1966-1991 1966-1999	Y-chromosomal testing as part of official sex segregation policy of the International Association of Athletics Federations and of the International Olympic Committee, respectively[24]
2001	Professional Boxing and Martial Arts Board of Victoria considers compulsory genetic screening for APOE4 variant in boxers[25]
2003	World Antidoping Agency prohibits methods of gene doping[26]
2005	Eighteen Australian male rugby players were tested and analyzed for 11 genes[27]
	The Chicago Bulls attempt genetic testing of free agent, Eddy Curry, for the purpose of ruling out hypertrophic cardiomyopathy[28]
2009	23andMe analyzes DNA samples from 100 current and former NFL linemen[29]
	Major League Baseball begins using genetic testing with prospective players from the Dominican Republic and other Latin American Countries[30]
2010	The National Collegiate Athletic Association implements mandatory sickle cell trait screening[31]
2011	An English Premier League soccer team analyzes players' DNA samples at 100 genetic loci[32]
	The National Football League screens for genetic conditions sickle cell trait and G6PD under the 2011 NFL collective bargaining agreement[33]
2012	English Institute of Sport expresses interest in the integration of genetic technologies to "tailor the training, conditioning, and preparation" of Britain's Olympic and Paralympic athletes[34]
2014	Two Barclay's Premier League soccer teams commission tests of their players' DNA for 45 variants[35]

TABLE 2. Genetic Testing Companies for Athletes

Company	Cost	Markers Tested*	Performance/Injury Categories Tested	Nutrition Categories Tested	Time
Stanford Sports Genetics, sportsgenetics.stanford.edu, Stanford, CA	$299	195	Achilles Tendinopathy ACL rupture Lung function Stress fracture and low BMD Osteoarthritis Disc degeneration Sickle cell trait	Caffeine Metabolism Vitamin D, E, B6, B12, and B9 levels Iron levels Trace mineral levels Magnesium levels Calcium levels Phytosterol levels Homocysteine levels	3-4 wk
23andMe, www.23andme.com, Mountain View, CA	$99	9	ACTN3—power and fatigue Response to exercise Asthma	Hemochromatosis Lactose intolerance Blood glucose Caffeine consumption LDL cholesterol levels Response to diet	3-4 wk
DNAFit, www.dnafit.com, London, United Kingdom	Fitness: $189-399 Nutrition: $159-399	45	Injury risk profile (tendinopathies) $\dot{V}O_2$max potential Postexercise recovery speed Recovery nutrition needs Sunburn and sunstroke	Antioxidant needs Vitamin D levels Vitamin and micronutrient intake Carbohydrate and saturated fat sensitivity Salt, caffeine, and alcohol sensitivity	2 wk
Genetic Performance, https://geneticperformance.com, Dublin, Ireland	$248-675	10	Power and fatigue Lactate levels $\dot{V}O_2$max Body fat Isometric grip strength Muscle mass and strength Exercise blood pressure Aerobic fitness Muscle efficiency Endurance performance	N/A	6-8 wk
XR Genomics, www.xrgenomics.com, London, United Kingdom	£149	75	Ability to improve $\dot{V}O_2$max	N/A	3-4 wk
Pathway Genomics, www.pathway.com, San Diego, CA	Unknown, practitioner mediated	75	Achilles tendinopathy Aerobic capacity ($\dot{V}O_2$max) Blood pressure response to exercise BMI response to exercise Endurance training HDL cholesterol response to exercise Insulin sensitivity response to exercise Loss of body fat response to exercise Strength training	Decreased omega-6 and omega-3 Response to monosaturated fats Response to polyunsaturated fats Food reactions (alcohol, caffeine, lactose) Decreased vitamins (folate, A, B2, B6, B12, C, D, and E) Decreased HDL cholesterol Elevated LDL cholesterol Elevated triglycerides	2-4 wk

(*continued on next page*)

TABLE 2. (*Continued*) Genetic Testing Companies for Athletes

Company	Cost	Markers Tested*	Performance/Injury Categories Tested	Nutrition Categories Tested	Time
Gonidio, www.gonidio.com, Hagendom, Switzerland	409-899€	100	Endurance capacity Susceptibility to injuries (tendon and bones) Psychological aptitude Substance abuse Body mass index	Lipid metabolism Folic acid metabolism Iron absorption and storage Inflammatory response Antioxidation Detoxification Salt sensitive hypertension Alcohol metabolism Lactose tolerance Gluten tolerance	Unknown

