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Snowy stardom

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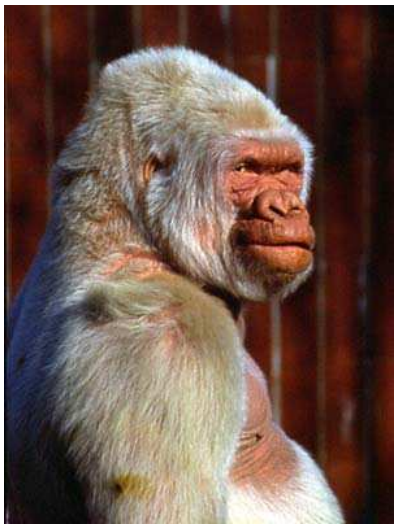
One higher primate gained recognition for being sent up into space, another for memorising language signs and yet another for saving the life of a young boy. But none of them reached the heights of fame the albino gorilla 'Snowflake' reached: Snowflake was the first case of albinism in great apes ever recorded. He suffered from the well-documented pathology: oculocutaneous albinism type 1 (or OCA1). This type of albinism is the most common form in humans and is caused by the malfunction of a tyrosinase, an enzyme which has a key role in the synthesis of the pigment melanin.

Snowflake was a Western lowland albino gorilla (*Gorilla gorilla gorilla*), captured in Equatorial Guinea in October 1966, by a Catalan primatologist Jordi Sabater Pi. He was originally named Nfumi Ngi, meaning 'white gorilla' in the native Guinean language, before National Geographic nicknamed him 'Snowflake'. Snowflake was taken to Spain where he became the icon of Barcelona Zoo and was known as 'Floquet de Neu', which is Catalan for snowflake. Snowflake fathered no less than 22 offspring, none of which were albinos, and even lived to see his grandchildren! In 2001 however, at the mature age of almost 40 – well over the average lifespan of 25 years for wild gorillas – the gorilla was diagnosed with skin cancer, until then a disease quite unknown within the species but sadly quite frequent in human albinos. He was euthanised in 2003, and the news of his death made the headlines worldwide.



Snowflake, the albino gorilla

Courtesy of Barcelona Zoo

The first hints of tyrosinase activity arose in the late 1800s when the French naturalists Bourquelot and Bertrand observed that the toadstool *Russula nigricans* bore a colourless substance which blackened upon exposure to air. A year after the discovery, Bertrand recognised the substance as tyrosine, and in 1904 – barely a year later – it was shown that extracts of a mammalian melanoma could convert tyrosine to melanin. Scientists were beginning to grasp the intricate process of melanogenesis, i.e. the synthesis of the natural pigment melanin. The British physiologist H.S.Raper carried out the most important studies on melanogenesis from 1920 to 1935, but it was only during the 1950s that some real sense was made out of the melanin biosynthetic pathway. Tyrosinase is the enzyme which acts upon tyrosine, which ultimately leads to the formation of the natural pigment melanin.

The discovery of the mechanisms which lurk behind albinism followed the discovery of tyrosinase activity. Already in 1908, Sir Archibald Garrod (1857-1936), a British physician and scientist, suggested that albinism was probably due to the failure of an intracellular enzyme. Though he did mention the fact that tyrosinase had a role in melanogenesis, he did not make the link between albinism and loss of tyrosinase activity. For decades it remained obscure as to whether albinism was a consequence of the loss of tyrosinase activity or an absence of melanocytes – the cells in which melanin is synthesized. And it was only towards the end of the 1950s, that

albinism – at least the form that was being studied – proved not to be due to a lack of melanocytes but the cause of tyrosinase inactivity.

There are a different forms of albinism but, on the whole, the condition is caused by a lack of melanin formation, which can bring on a number of complications. The most frequent form is known as oculocutaneous albinism type 1 (OCA1) which results from a malfunction of the tyrosinase enzyme. Individuals with OCA1 suffer from hypopigmentation of the skin and hair, as well as visual disorders which are a direct consequence of the non-synthesis of melanin. In humans, this type of albinism occurs in 1 of 40'000 births. Since it has a particularly visible phenotype, the disease was one of the earliest genetic disorders to be studied and the analysis of its distribution – once inherited – demonstrated that Mendel's laws of segregation not only applied to plants but also to mammals.

Tyrosinases are essential to melanin formation and may well function as multienzyme complexes. They trigger off the reaction that ends up converting the amino acid tyrosine to the melanin biopolymer. What tyrosinase does in this crucial step is catalyse the hydroxylation of L-tyrosine to 3,4-dihydroxyphenylalanine (DOPA), followed by the oxidation of DOPA to DOPAquinone. And DOPAquinone is the key intermediate in the formation of two different types of melanin: the pheomelanins – which are yellow and red – and the eumalanins, which are brown and black.

Tyrosinases are securely lodged within the melanocyte membranes. Their catalytic domain houses two copper atoms ligated to a series of histidine residues. The hydroxylation of tyrosine begins by the binding of a dioxygen to the copper atoms, which lie at a distance of 3.6 Å. When the tyrosinase gene is mutated one way or another (frameshifts, splice site mutations, deletions, substitutions…), what frequently happens is that the enzyme's structure is modified in such a way that the distance between the copper atoms is altered thus leading to the impossibility of tyrosine hydroxylation.

Despite the fact that over 100 different mutations within the tyrosinase gene are now known to cause OCA1, scientists still have not found which one applies to Snowflake's albinism. His condition was certainly due to a malfunction of the tyrosinase enzyme but no substitutions in the sequence have been spotted. There could be a mutation in an upstream regulatory element though, and only time will tell.

Besides clarifying the processes involved in Snowflake's albinism, melanogenesis and the function of the tyrosinase enzyme itself, such studies are also helping in the fight against skin cancer. The antigenic properties of tyrosinases, for example, should be helpful as early markers for the detection of metastases whilst the specificity of their promoters could also be used in gene therapy.

Cross-references to Swiss-Prot

Tyrosinase, *Gorilla gorilla gorilla* (Lowland gorilla) : Q9BDE0

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