

Charles Darwin's Mitochondria

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ABSTRACT Charles Darwin's long-term illness has been the subject of much speculation. His numerous symptoms have led to conclusions that his illness was essentially psychogenic in nature. These diagnoses have never been fully convincing, however, particularly in regard to the proposed underlying psychological background causes of the illness. Similarly, two proposed somatic causes of illness, Chagas disease and arsenic poisoning, lack credibility and appear inconsistent with the lifetime history of the illness. Other physical explanations are simply too incomplete to explain the range of symptoms. Here, a very different sort of explanation will be offered. We now know that mitochondrial mutations producing impaired mitochondrial function may result in a wide range of differing symptoms, including symptoms thought to be primarily psychological. Examination of Darwin's maternal family history supports the contention that his illness was mitochondrial in nature; his mother and one maternal uncle had strange illnesses and the youngest maternal sibling died of an infirmity with symptoms characteristic of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome), a condition rooted in mitochondrial dysfunction. Darwin's own symptoms are described here and are in accord with the hypothesis that he had the mtDNA mutation commonly associated with the MELAS syndrome.

Charles Darwin (1809–1882) suffered a debilitating illness for most of his adult life with many very varied and bizarre symptoms. The nature of this illness has been the subject of much academic industry and more than 40 different diagnoses have been proposed at various times (Colp 2008). The illness was such that Darwin would be incapacitated for days, weeks at a time. Despite this, he produced an enormous and impressive volume of work, writing 19 books, numerous papers, and thousands of letters, many of which are preserved today (Darwin *et al.* 2009). Apart from his most famous work, *On the Origin of Species . . .*, Darwin's other publications, such as *Variations in Domesticated Animals and Plants*, published in two volumes, were works that represented years of study and experimentation.

Darwin never ascertained the genetic basis of hereditary, despite his interest in and work on the subject and his awareness that evolution depends on the existence of heritable variability within a species (Charlesworth and Charlesworth 2009). He carried out extensive plant breeding experiments in his garden and hothouse at Down House in Kent and meticulously recorded numbers of resulting varieties. He failed, however, to interpret these numbers as evidence of heritable units

(Howard 2009). Despite this failure to produce a convincing theory of heredity, he made the single most important contribution to our understanding of biology, his theory of evolution.

In this article, it is proposed that Darwin himself may have had an unusual heredity condition, a mitochondrial genetic disease. Several mitochondrial diseases show bizarre and variable symptoms and those of one in particular, the MELAS syndrome (Finsterer 2007), closely mirror those of Darwin's condition.

Charles Darwin's Illness

Charles Darwin suffered illness for most of his adult life with many very differing symptoms. Some of these symptoms were present when he was a university student, both in Edinburgh and Cambridge. In Edinburgh he was known to have a "weak stomach" and was unable to watch surgical operations; at Cambridge he suffered from eczema of his lips and hands. When attending two recitals in 1 day at a Birmingham Music Festival, he experienced extreme fatigue—"most terribly knocked up," as he expressed in his autobiography (Barlow 1958). When he was a resident in Plymouth, before he sailed on HMS Beagle, he experienced an episode of rapid heartbeat with "pain around the heart."

During his voyage on the Beagle, Darwin suffered greatly from seasickness. This was not ordinary seasickness but a sickness that became worse throughout the 5-year voyage. When ashore, he also had periods of illness, including attacks

Table 1 Darwin's primary symptoms are listed together with a probable medical diagnosis for that symptom or symptom group

Darwin's symptoms	Proposed medical condition, with reference linking to A3243G mutation
Episodic nausea, retching, vomiting	CVS, episodic vomiting (Pavlakis <i>et al.</i> 1984)
Flatulence, bloating, abdominal pain	Gastric dysmotility (Fujii <i>et al.</i> 2004)
Tiredness, fatigue, general weakness	Lethargy (Finsterer 2007)
Headache	Migraine? encephalopathy (Kaufmann <i>et al.</i> 2009)
Eczema—lips, hands, face	Atopic dermatitis (Pronicki <i>et al.</i> 2002)
Excessive sea sickness	Vestibular dysfunction (Iwasaki <i>et al.</i> 2011)
Palpitations, chest pain	Heart block, paroxysmal tachycardia? (Anan <i>et al.</i> 1995)
Trembling of hands, numbness of the fingers	Peripheral neuropathy (Kaufmann <i>et al.</i> 2006)
Shivering, sweating, temperature sensitivity, fainting sensations, sinking feeling, "whizzing feelings," "swimming" of the head, dizziness	Dysautonomia, may be associated with CVS (Chelimsky <i>et al.</i> 2009)
Muscle twitching, muscle weakness	Myopathy (Finsterer 2007)
Anxiety, episodes of fear, dying sensations (acute panic attacks)	Lactic acidosis (Ehlers <i>et al.</i> 1986)
Periods of dejection, true depression	Depression, mood disorder (Kaufmann <i>et al.</i> 2009)
Eye symptoms, visual disturbances	Migraine associated? MELAS-type symptom?
"Heaviness"—coughing, breathing difficulties, tightness of chest	Asthma—may be associated with impaired mitochondrial function (Reddy 2011)
Backache—"lumbago," "rheumatism in the back"	Fibromyalgia? (DeSouza <i>et al.</i> 2004)
Swelling, redness of the face, swelling of a knee, an arm, one leg	Acute local edema? "carcinoid like" syndrome (Hayman 2011)