*Number of single-nucleotide polymorphisms (SNPs) tested.
ACL, anterior cruciate ligament; BMD, bone mineral density; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; BMI, body mass index.

guidelines regarding genetic testing of athletes are currently unclear. The Genetic Information Nondiscrimination Act of 2008 places employees in a protected statutory class and prohibits employer discrimination based on genetic information and family medical history[36]; it is unclear whether this act protects collegiate athletes who do not qualify as employees of universities.[33,36] However, collective bargaining agreements in major league sports may permit mandated genetic testing of athletes.[36] Genetic testing has the potential to empower athletes with new information that might increase their competitive edge. As teams begin to adopt genetic programs, careful steps should be taken to ensure that players are not coerced into participating as part of a screening process that determines athletic eligibility or playing time.

Genetic information is growing at an exceptional rate, producing new information faster than Moore Law—which predicts that overall processing power doubles every 2 years. We anticipate that the power of genetic testing to predict the likelihood of sports-related injuries sustained by athletes will grow rapidly. This new field of study is exciting; it holds great potential for injury prevention for athletes at every level.

REFERENCES

1. Hootman JM, Dick R, Agel J. Epidemiology of collegiate injuries for 15 sports: summary and recommendations for injury prevention initiatives. *J Athl Train.* 2007;42:311–319.
2. van Mechelen W. Running injuries. A review of the epidemiological literature. *Sports Med.* 1992;14:320–335.
3. van Gent RN, Siem D, van Middelkoop M, et al. Incidence and determinants of lower extremity running injuries in long distance runners: a systematic review. *Br J Sports Med.* 2007;41:469–480.
4. O'Toole ML, Hiller WD, Smith RA, et al. Overuse injuries in ultraendurance triathletes. *Am J Sports Med.* 1989;17:514–518.
5. Egermann M, Brocai D, Lill CA, et al. Analysis of injuries in long-distance triathletes. *Int J Sports Med.* 2003;24:271–276.
6. Carroll W. *2013 MLB Team Health Reports: Introduction to Injury-Risk Series. Bleacher Report*. 2013. Accessed June 22, 2014.
7. O'Brien C, Rutherford G, Marcy N. *Hazard Screening Report: Sports Activities and Equipment*. In: Commission USCPS, ed. 2005.
8. Eirale C, Tol JL, Farooq A, et al. Low injury rate strongly correlates with team success in Qatari professional football. *Br J Sports Med.* 2013;47: 807–808.
9. O'Brien M. Structure and metabolism of tendons. *Scand J Med Sci Sports.* 1997;7:55–61.
10. Fujii K, Yamagishi T, Nagafuchi T, et al. Biochemical properties of collagen from ligaments and periarticular tendons of the human knee. *Knee Surg Sports Traumatol Arthrosc.* 1994;2:229–233.
