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What's love got to do with it?

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Abstract

Clifford the Big Red Dog has grown to be around 25 feet tall and the reason for this is still unknown. His owner Emily Elizabeth has said that his size is due to her love: the more she loves him, the bigger he gets. However, this paper disputes that there are other reasons causing his abnormal growth. Gigantism could be a reason as to why he has grown so much as a puppy. His continued growth, even as an adult, is likely to be due to Acromegaly. Both are caused by excessive growth hormone (GH) being secreted. A high in protein diet can increase the secretion of GH and IGF-1 due to its high L-Arginine content. *ACSL4*, a gene found in large dog breeds, may have been over-expressed and led to his increased growth and bulking.

Keywords: Book; TV Programme; Biology; Genetics; Growth hormone; Clifford the Big Red Dog

Introduction



Figure 1 – Clifford the Big Red Dog is pictured with his owner Emily Elizabeth and friends Cleo (left) and T-bone (right) [1].

Clifford the Big Red Dog, as his name suggests, is a giant dog with bright red fur as seen in Figure 1 [2]. His exact height and weight have never been confirmed but he is predicted to be around 25 feet [3]. Over the years, speculation has arisen as to how he has reached this height. According to his owner, Emily Elizabeth, he was the smallest of his litter and was not expected to grow to this size. Elizabeth claims that due to her love and affection, he grew exponentially [3]. The phenotype of an organism is determined by genetic and environmental factors which contradicts Elizabeth's claims that her love is the reason for his abnormal growth.

Normal Growth

Growth is controlled by the hormones Growth hormone (GH) and insulin-like growth factor (IGF-1). GH, also known as somatotropin, is the main regulator of cell proliferation, reproduction, and repair [4]. It is secreted by the somatotrophic cells in the anterior pituitary gland in the brain [4]. On release, it binds to its complementary receptors which are found in liver cells called hepatocytes [4]. This triggers the JAK-STAT signalling pathway which stimulates the secretion of IGF-1 [4]. This hormone also plays a part in regulating cell proliferation and growth [4].

Gigantism

Benign tumours, called Pituitary Adenomas, can grow on the pituitary gland [5]. When pituitary adenomas enlarge, they are called Macroadenomas [5]. These cause the excessive production of GH which can lead to the Gigantism. Also known as Paediatric Acromegaly, Gigantism is an extremely rare disorder that causes excessive growth and increased height [5]. Pituitary Hyperplasia, the enlargement of pituitary glands, can also cause Gigantism [5].

This disorder speeds up the growth of tissues, muscles, and bones, causing above average growth [6]. Clifford seems to display the symptoms of this including enlarged paws, legs and head and a large

appetite [2]. It is very likely that Clifford has a tumour on his pituitary gland causing Gigantism which has ultimately resulted in his increased growth rather than love given by his owner.

Acromegaly

After puberty, the tissues at the end of the bones called growth plates, begin to close off which prevents further growth of bones as an adult [7]. As Clifford continues to grow as a two-year-old adult dog, it means his growth plates have not closed off [2]. This could be a sign of Acromegaly, also known as Hypersomatotropism (HST) [7].

Acromegaly is a result of excess GH causing disproportional growth in limbs [7]. Increased IGF-1 triggers the pituitary gland to secrete more GH. IGF-1 is encoded by the *IGF1* gene. It is the main reason for varying sizes in dogs [8]. Repression of *IGF1* has been found in all small dog breeds [9]. Over expression of this gene has been linked with Acromegaly in dogs [9].

The symptoms seem to be present in Clifford: excessive weight gain, lethargy, large face, tongue, and abdomen as seen in figure 1 [1, 7]. It is more likely that over expression of the *IGF1* gene has led to over production of IGF-1 in the liver which has triggered over production of GH causing Acromegaly in Clifford, rather than love leading him to grow.

L-Arginine

Diet can also influence the secretion of GH. L-Arginine is an amino acid which is found in many foods which are high in protein such as red meats and fish [10]. It has been found that L-Arginine increases the release of GH as it represses the hormone somatostatin which is an inhibitor of GH releasing hormone (GHRH) [4]. Moreover, L-Arginine escalates the phosphorylation of p-38 MAPK, MEK and JNK in liver cells which triggers the MAPK signalling pathway. This increases the secretion of IGF-1 [4].

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Most dog foods have high contents of L-Arginine present in them. It is likely that Clifford was given a very high protein diet as a puppy which has increased his GH and IGF-1 levels, leading to his excessive growth.

ACSL4

ACSL4 (*Acyl-CoA Synthetase Long-chain family member 4*) is a gene which is needed in lipid biosynthesis and fatty acid degradation [11]. It has been nicknamed the 'bulky allele' as it can lead to a larger, muscular phenotype in dogs. [11] Most large breed dogs over 41 kg, such as Cane Corso and Great Dane, have this gene present. However, small and medium dog breeds did not carry this gene [11]. This proves that this gene must also be present in Clifford. It is likely that the *ACSL4* is mutated. A mutation in *ACSL4* could have led to over expression of the gene causing it to increase the muscle and fat in Clifford, leading to his abnormal size.

Conclusion

Elizabeth's claims are incorrect: her love is not the reason for Clifford's growth. It is very likely that when he was a puppy, his anterior pituitary gland was secreting excessive growth hormone due to a benign tumour. This developed into Gigantism. The further growth as an adult dog can be explained by the over-production of IGF-1 which can trigger the further release of GH, causing Acromegaly. Clifford's diet, especially as a puppy could have had an influence on his GH levels. High protein diets have L-Arginine which stimulates the secretion of both hormones. Furthermore, as a large breed dog, he has the *ACSL4* gene. Over-expression of this gene would lead to him becoming bigger and bulkier. Therefore, Elizabeth's love cannot be credited as the reason for his growth; it is his genetic mutations and environmental influences that have determined his size.

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