

A dog's life

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Dogs were not meant to fit into a bag. Yet, some do. Consequently, instead of enjoying a healthy walk in the countryside they can go shopping with their owners. Convenience – both for humans and dogs – has trimmed down canine size in the past few hundred years. It is easier for dogs to be part of a household if they are medium-sized and more practical for humans to keep them if they are not too large. As such, natural selection coupled with selective breeding has supplied us with dogs ranging from barely twenty centimetres to giant samples which measure over one metre. And the stakes that a cross between a large poodle and a tiny Chihuahua will produce a medium-sized mongrel are high. So there must be a straightforward mechanism which is involved in their size. IGF1 – or insulin-like growth factor I – seems to be at the heart of such a mechanism. Indeed, scientists have discovered that small dogs all carry a certain variant of IGF1 while large dogs do not – or very few. This would suggest that the IGF1 variant has the power to reduce the size of a dog.



'Skinny Vinny' by Lisa Ballard

Dream Dog Paintings
Courtesy of the artist

Every single dog the human race has ever known not only belongs to the same species, *Canis familiaris* but is also descended from only one other species: the grey wolf, *Canis lupus*. The variation in size – which no other mammalian species has experienced – results from the selective breeding of dogs over the years and can be tracked all the way back to the

beginnings of animal domestication. Medium-size dogs are probably more popular because they are easier to look after. Likewise, if a dog wants to be part of a household, it is better off medium-sized. Fossils, the size of Great Danes or of terriers, date back thousands of years. However, the huge variation we can testify to on a daily basis – from pocket dogs that hardly weigh a kilo to a hundred kilo Saint Bernard – is the result of strong selective breeding which has taken place within the past few hundred years only and has produced an array of 350 declared breeds.

Whatever it is that has made dogs small has been present for a long time. Scientists discovered an insulin-like growth factor I (IGF1) variant that is widespread in small dogs meaning – on evolutionary terms – that it was fixed in *Canis familiaris* many years ago. It is not present in the grey wolf's genome and the early appearance of the IGF1 variant will have driven the rapid genesis of size diversity in the domestic dog. What is more, this particular variant is geographically widespread – most probably as a result of trading and human migration – thus supporting the fact that it appeared early on in time.

A study was carried out on one particular breed of dog – the Portuguese water dog. The samples varied substantially in size due to strong

selective breeding. What the scientists discovered was that every single small-sized dog carried the IGF1 variant while the larger dogs did not. They then turned to other dog breeds to discover the same thing: all the small dogs carried the variant. Although most of the bigger dogs did not, a few did. This means that there is a 'stronger' mechanism which exists to dictate the size of larger dogs. It also means that size – like all other phenotypes – is defined by something far more complex than the mere action of just one protein.

Insulin-like growth factor I promotes the growth of an organism by firing off a network of reactions – loosely known as the IGF pathway – which ultimately promote protein turnover, cell proliferation, tissue differentiation and even protection against cell apoptosis. Upstream, IGF1 action is triggered off by the pituitary growth hormone, or GH. IGF1 is at the heart of an organism's maturity. It is synthesized in the liver from where it acts on a wide variety of tissues and mediates its action by binding to its receptor. This launches multiple IGF1 signals transduced by way of phosphorylation reactions to hosts of kinases downstream. IGF1 exists in two forms. It can either bind directly to its receptor or bind to IGF-binding proteins where it is buried in a protective envelope, thus delaying and modulating IGF1's interaction with its receptor.

Besides finding a way to fit a dog into a matchbox, what is the point of such studies? Such a huge variation in a phenotype within one same species provides valuable information on two fronts. On the one hand, it can reveal how key elements are involved in intricate pathways and, on the other, it can give an idea as to how sets of genes interact to come up with a specific phenotype such as size, or even behaviour. The *Canis familiaris* model is also precious for the analysis of genetic polymorphism and the understanding of the differences between a healthy genome and a pathological one.

The IGF pathway has been under close scrutiny for some time. Not only is it involved in an organism's maturity but, unsurprisingly perhaps, it also seems to play a part in an organism's longevity. A faulty IGF, or indeed, a faulty receptor is likely to create some kind of havoc. One interesting study was carried out on a number of women with a faulty IGF pathway, who had not only lived to be a hundred years old but whose stature was slightly under the average, echoing the effect the IGF1 variant has on dog breeds... Do small dogs live longer than big dogs? The issue was not raised. Though there are no doubt many handbags out there that would enjoy the knowledge that they will get old with their closest companion.

Cross-references to Swiss-Prot

Insulin-like growth factor I, *Canis familiaris* (Domestic dog) : P33712

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