11. *Database of Single Nucleotide Polymorphisms (DbSNP): Rs1800012*. National Center for Biotechnology Information. http://www.ncbi.nlm.nih.gov/SNP. Accessed June 12, 2014.
12. Mann V, Hobson EE, Li B, et al. A COL1A1 Sp1 binding site polymorphism predisposes to osteoporotic fracture by affecting bone density and quality. *J Clin Invest.* 2001;107:899–907.
13. Deak SB, van der Rest M, Prockop DJ. Altered helical structure of a homotrimer of alpha 1(I)chains synthesized by fibroblasts from a variant of osteogenesis imperfecta. *Coll Relat Res.* 1985;5:305–313.
14. Khoschnau S, Melhus H, Jacobson A, et al. Type I collagen alpha1 Sp1 polymorphism and the risk of cruciate ligament ruptures or shoulder dislocations. *Am J Sports Med.* 2008;36:2432–2436.
15. Ficek K, Cieszczyk P, Kaczmarczyk M, et al. Gene variants within the COL1A1 gene are associated with reduced anterior cruciate ligament injury in professional soccer players. *J Sci Med Sport.* 2013;16:396–400.
16. Collins M, Posthumus M, Schwellnus MP. The COL1A1 gene and acute soft tissue ruptures. *Br J Sports Med.* 2010;44:1063–1064.
17. Gayagay G, Yu B, Hambly B, et al. Elite endurance athletes and the ACE I allele–the role of genes in athletic performance. *Hum Genet.* 1998;103:48–50.
18. Maffulli N, Margiotti K, Longo UG, et al. The genetics of sports injuries and athletic performance. *Muscles Ligaments Tendons J.* 2013;3: 173–189.
19. Yang N, MacArthur DG, Gulbin JP, et al. ACTN3 genotype is associated with human elite athletic performance. *Am J Hum Genet.* 2003;73:627–631.
20. Zanoteli E, Lotuffo RM, Oliveira AS, et al. Deficiency of muscle alpha-actinin-3 is compatible with high muscle performance. *J Mol Neurosci.* 2003;20:39–42.
21. Pruna R, Artells R, Ribas J, et al. Single nucleotide polymorphisms associated with non-contact soft tissue injuries in elite professional soccer players: influence on degree of injury and recovery time. *BMC Musculoskelet Disord.* 2013;14:221.
22. Wolfarth B, Rankinen T, Hagberg JM, et al. Advances in exercise, fitness, and performance genomics in 2013. *Med Sci Sports Exerc.* 2014;46:851–859.
23. Ostrander EA, Huson HJ, Ostrander GK. Genetics of athletic performance. *Annu Rev Genomics Hum Genet.* 2009;10:407–429.
24. Foddy B, Savulescu J. Time to re-evaluate gender segregation in athletics? *Br J Sports Med.* 2011;45:1184–1188.
25. Robotham J. Pro boxers face going down for the gene count. *The Sydney Morning Herald*. June 1, 2001:A3.
26. *Gene Doping*. World Anti-doping Agency Website. http://www.wada-ama.org/en/Science-Medicine/Science-topics/Gene-Doping/. Accessed June 15, 2014.
27. Dennis C. Rugby team converts to give gene tests a try. *Nature*. 2005; 434:260.
28. Litke J. *Curry's DNA Fight With Bulls "Bigger Than Sports World"*. ESPN. http://sports.espn.go.com/nba/news/story?id=2174877. Accessed May 30, 2014.

