Anti-Doping Awareness in Sports

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Lecture -33

Genetic Doping Control

Good morning friends, and welcome to today's edition of the anti-doping course brought to you by NPTEL in association with Madras IIT. This is a continuation of week 7 lecture, lecture number 3. Today we are going to discuss genetic doping control. I am Professor Dobson Dominic, a sports medicine specialist. In the previous lectures in week 7, we looked into what strategies we can adopt for proper anti-doping control. We looked into the main principle, the main strategy adopted by the World Anti-Doping Agency, that is, the Athlete Biological Passport, and in this lecture we are going to look into how we can minimize the newer forms of doping strategies adopted by athletes, the latest one being genetic doping.

We will look into that in this lecture. These are the broad learning outcomes in today's lecture: what are the doping-relevant genes? It is very important to know what genes athletes misuse as a form of performance-enhancing genes. Doping in this new modern era has moved from performance-enhancing substances or performance-enhancing drugs or even performance-enhancing methods to the newer, latest performance-enhancing genes, that is, gene doping. We will see what the different mechanisms are by which this strategy is adopted, that is, the gene doping mechanisms.

We will look into the difficulties the anti-doping agencies have in detecting this newer form of doping, and we will conclude with an update on the future of doping control, the way ahead. To begin with, we will look into what a sports gene is. Genetics, as we know, has a very large influence on athletic excellence, such as strength, muscle size, muscle fiber composition (whether it's slow-twitch fibers or fast-twitch fibers), anaerobic threshold, lung capacity, and flexibility. Now, if you see the effect of genes on structure, function, and performance, certain morphological characters or kinanthropometry like height and length of arms; the effect of genes is very large. So, this becomes beneficial for certain sports like basketball and swimming. Certain morphological traits like lung size and volume are again dependent on genetics. The implications of movement speed, balance, flexibility of joints; all are influenced by genetics. Genetics plays a very important role even in lung size and volume, the accuracy of movements, reaction time, and flexibility of joints. So, pretty much all the performance characteristics for athletics, genes play a vital role, and hence athletes misuse genetic doping in the expectation to improve performance.

So, what are the doping-relevant genes which athletes have been trying to influence? The most important ones are the speed genes: the ACE gene and ACTN3 gene, which are coding for fast-twitch fibers. Especially the ACE-D gene is involved in fast-twitch fibers. Similarly, the ACTN3 gene, which is predominantly seen in certain Caribbean athletes like Jamaicans; Usain Bolt, for example, in certain countries like Trinidad and Tobago and Jamaica, athletes are blessed with a lot of fast-twitch fibers. Again, it is due to genetic influence, especially the ACE-D gene and ACTN3 gene. Similarly, in certain areas like Kenya and Ethiopia in Central Africa, athletes are born with more slow-twitch fiber genes like PPAR-delta. These are all present in skeletal muscles and adipocytes. They promote fat metabolism and increase the number of slow-twitch fibers, which is very important for endurance events like marathon running. Even for strength-based sports like weightlifting and powerlifting, certain genes become very important, like myostatin. This gene regulates skeletal muscle and inhibits muscle size, power, and recovery. So, in these genes, if coded well, then athletes are benefitted.

So, we looked into the different genes which influence athletic performance. Now, how does gene doping happen? Gene doping refers to the use of gene therapy. There is something called gene therapy, which is a medical procedure used for certain congenital conditions. This gene therapy is misused by athletes in the prospect of enhancing athletic performance. Gene doping involves the modification or introduction of genes into an athlete's body to increase the production of specific proteins or hormones, which can enhance muscle growth, muscle size, muscle endurance, or even facilitate faster recovery from certain bouts of exercise.

This form of gene doping helps in recovery, enabling athletes to train in multiple sessions. We all know the importance of recovery for a professional athlete. Gene doping has the potential to improve the recovery performance of an athlete. So, gene doping has a possibility to improve muscle growth, muscle endurance, and also recovery in an athlete.

