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a gait on the wild side

Vivienne Baillie Gerritsen

Never take a walk for granted. Putting one leg in front of the other is not a simple affair. To most of us, it seems so easy. Yet walking – and its faster version, running – demands intricate neuron development and networking that is gradually set in place during the course of embryogenesis and very early childhood. Walking can be learned, as long as you have the correct bases to begin with. Watch a toddler taking its first steps. They lose balance. Cave in. Fall. But, within a few weeks, a small human – although far slower than most vertebrates – manages to master the technique of standing up and moving forward by using its two legs very successfully. The art of walking, or locomotion, demands close coordination between left, right, forward and backwards, as well as the limbs' muscles – without which walking would be a difficult enterprise*. In the case of four-legged vertebrates, coordination is even more complex. Recently, Swedish scientists discovered a protein – the Duplex and Mab-3 related Transcription Factor – which is directly involved in a horse's gait, and gives an insight into how locomotion, as a whole, is managed and organised both on the cellular and molecular level.

Photo by Eadweard Muybridge
(probably taken in 1878)

Source: wikipedia

Horses have two more legs than humans do, and it shows. They are able to move forwards, much faster and in a greater variety of ways – or gaits – than we are. Not only can they walk, trot, canter and gallop, but they can also pace and perform what is known as the tölt. We are all acquainted with the first types of gait but not all of us have heard of the pace and the tölt that are specific to certain kinds of horses, amongst which the Icelandic horses. To cut a long story short, the tölt is a very fast trot and the four legs touch down independently. While in a pace, the lateral foreleg and hind leg of the horse touch down at exactly the same time. The moving image shows a horse doing the pace. And it is thanks to the observation of these two gaits in Icelandic Horses that a team of scientists demonstrated the importance of a gene they called DMRT3.

DMRT3 can actually be used to discriminate between horses that are able to pace and those that cannot. This came as a surprise to the scientists since it is a very rare thing for one sole gene to define, on its own, a given phenotype; in this case, the way a horse is able to move forward. They did this by screening 70 Icelandic horses for a gene that could have a role in the species-specific pace. The gene that came up was a truncated form of wild-type DMRT3. The scientists then ran a blind test on 61 horses in a Swedish stable, two of which – though unknown to them – had trouble keeping their fast trot, and would break into a gallop. It turned out that these two horses lacked the mutated form of DMRT3. It is not difficult to see the commercial interest in such a gene. In fact, following these results, the stable decided to extract the two horses from racing careers…

Why, though, are some horses able to pace, while others are not? How did these differences come about? It seems that the truncated form of DMRT3 appeared a few thousand years ago, most probably with the domestication of the horse. An Icelandic horse homozygous for mutated DMRT3 is unable to break into a gallop. From a purely biological point of view, this is not an advantage since a horse unable to gallop cannot move as fast as one that can, and its chances of survival in the wild are thus weakened. Thus the pace and the tölt are most probably the result of selective breeding by man. Indeed, the two gaits offer a smooth ride on a horse's back, and the tölt is said to be as comfortable as sitting on a sofa… These two gaits were probably sought after for travelling and the transport of merchandise, for instance and, later, for racing.

But what is DMRT3? DMRT3 belongs to the very large family of transcription factors. Horses that are able to perform the pace and the tölt own a truncated form of DMRT3, which arises from a change in only one base that results in a stop codon. The mutated form is 174 amino acids shorter at its C-terminal end. Surprisingly, instead of creating a gene whose product is non-functional, this particular mutation turned out to be not only viable but also to the advantage of humans and their comfort: it conferred a new gait to the horses carrying it. How?

The scientists screened mice for DMRT3 mutations. Knockout mice lacked coordination in their movements although, in time, other neurons seemed to come to the rescue. Despite this, it demonstrates that DMRT3 has a direct role not only in coordinating the animal's left and right sides but also in the movement of its forelegs and hind legs – and must, therefore, be involved in signalling that occurs between neurons and muscles in the legs. Immunostaining techniques revealed the existence of DMRT3 early on in embryogenesis, where it seems to be involved in organising neurons along the centre of the spinal chord, as well as laterally. It also promotes synaptic connections to motor neurons. DMRT3 thus plays a critical role in the spinal circuitry that controls stride and limb coordination. And if it is true for horses and mice, there is a great chance it is the case for all vertebrates, humans included.

So DMRT3 is necessary for the normal development of coordinated locomotion in vertebrates. And a truncated form broadens a horse's abilities to move forward! The history of a horse's gait – and hence DMRT3 – is mingled with the work of an intriguing photographer: Eadweard Muybridge (1830-1904). This successful bookseller became a professional photographer following a stagecoach accident and a doctor's advice. He suffered from serious head injuries which had an effect on his personality, making him irritable but also liberating him creatively. In time, he became known for his work on movement and was the first to film horse motion by using multiple cameras which were set off as the horse advanced. It was thanks to this that he was able to demonstrate that when horses trot, there is a point when all of their hooves are above ground – a popular debate in the 1870s. There is no doubt that DMRT3 will be used in the realms of money and horses in the future. But perhaps, too, it will help scientists understand how vertebrates are able to move, and provide future therapies for individuals who have lost their means of locomotion.

**** Just for fun, "The ministry of silly walks" (http://www.youtube.com/watch?v=IqhlQfXUk7w)***

Cross-references to UniProt

Doublesex- and mab-3-related transcription factor 3, *Mus musculus (Mouse)* : Q80WT2
Doublesex- and mab-3-related transcription factor 3, *Homo sapiens* (Human) : Q9NQL9
Doublesex- and mab-3-related transcription factor 3, *Equus caballus* (Horse) : F6W2R2

References

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