The references link the designated diagnosis to proposed mtDNA mutation. CVS, cyclic vomiting syndrome.

of headache and visual disturbances. These episodes were severe enough for him to be incapacitated for days on end.

Before the voyage, apart from these unusual but mostly sporadic episodes of illness, Darwin was a fit young man. After the voyage, however, his illness progressed and he had attacks of sickness during which he was incapacitated for weeks, even months at a time. He suffered with nausea, retching, vomiting, flatulence, episodes of abdominal pain, "lumbago" or backache, and symptoms of asthma. His "eczema," diagnosed as atopic dermatitis (Sauer 2000), was at times severe and was complicated by frequent boils. He complained of numbness in his fingers (peripheral neuropathy), together with shivering, sweating, and giddy turns (dysautonomia). He had psychological symptoms, waking at night with intense, irrational fear and other episodes of hysterical crying. He continued to have periods of severe lethargy, with times when he could only lie on a sofa and do nothing. Darwin's main symptoms are listed in Table 1; symptoms that may be considered secondary in nature are listed in Table 2 together with their proposed relationship to his primary symptoms.

Interestingly these symptoms improved in later life. His attacks were characteristically brought on by any forms of stress, even by pleasurable events. Darwin learned to prevent these events by restricting visitors and avoiding scientific and social occasions. In older age there was no pressure to publish and Darwin could work at a pace that suited him and, evidently, his frail condition.

Diagnoses of Darwin's Illness

Many of the different diagnoses that have been proposed for Darwin's illness are psychogenic or psychological in nature.

These include repressed hatred for a dominating father, or, alternatively, as a means of bonding with his father by developing a patient–doctor relationship (Colp 2008).

The late Dr. John Bowlby, an English psychiatrist, propounded psychogenic causes for many illnesses, in particular mother–child separation. He suggested that unresolved grief over the death of his mother when he was 8 years old was the cause of Darwin's psychosomatic illness (Bowlby 1965). There is, however, no evidence that Darwin suffered any unusual grieving process. Dr. Bowlby suggested that his hypothesis could be tested by showing that Darwin's symptoms were worse at "anniversary dates," such as the date of his mother's death, and that his symptoms were similar to those of his mother's. Colp diligently examined the state of Darwin's illness on these dates and found no such association (Colp 1977). It will be proposed here, however, that there was an important maternal link to Darwin's illness but that it was genetic, not psychological. Indeed, Darwin and his mother seem to have shared a number of symptoms as would be expected for such a connection.

Other psychogenic causes that have been proposed include inner emotional conflict (repressed hatred) toward his loving and devoted wife Emma and guilt over conflict with religious beliefs and his ideas of evolution (Colp 2008). Darwin certainly had psychological symptoms, including symptoms of a panic disorder with periods of irrational fear (Barloon and Noyes 1997), episodes of hysterical sobbing, and other symptoms that may be psychological such as sweating, tremors, and palpitations. Darwin's illness, however, was not primarily psychogenic in nature.

Other diagnoses relate to possible acquired infection during the voyage of the HMS Beagle; the most persistent

Table 2 Symptoms that may be regarded as secondary in nature, with an explanation as to how these symptoms may be seen as complications of Darwin's primary disorder

Secondary symptom	Interpretation
Recurrent boils	Recognized complication of atopic dermatitis
Hematemesis	Complication of forceful vomiting
Dental caries	Complication of recurrent vomiting
Skin pigmentation	Addisonian pigmentation, due to increased ACTH/MSH secretion following excessive salt and fluid loss with repeated vomiting (Hayman 2011)

ACTH, adrenocorticotrophic hormone; MSH, melanocyte-stimulating hormone. The two hormones are released together from the pituitary, molecule for molecule, by splitting of a large parent molecule.

of these is that Darwin had Chagas disease (American trypanosomiasis) (Adler 1959). Despite a comprehensive rebuttal by Woodruff and others this diagnosis persists (Woodruff 1965). Woodruff pointed out that although Darwin was bitten by a known vector, and certainly bitten several times, the insect in that place and at that time would be unlikely to have been carrying the infectious agent. Darwin suffered from severe incapacity but he lived to the age of 73; he almost certainly would not have survived to this age with advanced trypanosomal heart and intestinal disease. In addition, Darwin consulted the best physicians of his time and no physical abnormality in their examinations is recorded. Woodruff concluded: "... it is beyond credibility that severe incapacity could have been produced (by Chagas disease) for 40–50 years without the development of physical signs ..."

