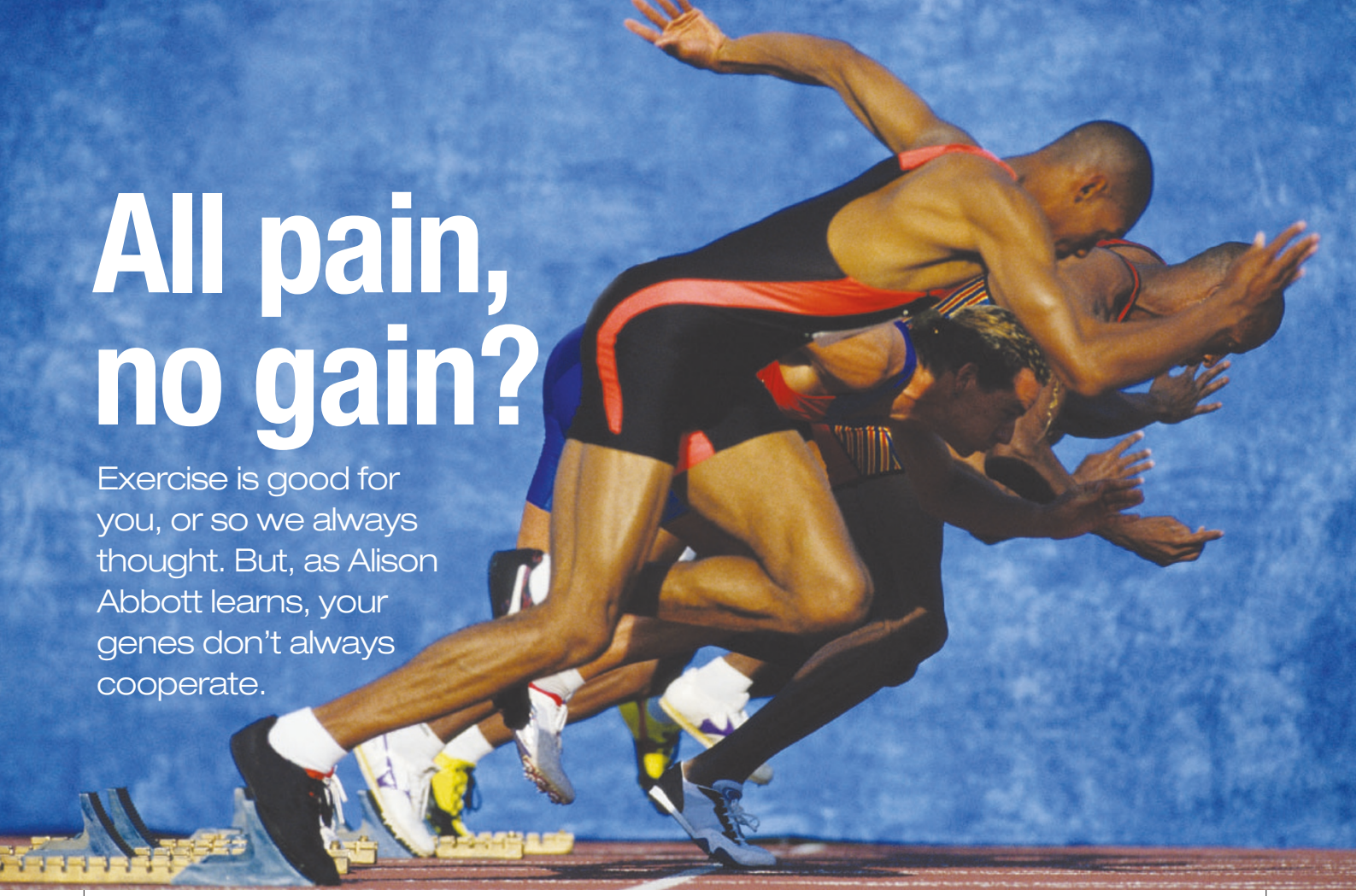

All pain, no gain?

