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Editorial Comment

What is new in neuro-musculoskeletal interactions? Studies on muscle genetics and the smartness of tendons

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Since its start in 2000, JMNI has featured a regular column entitled "What is new in neuro-musculoskeletal interactions?" that highlights recent research articles in the field covered by JMNI. The column is based on the assumption that JMNI readers have more than adequate intake of dry research prose during their regular activities and require something different to maintain a varied reading diet. The "hit count" on the JMNI website suggests that readers agree. In recent JMNI issues this column could make only scarce appearances. Now, however, "What is new?" micro-reviews will become a regular feature of the journal once more.

Muscular genetics: From SNPs to twins

Most JMNI readers probably agree that science can be a tough business. You constantly concoct brilliant new hypotheses to make your grant applications shine and sparkle, only to find one reviewer grumbling that your idea is not visionary enough, while another nags that it is too speculative. Would it not make life simpler if one could get rid of hypotheses altogether? If that is your current frame of mind, genome-wide association studies may be your thing. All you need is a study group, an outcome parameter and DNA samples. No hypothesis required! Using one of those state-of-the art microarray chips, you analyze a million single-nucleotide polymorphisms on each DNA sample, you feed the results into a computer program and look for associations between your outcome measure and each polymorphism. With a bit of luck, you will unearth a new role for a gene that none of those hypothesis-testers had ever thought about. The little drawback is that you need a lot of of study participants to generate valid results. And then a few thousand more to confirm the results of the first cohort.

JMNI Editorial Board Member Hong-Wen Deng is one of the most active players in the field of musculoskeletal genome-wide association studies. One of the recent projects from his group looked for genes that influence lean body mass[1]. After assessing 379,319 single-nucleotide polymorphisms in 1,000 unrelated US whites they found that only two polymorphisms, both located in the thyrotropin-releasing hormone receptor, met their stringent criteria for establishing an association. Subjects carrying unfavorable genotypes at these two locations had, on average, about 2.5 kg lower lean body mass. These results were nothing if not consistent, as they could be replicated in separate groups of 1488 unrelated US whites, 2955 unrelated Chinese subjects, and another group of 1972 US whites. So far so good, but what does the thyrotropin-releasing hormone receptor have to do with lean body mass? At that stage in the project, the researchers actually felt compelled to generate a hypothesis. They suspected that this receptor exerted its effect on lean body mass by influencing the growth hormone and insulin-like growth factor systems. Indeed, they found a strong statistical interaction with some polymorphisms in this pathway, in particular with the insulin-like growth factor binding protein 5.

Knowing factors that influence lean body mass and thus muscle mass is certainly interesting, but what about muscle function? It seems that at present no genome-wide association studies on muscle function have been published. However, the overall contribution of heritability to interindividual variation in muscle function has been examined in a number of twin studies. Tiainen et al have followed a cohort of older female twins (63 to 76 years of age) and estimated the heritability of isometric knee extensor force and leg extensor power twice over a three-year period[2]. They found that genetic effects explained 58% of the variance in muscle force and that this figure remained about constant over the next three years. However, the estimate of heritability for muscle power decreased quite considerably during the study period, from 67% to 48%. The authors think that the onset of new disease processes may have decreased the effect of heritability, even though these new disease processes were somewhat hard to

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pinpoint. Whatever the reasons for the decreasing heritability may be, this study serves to remind us that heritability estimates are not fixed constants but can change with time, even in the same population. Many papers contain generalizing claims like "the heritability of parameter xyz is 80%". Take such statements with moderation and a grain of salt.

Tendons: cool, smart and estrogen-responsive!

Tendons are the wall flowers of the musculoskeletal system. Everyone is aware of them but few take much interest. Their more conspicuous neighbors, the muscles and the bones, get far more scientific attention. Yet, although tendons have a reputation of being dull and inert force transmitters, they would certainly be branded "cool" and "smart" if they had been invented by some high-tech company. Tendons adapt to mechanical requirements just as muscles and bones do.

Ruminan et al examined this adaptive process in sheep[3]. They used a new device that removes all mechanical stress from the patella tendon while leaving knee mobility intact. After six weeks of stress shielding, the patella tendon of their sheep had weakened considerably, even though the cross-sectional area of the tendon had not changed. The cause of the tendon weakening therefore was degradation in the material properties of the tendon tissue. After six weeks of reloading, the tendon had regained its former strength. However, this occurred by increasing the cross-sectional area of the tendon, whereas the material properties still remained impaired.

Reeves et al came to surprisingly similar conclusions in a clinical study[4]. They examined the mechanical properties of the human patella tendon in men who previously had undergone surgical reconstruction of the anterior cruciate ligament using a bone-patellar tendon-bone graft. In this operation, the central third of a healthy patella tendon is removed, which should result in overloading of the remaining tendon tissue. One to ten years after the intervention, overall tendon stiffness was normalized. However, this was due to the combined effect of an abnormally high tendon cross-sectional area and an abnormally low Young's modulus on the material level. Thus, in both the animal experiment and in the clinical example, the patella tendon seemed to recover its strength by increasing its cross-sectional size while material properties remained suboptimal.

Some of the popular prejudice against tendons may stem from the perception that they are "merely mechanical" organs whereas many musculoskeletal researchers get more excitement out of soluble factors and molecular pathways. If so, a report by Hansen et al may help to deal with the tendons' image problems[5]. These researchers examined the influence of estrogen on the patella tendon in response to a single exercise session. Postmenopausal women using estrogen replacement therapy had a markedly higher rate of collagen type I synthesis in their patella tendon than women not taking estrogen replacement. The study also revealed that the relative tendon stiffness during mechanical loading was lower in users of estrogen replacement therapy. It appears that estrogen increases tendon collagen turnover and that estrogen also has an effect on collagen cross-linking. Whether this is good or bad is anyone's guess at present. As the authors of this study point out elsewhere, the "mystery of female connective tissue" largely remains to be unveiled[6].

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