Intestinal disorders have also been proposed including peptic ulceration, biliary disease, Crohn's disease, and the irritable bowel syndrome (IBS) (Shanahan 2012). Darwin certainly had symptoms of IBS; he also had symptoms of another suggested diagnosis, that of paroxysmal tachycardia (Dent 1965). The symptoms of IBS, panic disorder, atopic dermatitis, and paroxysmal tachycardia may all occur with Darwin's proposed diagnosis. Other diagnoses may be dismissed simply on the grounds that Darwin had some early symptoms of his disorder before he sailed on the *Beagle*, before he developed any ideas about evolution, and before his proposal and marriage to Emma. In fairness, it should be remembered that many of these more imaginative diagnoses were put forward before there was much knowledge of mitochondrial genetic diseases.

Proposed Diagnosis: a Mitochondrial DNA Disorder

Most of Darwin's symptoms are similar to those seen in patients with cyclic vomiting syndrome (CVS) (Hayman 2009), including some of the more unusual features of this rather poorly defined disorder. Patients with CVS suffer from motion sickness, attacks may be brought on by pleasurable events ("positive stress"), and patients often have relief from water exposure (Fleisher *et al.* 2005). Only one of the many treatments that Darwin tried seemed to bring him any relief and that was "hydropathy" or the "water cure." Patients with CVS today will spend hours in a bath or under a shower (Cyclic Vomiting Association 2010).

Some of Darwin's symptoms, however, were not symptoms experienced by patients with CVS. In his 50's, Darwin experienced episodes of transient partial paralysis, inability to speak, and memory loss (Jones 1867). These symptoms, together with many of his other symptoms such as headache and visual disturbances may occur in MELAS syndrome (Pavlakakis *et al.* 1984). This syndrome, usually regarded as a fatal childhood disorder, may have less severe manifestations and symptoms may first appear in adult life (Higashikata *et al.* 2001). Lactic acidosis, which is a biochemical feature of the disorder (and part of the acronym) may be associated with feelings of panic (Ehlers *et al.* 1986), one of Darwin's symptoms. In the original paper defining the syndrome, 7 of the 11 patients listed experienced "episodic vomiting" (Pavlakakis *et al.* 1984), again a key element of Darwin's condition. Eighty percent of patients with this disorder have been shown to have a particular mitochondrial DNA mutation, an A-to-G transition at nucleotide 3243 in the gene for leucine transfer RNA in the mitochondrial ring chromosome (Goto *et al.* 1990). This same mutation may be associated with cardiac and vestibular symptoms, atopy (atopic dermatitis, asthma), dysautonomia, and peripheral neuropathy (Finsterer 2007). It is a reasonable contention that Darwin had this mutation. Darwin's symptoms and their similarities to the effects created by the mtDNA mutation associated with MELAS syndrome are summarized in Table 1.

Although MELAS syndrome as initially described was progressive and fatal in early life, patients carrying the mutation commonly associated with the condition may have lesser symptoms and a normal lifespan (Manwaring *et al.* 2007).

Darwin's Family Illnesses

Mitochondria and mitochondrial disorders are maternally inherited. An examination of Darwin's family history provides supporting evidence that Charles Darwin had such an inherited mitochondrial disorder.

Erasmus Alvey Darwin (1804–1881), Charles elder brother, graduated in medicine from the University of Edinburgh but never practiced. Instead, he spent a life in London partly as a socialite and partly as a chronic invalid (Healey 2001). He suffered from abdominal pain and lethargy; today he would probably be diagnosed as having chronic fatigue syndrome. His symptoms are consistent with his having had the same