Exercise is good for you, or so we always thought. But, as Alison Abbott learns, your genes don't always cooperate.

M. POWELL/GETTY IMAGES

When Claude Bouchard set out to see whether genes play a role in physical fitness, he assumed, like most people, that exercise training makes everyone fitter. Although he expected genes to modulate some individual responses to diet and exercise, he also anticipated that regular workouts would improve fitness indicators such as lung efficiency and blood cholesterol for everybody.

Some 20 years later, it has become clear from the work of Bouchard and others that this is not the case. Looking at certain measures of fitness, some people actually fare worse after exercise, whereas others show little or no improvement.

But this isn't vindication for couch potatoes. Everyone's health improves in some way or other from exercise, but just how it improves is largely dependent on genes. Now, the growing field of fitness genetics is attempting to tease those genetic components apart, and the studies are generating fresh insights into the benefits of exercise as well as unexpected pay-offs for medicine.

Bouchard's attempts to track fitness genes began in the mid-1980s at Laval University in Quebec, Canada. He and his colleagues focused on the maximum amount of oxygen absorbed by the body from a lungful of air — a standard measure of aerobic fitness, usually abbreviated as V_{O_2max}. They found that most people can get more oxygen out of each breath after training but that a minority were no better off, regardless of how efficient their lungs were at the start. Because the variation was much less extreme within pairs of identical twins, Bouchard concluded that the effect was largely dictated by genes[1].

That initial study was fairly small, so Bouchard extended the work in 1992 by helping to set up a multicentre research effort called the HERITAGE Family Study, which is still running today. Now based — together with Bouchard — at the Pennington Biomedical Research Center in Baton Rouge, Louisiana, the study's main data set comes from some 740 sedentary adults who were subjected to an intense exercise regime in the lab. The researchers monitored changes in the participants' blood pressure, heart rate, blood chemistry and V_{O_2max} over 20 weeks.

> "Our work on athletes is feeding back into the clinic. How efficiently we use oxygen is decisive when we are desperately sick."
> — Hugh Montgomery

Survival of the fittest

The study's main aim was to determine how exercise reduces risk factors for cardiovascular disease and diabetes, but Bouchard and researchers at the four other collaborating institutions also took blood samples for genetic analysis. "We were trying to find as many genes as possible that influence fitness and performance," Bouchard says.

The resulting reams of data and frozen blood samples are still being analysed, but the results so far confirm Bouchard's earlier studies. The average increase in V_{O_2max} after the training programme was 19%. But 5% of the subjects had virtually no change, and another 5% had improved by more than twice the average amount. Similarly, most people had lower exercising heart rates and blood pressure after the training programme — an indication of improved fitness — but the extent of the reduction was extremely variable. In a few people there was even a small rise in these numbers[2].

Much of this variability seems to be attributable to genes. The researchers found more variation between than within families, suggesting at least a portion of a person's ability to benefit from exercise is inherited. "We concluded that just about half of the difference in trainability was heritable," says Tuomo Rankinen, the study's project manager.

It is unclear to what extent fitness parameters such as V_{O_2max} are indicative of long-term health prospects, but even presumed health indicators such as cholesterol, a factor in heart disease, did not follow the expected pattern of more exercise is better. Conventional wisdom has it that regular exercise reduces the risk of heart disease by raising blood levels of high-density lipoprotein (HDL) cholesterol, a complex that helps prevent cholesterol from forming fatty deposits on blood-vessel walls. This is considered one

C. HAWKINS/GETTY IMAGES

G. PALMER/ALAMY

of the key benefits of taking up sports such as running. But the HERITAGE data show that training does not inevitably increase levels of HDL cholesterol. In fact, in about one-third of exercisers, the level of the complex fell.

Does this all mean that exercise could actually be bad for those of us with the 'wrong genes'? Not at all, insists Rankinen. "We found not a single 'universal non-responder'," he says. In other words, everyone improved on some score. Even those who could not raise their V_{O_2max} through exercise were still getting some other health benefit such as higher HDL cholesterol levels or lower blood pressure. And overall, the HERITAGE data show that the risk of cardiovascular disease and type 2 diabetes falls in those who exercise regularly, Rankinen says.

