The Kentucky family with blue skin

NZASE resource

The original Fugate family of Troublesome Creek. Painting by Walter Spitzmiller, CC BY 4.0, PLOS.

Mike Stone summarises what is known about the science behind a family of people who lived in isolation in Kentucky, and many of whom had blue skin.

You may have heard of people with blue skin; for example the Picts, fierce Scottish people who fought the Romans, or a nomadic African tribe called the Tuaregs. The cause of their blue skin is external – the Picts due to the dye in their tattoos, and the Tuaregs due to dye leaching out of their blue robes.

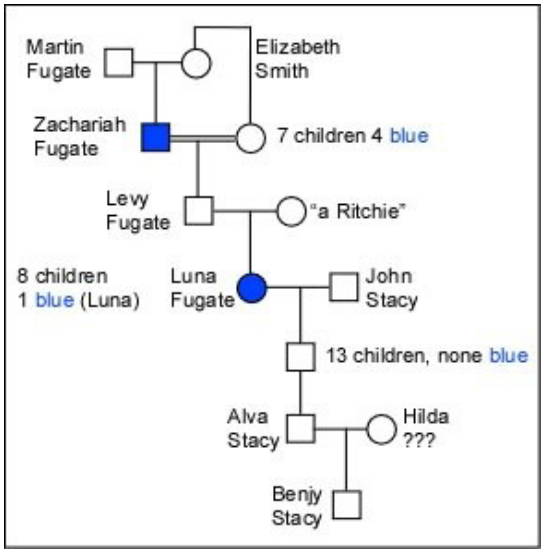
The Fugate family

For other people with blue skin, the colour is due to an anomaly in their blood, rather than dye. The most well-known are the Fugate family in Kentucky and some Inuit populations in Alaska. Both groups of people live in isolated communities where relatives often marry.

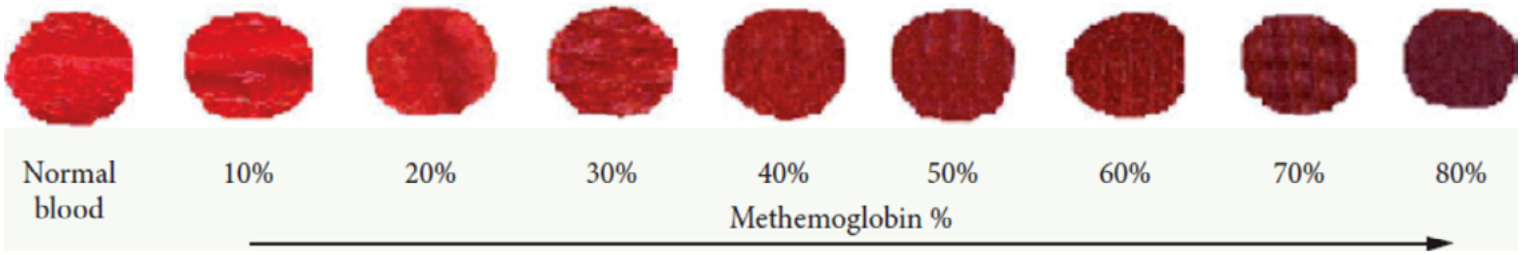
Eastern Kentucky is a remote and mountainous region in the USA. Until the 1940s, there were no paved roads or railways and only a few local settlements. The state was so isolated that it had 63 counties with no library services, until in 1935 a mobile library was begun using pack-horses.

Martin Fugate arrived in Kentucky in 1820, and was an early settler in an area called Troublesome Creek. He is reputed to have had a blue tinge to his skin but not the dark blue colour of later generations. He married a red-headed American woman, Elizabeth Smith, who had unusually pale white skin. They had seven children, four of whom had blue skin. This trait was passed down generations of Fugates and neighbouring families, the last-known being Benjamin Stacy, born in 1975. Benji was very blue at birth, scaring his doctors, but the colour faded as he grew.

Embarrassed by their blue skin, the families retreated even further from others. Cut off from the little contact available with wider society, they married cousins, aunts and other closely related kin, which greatly increased the odds of inheriting the condition. A stranger may have a one in 100,000 chance of having the same allele, compared with one in eight for cousins.