Looking into the history of gene doping in sport: gene doping initially came into the picture from gene therapy. In 2001, the first official discussion by the Gene Therapy Working Group under the International Olympic Committee was started. In 2003, gene doping was explicitly prohibited under the regulation of WADA. In 2004, WADA established a committee to investigate the latest advances in the field of gene therapy because they understood the implications of gene doping in performance. They suspected already that widespread gene doping was happening in the sporting world, and WADA constituted a committee to investigate and do research in the latest advances in the field of gene therapy and methods of detecting gene doping. WADA also published a laboratory guideline in 2021 for gene doping detection based on PCR (polymerase chain reaction), indicating the establishment of standardized methods on the way. Thus, WADA has recognized the importance of newer technologies to identify gene doping at the earliest stage. So, this is the history of gene doping.

If you look into the mechanism of how gene doping happens, one important method is gene modification. It involves altering genes to improve the body's physiological response to exercise or increase efficiency in energy use. Several techniques may include the transfer of genes that promote muscle hypertrophy or muscle growth or enhance oxygen delivery through increased red blood corpuscle production. So, both in resistance-trained athletes and in aerobic athletes like cyclists, marathoners, or skiers, there are implications for gene doping.

Potential methods of gene transfer include direct gene transfer, whereby desired genes are introduced into athlete cells using a vector or medium, such as a virus. The most common vectors are adenovirus, followed by retrovirus, lentivirus, or adeno-associated virus, whereby these are inserted directly into the genes using these vectors. The second method is through cell therapy, where the athlete's modified cells are altered in a laboratory and then reintroduced into the body. So, it can be in vivo or ex vivo. These are the two techniques by which gene doping methodology happens.

Types of mechanisms of gene doping: one is through somatic gene editing, whereby changes are made to non-reproductive cells, that is, somatic cells. Genetic modifications are not passed on to future generations. The second one is germline gene editing, whereby changes are made to reproductive cells. Here, genetic modifications are passed on to future generations. The types of gene doping also include gene expression modification, where existing gene expression is modified rather than introducing new genes, through several techniques like RNA interference (RNAi) or the latest CRISPR-Cas9 gene editing.

The final one is gene transfer, where genetic materials like DNA or RNA are transferred into an individual's cells to enhance athletic performance. All these forms of gene doping constitute a sports doomsday scenario: a new generation of bioengineered performance. Imagine athletes injecting artificial genes right into the muscle. Scary; it literally becomes a doomsday scenario.

Now, there are risks in gene doping, starting from ethical concerns. WADA has a principle of clean sport, so there should be fairness in competition. With the advent of gene doping, this is threatened significantly. There is also access and inequality; if some countries adopt new doping strategies like gene doping, then obviously they are at an advantage, and this leads to inequality.

Gene doping also has several health risks for the particular athlete. There is the possibility of unintended genetic mutation, which could lead to health complications including increased risk of carcinoma, cancer, and immune disorders. So, there are several health risks involved in gene doping.

Now, coming to detection techniques: how is gene doping detected? This is through genetic and epigenetic analysis. There are several methods which labs use to identify gene doping, either through direct or indirect methods.

The direct method, the most common, is PCR (polymerase chain reaction) and Southern blotting technique, whereby detection of the inserted vector or the inserted gene's length is done. This is achieved through PCR technique. Indirect detection of gene doping happens by identifying quantitative transcriptomics or by identifying quantitative proteomics. This is done through different techniques like real-time polymerase chain reaction, mass spectroscopy, and 2D electrophoresis, which are all latest gene doping detection techniques. It can also be done through an indirect method by observing the immune response, through techniques like ELISA and Western Blot.

What are the challenges faced in detecting gene doping? Detection methods for gene doping are still under development, making it difficult to identify athletes using these advanced techniques. The biological passport monitoring, although it helps in detecting athletes' biological markers, still faces difficulty; identifying specific gene modifications remains complex. The Athlete Biological Passport is more suited for observing changes in biological markers like urine or blood, but not for detecting specific gene alterations.

These are the references for today's lecture. Thank you and Jai Hind.