One way to begin to untangle these apparently contradictory effects is to go after the genes involved. This could ultimately reveal a great deal about how exercise produces health benefits, and may lead to treatments for diseases of metabolism and physiology.

To this end, scientists at the HERITAGE study are scanning the genomes of participants for gene variants that occur more frequently in association with different fitness responses. Although some metabolism genes have been identified that may play a role, the most strongly linked gene so far is *Titin*. This produces protein fibres that contribute to the elasticity of heart muscle cells. It may be that some forms of the gene allow the heart to pump larger volumes of blood than others[3].

"Genetic destiny should not become a new excuse for couch potatoes — everyone gets at least some benefit from regular exercise."

Physical attractions

Other teams are also on the hunt for fitness genes. Paul Williams, a health researcher at the Lawrence Berkeley National Laboratory in Berkeley, California, for instance, suspects that a gene related to the synthesis of HDL cholesterol might be involved. Ten years ago, he found that people who have an easier time taking up running after leading sedentary lives also started out with higher levels of HDL cholesterol in their blood — and increased those levels more quickly — than those who find running difficult[4]. It turns out that an enzyme that boosts HDL cholesterol is found in 'slow-twitch' muscle fibre, the type that takes longer to fatigue and so makes distance running easier. Williams is now beginning a large-scale genetic study to see whether differences in that enzyme are associated with differences in lifestyle choice.

Meanwhile, Gaston Beunen, a sports scientist at the Catholic University of Leuven in Belgium, is looking at the half-dozen or so key genes that contribute to the synthesis of myostatin, a protein that blocks new muscle growth. His study of some 300 young sibling males, published in May last year, hints that three of these genes may help to determine a person's physical strength[5].

In the end, the number of fitness-linked genes is expected to be large. So far, more than 100 appear in the literature, most of which have been identified in the past four years[6], although in many cases more work is needed to confirm the link. And some of these now seem likely to prove their worth in the clinic.

One gene drawing a lot of attention encodes an enzyme called ACE, or angiotensin-converting enzyme. ACE activates the hormone angiotensin, which helps to maintain blood pressure and promotes the growth of the heart in response to exercise. One common gene variant, known as *ACE D*, makes more ACE than the other common version, *ACE I*. And athletes who have inherited *ACE D* from both parents experience about three times more heart growth in response to exercise than those who have inherited two *ACE I* genes[7]. They also seem to perform better in sports that rely on sheer strength and power, such as weight-lifting or sprinting. The *I* variant, in contrast, is more common among élite athletes in endurance sports such as long-distance running and swimming, which require more efficient metabolic use of energy and oxygen[8,9].

As the lower levels of ACE associated with *ACE I* improve endurance, Hugh Montgomery, a cardiovascular geneticist at University College London, wondered whether *ACE I* might also be advantageous to those suffering serious illness. He found that children with potentially deadly meningitis were more likely to require intensive care or to die if they had two copies of the *ACE D* gene rather than two copies of *ACE I*[10]. His team also found that premature babies with *ACE I* fare better[11]. "Our work on athletes is feeding back into the clinic," says Montgomery. "How efficiently we use oxygen is decisive when we are desperately sick."

It may eventually be possible to help such patients with drugs that slow down ACE activity. Already, in unpublished work, ACE inhibitors have been shown to reduce muscle wasting in mice. And London-based drug company Ark Therapeutics is currently running final-stage clinical trials on the use of the ACE inhibitor imidapril to treat severe muscle wasting in cancer patients.

Fitness genetics may be feeding ideas into the clinic, but could genetic destiny become a new excuse for couch potatoes? "If they think their performance is limited by their genes, people tend to give up," says Montgomery. "People are afraid of trying and failing — it's part of the human condition." Nevertheless, his advice to those who long to be fitter is to do serious exercise come what may. For everyone, it seems, there is at least some benefit. ■

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