A summary of the Fugate family tree.



The colour of blood with increasing levels of methaemoglobin. From Dr Ward Abajwa.

Methaemoglobinaemia

The Fugate family's blue skin is a symptom of a condition called methaemoglobinaemia. To understand this we need to know some detail about how the blood carries oxygen.

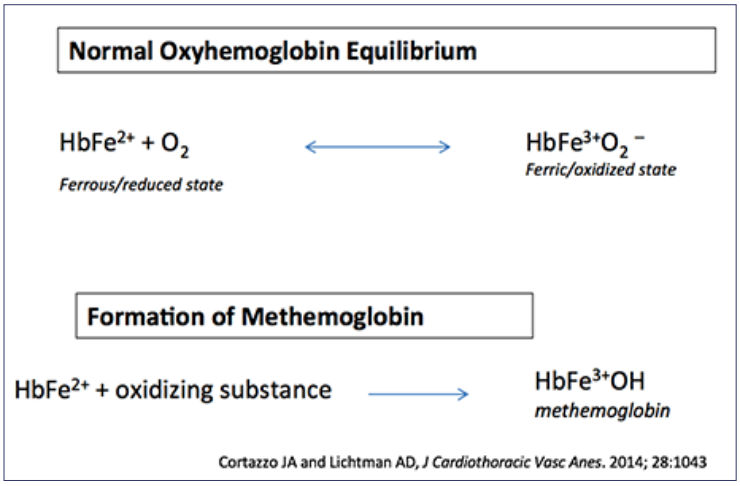
The protein haemoglobin in our blood contains four folded polypeptide chains, each with a central Fe^{+2} (ferrous) ion. As the haemoglobin travels around the body it transports oxygen: this ion latches on to oxygen when O_2 levels are high (e.g., in the lungs) and releases oxygen when O_2 levels are low (e.g., in the muscles).

When exposed to highly reactive molecules (oxygen free radicals), haemoglobin can form methaemoglobin (pronounced met-heemo-globin). In molecules of methaemoglobin, one of the central ions is Fe^{+3} (ferric), which does not bind to oxygen. When present, the remaining three Fe^{+2} ions bind so strongly to oxygen they do not release it. And it is the resulting lack of oxygen in the tissues which causes a blue hue to the skin (cyanosis). This is most easily seen where the skin is thin, such as in the lips, earlobes and fingernails.

Methaemoglobin is normally found in low levels (2%) in our blood, and is converted back to haemoglobin by an enzyme, diaphorase 1, or NADH-cytochrome b5 reductase. When methaemoglobin levels rise above 20 percent, as well as cyanosis it can cause shortness of breath, headaches, fatigue, dizziness and brown rather than red blood.

People with methaemoglobinaemia don't produce enough diaphorase 1. This enzyme normally converts any stray methaemoglobin back into regular haemoglobin. It is the low amount of this enzyme which leads to too much methaemoglobin in the blood, and the symptoms above.

In the Fugate family, methaemoglobinaemia is caused by a genetic condition – an autosomal recessive disorder. Two recessive alleles will reduce the levels of diaphorase 1 enzyme and so cause methaemoglobinaemia. People with this condition have skin with a strong blue colour, while carriers



How met-haemo-globin forms.

(not usually affected but able to pass on the allele) may have paler skin or a faint blue tinge.

Methaemoglobinaemia can also be caused by oxidising agents, such as lidocaine or benzocaine anaesthetics, aniline dyes and nitrates. These substances cause methaemoglobin to form 1,000 times faster than normal, overwhelming the protective enzyme system.