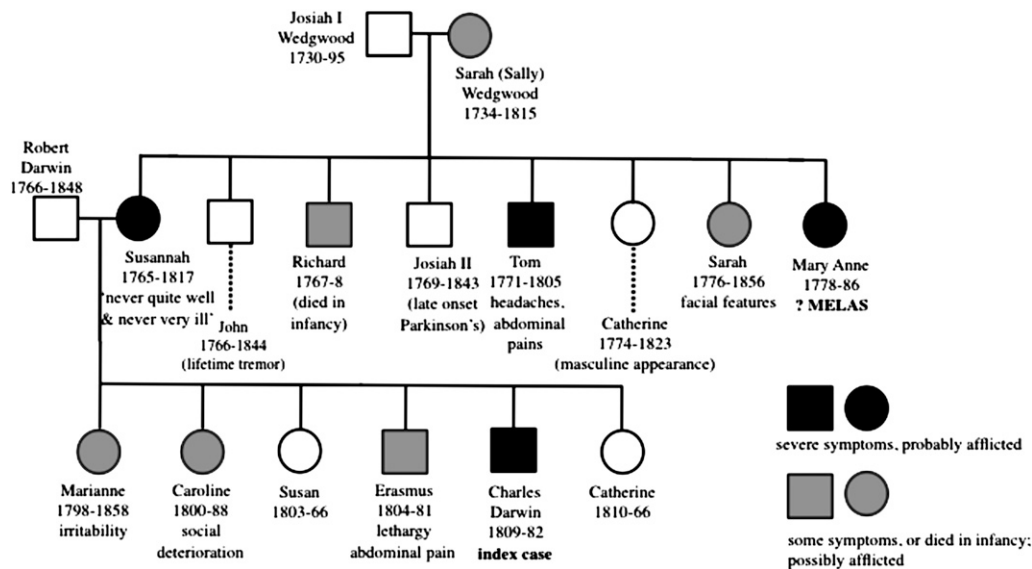


Figure 1 Diagram showing Charles Darwin's siblings and his maternal ancestors, with their major symptoms. Most, if not all of these symptoms may occur with the A3243G mtDNA mutation.

mtDNA mutation as his younger brother but with a lower level of heteroplasmy.

Susannah (“Sukey”) Darwin (Wedgwood) (1765–1817), Charles and Erasmus’ mother, suffered chronic ill health and was “never quite well and never very ill” (Wedgwood and Wedgwood 1980). As a child she suffered from vomiting and boils, and had “difficulties” with her pregnancies, spending much time in bed and suffering from what most likely was hyperemesis. She also experienced motion sickness and preferred to ride in a phaeton rather than a carriage. She complained that “Everyone seems young but me.” Her symptoms are those that may occur in CVS; female patients frequently have hyperemesis during pregnancy (Fleisher *et al.* 2005).

Tom Wedgwood (1771–1805), Susannah’s youngest brother, was unwell for most of his short life. As a student he suffered from headaches and later severe abdominal pains and “would roll around the floor in agony.” On his trip to the West Indies he also suffered from seasickness and was confined to his cabin for the entire voyage with both vomiting and abdominal pain (Wedgwood and Wedgwood 1980). He died with opium overdosage at the age of 34. His symptoms are consistent with what today would be called abdominal migraine, a disorder that may be associated with CVS and with the same mtDNA mutation (Pronicki *et al.* 2002).

Mary Anne Wedgwood (1778–1786), the youngest child in the family, had short stature and was physically and mentally retarded. She suffered from recurrent fits followed by partial paralysis episodic blindness. She died with progressive dementia at the age of eight (Wedgwood and Wedgwood 1980). Her symptoms are typical of the severer cases of MELAS syndrome, as associated with the A3243G mtDNA mutation (Goto *et al.* 1990).

Other siblings in the family suffered more ambiguous symptoms such as social and cognitive decline, while daughters of Susannah’s sisters also had similar problems. Although less

specific as a symptom, psychosocial abnormality may also occur with the A3243G mutation (Finsterer 2007). Two brothers had tremors; one had a lifetime tremor and the other developed classical Parkinson’s disease in later life. A diagram, giving symptoms of Charles Darwin’s siblings and his maternal ancestors is shown in Figure 1.

Charles Darwin’s 10 children were in general a sickly lot; one died in infancy, one in childhood, and their first daughter died at the age of 10. Their illnesses do not seem to be related to one another and not related to the illness of their father. As well as other symptoms, the children suffered from various infections. Their sicknesses may have at least in part been due to the consanguinity of their parents (Charles and his wife Emma were first cousins) as there may be increased susceptibility to infection in the children of such partnerships (Berra *et al.* 2010).

Conclusion

Darwin’s illness, the illnesses of his brother, their mother, his maternal uncle Tom, and a child belonging to the maternal generation as well as other family members show a pattern of maternal inheritance that is the hallmark of mitochondrial mutations, while the particular symptoms point to one specific well-characterized mitochondrial disorder, MELAS syndrome. The evidence is circumstantial, of course, but it is considerable and consistent. As Darwin said of evolution and natural selection: “Let me add that there are many difficulties not satisfactorily explained by my theory of descent with modification, but I cannot possibly believe that a false theory would explain so many classes of facts as I think it certainly does explain.” Much the same may be said of this explanation for Darwin’s illness.

If the conclusion that Darwin’s illness was due to a mtDNA mutation is accepted, then the detailed, lifetime history of his illness and those of family members shows us the range of

symptoms that may occur with the one mtDNA abnormality. Further study of diseases associated with mtDNA mutations may lead us to a better understanding of Darwin's illness, in particular of his very diverse symptoms and the manner in which his attacks of illness were precipitated.

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