29. Assael S. *Cheating Is So 1999: A Reporter Spends a Year Searching for the Athletic Holy Grail—a Sports Gene*. ESPN The Magazine; 2012. http://m.espn.go.com/general/story?storyId=8153641&wjb=&pg=3. Accessed June 20, 2014.
30. Schmidt M, Schwarz A. Baseball's use of DNA tests on prospects finds controversy, too. *New York Times*. July 22, 2009:A1.
31. Zarda B. *Lawsuit Prompts NCAA to Screen Athletes for Sickle Cell*. USA Today; 2010. http://usatoday30.usatoday.com/sports/college/2010-06-30-sickle-cell-ncaa-cover_N.htm. Accessed May 30, 2014.
32. Marsh B. *DNA Clue to Football Injuries*. The Sunday Times; 2011. http://www.thesundaytimes.co.uk/sto/news/uk_news/article799536.ece. Accessed May 30, 2014.
33. Siegel A, Alvarez F. *Sickle-Cell Testing and the Implications of Gina*. Sports Litig Alert; 2010. http://www.sportslitigationalert.com/archive/2010_05_21.php. Accessed May 25, 2014.
34. Watts S. *Olympic Team GB Trials Gene Tests for Injury*. BBC News; 2012. www.bbc.com/news/health-18970982. Accessed June 16, 2014.
35. Williamson L. *Two Premier League Clubs Sign up With Top Genetics Company to Learn DNA Profiles of Players*. Daily Mail; 2014. http://www.dailymail.co.uk/sport/football/article-2582714/Two-Premier-League-clubs-sign-genetics-company-learn-DNA-profiles-players.html. Accessed May 30, 2014.
36. Wagner JK. Sidelining Gina: the impact of personal genomics and collective bargaining in professional sports. *Va Sports Entertainment L J.* 2013;12:1–19.
37. Synovitz R, Eshanova Z. *Uzbekistan Is Using Genetic Testing to Find Future Olympians*. The Atlantic; 2014. http://www.theatlantic.com/international/archive/2014/02/uzbekistan-is-using-genetic-testing-to-find-future-olympians/283001/. Accessed May 30, 2014.
38. Epstein D. *Sports Genes: Who Has the Speed Gene, and Who Doesn't?* Sports Illustrated; 2010. http://si.com/vault/article/magazine/MAG1169440/6/index.htm. Accessed May 30, 2014.
39. Klossner D, ed. *2012-2013 NCAA Sports Medicine Handbook*. 23rd ed. Indianapolis, Indiana: NCAA; 2012. http://www.ncaapublications.com/productdownloads/MD12.pdf. Accessed March 12, 2013.
40. Wagner JK, Royal CD. Field of genes: an investigation of sports-related genetic testing. *J Pers Med.* 2012;2:119–137.
41. *DNAFit*. http://www.dnafit.com/. Accessed June 24, 2014.
42. *Pathway Genomics*. https://www.pathway.com. Accessed June 24, 2014.
43. *23andMe*. https://www.23andme.com. Accessed June 24, 2014.
44. Kambouris M, Ntalouka F, Ziogas G, et al. Predictive genomics DNA profiling for athletic performance. *Recent Pat DNA Gene Seq.* 2012;6:229–239.
45. *Stanford Sports Genetics Project*. https://sportsgenetics.stanford.edu. Accessed June 24, 2014.
46. Panagiotou OA, Willer CJ, Hirschhorn JN, et al. The power of meta-analysis in genome-wide association studies. *Annu Rev Genomics Hum Genet.* 2013;14:441–465.
47. Bennell K, Matheson G, Meeuwisse W, et al. Risk factors for stress fractures. *Sports Med.* 1999;28:91–122.
48. Lewiecki EM, Baim S, Bilezikian JP, et al. 2008 Santa Fe bone Symposium: update on osteoporosis. *J Clin Densitom.* 2009;12:135–157.
49. Tenforde AS, Sayres LC, McCurdy ML, et al. Identifying sex-specific risk factors for stress fractures in adolescent runners. *Med Sci Sports Exerc.* 2013;45:1843–1851.
50. Fredericson M, Jennings F, Beaulieu C, et al. Stress fractures in athletes. *Top Magn Reson Imaging.* 2006;17:309–325.
51. Estrada K, Styrkarsdottir U, Evangelou E, et al. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. *Nat Genet.* 2012;44:491–501.
52. Field AE, Gordon CM, Pierce LM, et al. Prospective study of physical activity and risk of developing a stress fracture among preadolescent and adolescent girls. *Arch Pediatr Adolesc Med.* 2011;165:723–728.
53. Mountjoy M, Sundgot-Borgen J, Burke L, et al. The IOC consensus statement: beyond the Female Athlete Triad–Relative Energy Deficiency in Sport (RED-S). *Br J Sports Med.* 2014;48:491–497.
54. De Souza MJ, Nattiv A, Joy E, et al. 2014 Female Athlete Triad Coalition Consensus Statement on Treatment and Return to Play of the Female Athlete Triad: 1st International Conference held in San Francisco, California, May 2012 and 2nd International Conference held in Indianapolis, Indiana, May 2013. *Clin J Sport Med.* 2014;24:96–119.
55. Wagner JK. Playing with heart and soul…and genomes: sports implications and applications of personal genomics. *PeerJ*. 2013;1:e120.
56. Lehrer J. *Why Did Kobe Go to Germany?* Grantland; 2012. http://grantland.com/features/kobe-bryant-dr-chris-renna-regenokine-knee-treatment/. Accessed June 10, 2014.
57. Kulish N. Novel blood treatment lures athletes to Germany. *New York Times*. July 10, 2012:B12.
58. Mishra AK, Skrepnik NV, Edwards SG, et al. Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multicenter, randomized controlled trial of 230 patients. *Am J Sports Med.* 2014;42:463–471.
59. Schwellnus MP. Genetic biomarkers and exercise-related injuries: current clinical applications? *Br J Sports Med.* 2013;47:530–532.
60. Schneider KI, Schmidtke J. Patient compliance based on genetic medicine: a literature review. *J Community Genet.* 2014;5:31–48.