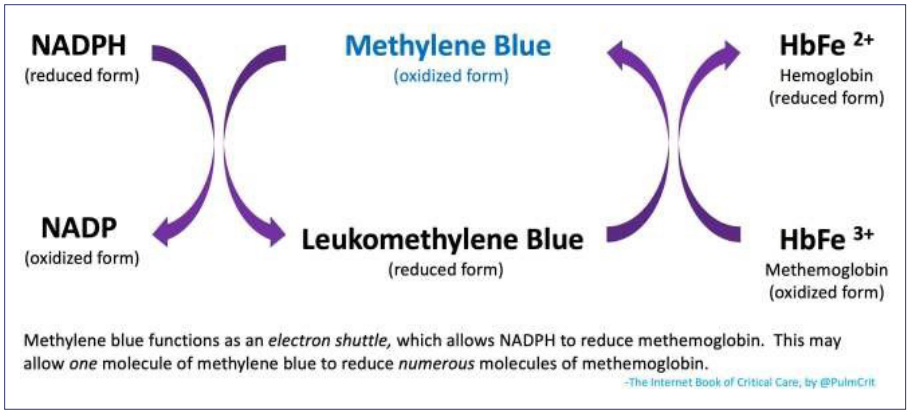
Babies can have lower levels of the enzyme so are at risk of methaemoglobinaemia if their drinking water contains nitrates, or if given teething gels, which contain benzocaine.

Treatment

Methaemoglobinaemia can be treated with methylene blue, as a solution injected once or as a pill taken daily. This restores the Fe^{+2} to Fe^{+3}, by accepting an electron from NADH. Or Vitamin C can be used when other conditions preclude the use of methylene blue.

Madison Cawein, a haematologist at the University of Kentucky, discovered the cure for methaemoglobinaemia. He was approached by a nurse when a blue-skinned brother and sister walked in to the Hazard County clinic.

How methylene blue works.



Madison wanted to know more about the blue skin so he asked the siblings a lot of questions and started to chart the family tree. They were embarrassed by their skin colour and said they didn't want to be blue, but had been born that way. They were otherwise healthy.

He found out that scientists studying methaemoglobinaemia in the Inuit had hypothesised that it was caused by a deficiency of the diaphorase 1 enzyme.

Realising the same thing was happening in the twins, Madison Cawein thought he could cure it if he found a substance that would donate a free electron to the methaemoglobin, allowing it to bond with oxygen. His solution was to inject 100mg of methylene blue. "Within a few minutes, the blue colour was gone from their skin," Cawein reported in an interview in 1982. "For the first time in their lives, they were pink. They were delighted."

When young people started moving away from the farms surrounding Troublesome Creek in the mid-20th century, they took their recessive blue genes with them. Over time, fewer and fewer babies were born blue, and those who were took a methylene blue pill once a day to put the pink back in their cheeks.

Resources

Video: Mysteries at the Museum, 2015, *Blue people of Kentucky* (3m).

Kim Richardson, 2019, *The Book Woman of Troublesome Creek,* a well-researched novel about a blue Kentucky woman who works on the pack-horse library.

References

Dave Roos, 2021, The true story of the blue people of Kentucky, *How Stuff Works*.

Wikipedia, 2021, Methemoglobinemia.

Kat Arney, 2018, Methaemoglobin and diaphorase 1, *Chemistry World* (podcast and article).

Shannon Quinn, 2019, The Fugate family of Kentucky had blue skin for generations, *History Collection*.

Possible activities

- Discuss possible genotypes of the original Fugate family, Martin, Elizabeth and their children.
- If the blue Fugates were healthy apart from their skin colour, what does this tell us about the amount of methaemoglobin in their blood?
- Why did the number of people with blue skin in USA reduce when later generations moved away from this area of Kentucky, although their genes were still in the total gene pool?
- Look at the family tree. Work out the probable genotypes of Luna and her parents, husband and children. What do we know about Benji? Zachariah married Mary – what relation was she to him?
- How is the cause of blue skin in the Fugate family different from the cause of blue skin in the Tuareg?
- What is the role of oxidation in this story? (Can chemists in the class explain it to the rest?)

Eastern Kentucky is hilly and isolated. Kaleid-oscope Adventures.

This article was improved by critique from Michal Denny.

Ngā Kupu

Hāora – Oxygen
Ira huna – Recessive gene
Iranga tuku iho – Genetic inheritance
Kawehā – Haemoglobin
Kirimoko – Skin
Ōrangi – Be blue
Rāpoi ngota – Molecule
Tohutohu – Sign, symptom
Toto – Blood
Toto hāoraora – Oxygenated blood.

Te Aka Maori Dictionary and *Paekupu*