Diagnosing the dead: the retrospective analysis of genetic diseases

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ABSTRACT The suspected presence of hereditary disease in important historical and political figures has interested researchers for many decades. Whether Abraham Lincoln suffered from Marfan syndrome, if George III became 'mad' because he inherited variegate porphyria, and if the Romanov dynasty collapsed because the heir Alexei inherited haemophilia are important questions; physical illness can adversely affect the ability of leaders to function within the social and political realm of their day. This article will outline an approach to such a medical-historical analysis including assessment of hereditary predisposition, family history and the use of DNA technology to confirm or deny the clinical suspicions of the investigator.

KEYWORDS History of medical genetics, porphyria, haemophilia, genetic diagnosis, consanguinity and disease, human mutations

DECLARATION OF INTERESTS No conflicts of interest declared.

FAMILY HISTORY AND GENETIC PREDISPOSITION

The establishment of the medical history of a historical figure begins with an assessment of the data common to every individual medical consultation. The propositus then becomes the index case if the available family pedigree suggests the presence of a genetic disorder. Because disease states routinely follow a similar (but not identical) course in most people, the medical historian then focuses not only on the 'sick man', but on the disorder that seems evident in the first patient within a family aggregation.1 The task of the medical historian will be to consider all available records, which by their historic nature will often be incomplete, for evidence of clinical symptoms that recur in other family members, suggesting inheritance of a genetic disorder. A review of all extant records from the physicians involved in the care of the family is important. A classification scheme for historical medical diagnoses has been modified from Professor Frederick Holmes.2 The techniques and aphorisms used by his illustrious fictional namesake Sherlock Holmes have also proved useful in this type of research.

1. Certain: When objective data is available such as an autopsy.
2. Probable: When detailed history of the family members is consistent with a known genetic disorder. Many disorders, of course, do not produce post-mortem changes that could be diagnosed by autopsy even when available.
3. Doubtful: When family history is not consistent with a genetic disorder. The importance of a complete pedigree is important here, as a genetic disorder may be absent in one lineage and present in another.
4. Uncertain: When data is insufficient to reach any conclusion regarding the familial occurrence of a genetic disorder.

Mental illness and the British Royal Family

Several of George III's children experienced recurrent episodes of physical and mental illness similar to those of their father. The royal physician Johan von Zimmerman noted to the King: 'It has come to our knowledge that several members of the Royal Family and in particular His Royal Highness the Duke of York and Prince Edward are subject to the same paroxysms, and this arouses our suspicion of a hereditary predisposition.'3 Letters from the family and close friends can also be very revealing about disease states that 'run in the family'. Edward of Kent, Queen Victoria's father, also experienced similar episodic illness. The Queen wrote literally thousands of letters to her children and other relatives over her long reign and these have proved to be valuable historical primary sources of information. Her daughter Victoria Adelaide, granddaughter Charlotte, and great granddaughter Feodora all suffered attacks of similar mental and physical derangement which resolved and then recurred. The women agreed that they all suffered from the same underlying condition. A recent biography of Prince William Henry, Queen Anne's son, provides an excellent example of a well-designed medical-historical analysis of a royal character. Observations of family and friends have been coupled with medical observations and autopsy findings to assess the nature of his medical condition.4
The three basic patterns for the inheritance of human disease are:

1. **Autosomal dominant:** One parent is affected and has a 50% probability of transmitting the disorder to his progeny. Huntington’s chorea is one example.

2. **Autosomal recessive:** Both parents are unaffected heterozygote carriers for the disorder and have a 25% chance of transmission to their offspring. An example is cystic fibrosis.

3. **Sex-linked recessive:** A female parent is an unaffected carrier and produces on average 50% affected male offspring. Haemophilia is an example.

It has always been a maxim of mine that the little things are infinitely most important.
(Sherlock Holmes)

**Haemophilia and the Royal Family**

Even minor details of family history can provide important clues regarding the exact diagnosis of hereditary diseases. The more common form of haemophilia for example is type A, due to a mutation in the gene for clotting factor VIII. A rare form of the disease, type B, results from a different mutation in the gene for clotting factor IX. The presence of a paternal age effect has been observed in families in which a woman inherits a new mutation from her father only in cases of haemophilia B. Edward of Kent was in his fifties when he fathered Victoria. That her son had haemophilia suggested that she was a carrier for the rare B form. Women who carry the haemophilia gene are usually asymptomatic, but may occasionally demonstrate a bleeding tendency. Tsar Nicholas and Tsarina Alexandra, a granddaughter of Queen Victoria, had four daughters before Alexei was born with the bleeding disorder. Other family members noted that the girls seemed to bleed more than usual from minor cuts and scratches. One suffered a severe haemorrhage during a routine tonsillectomy. It was therefore thought that the girls were also carriers for haemophilia.

**EFFECTS OF MEDICATION**

The effects of various treatments should also be considered as part of a retrospective analysis because genetic conditions may alter the normal response to certain medications. George III did not have a very good opinion of his physicians because their medicines often made him worse rather than better. He was dosed with James’s powder, a medicine based on arsenic and calomel, made with mercury. Chemical analysis of hair samples from the Royal Family demonstrated elevated levels of these heavy metals which are known to alter the chemistry of haem in individuals with porphyria and produce symptoms of the disease. Tsarina Alexandra also demonstrated symptoms of porphyria. She was prescribed veronal, an early barbiturate, which produced severe abdominal cramps, and arsenic products which triggered painful neuralgia. Princess Adelaide was diagnosed with porphyria during the 1940s. Her disease also appeared to recur after she received barbiturate medications.

Is there any other point to which you would wish to draw my attention?
To the curious incident of the dog in the night-time.
The dog did nothing in the night-time.
That was the curious incident.
(Sherlock Holmes)

**GENOTYPE AND PHENOTYPE**

During any genetic-historical analysis, it is important to consider the distinction between disease phenotype and genotype. Dominant traits such as Huntington’s disease are typically expressed as expected in virtually all offspring who inherit the character. But variable expression is also common among other dominant disorders. The majority of people who inherit variegate porphyria for example have no symptoms of the disease throughout their lifetime, but can transmit it to 50% of their offspring who may suffer in the next generation.

**CONSANGUINITY**

So-called ‘skip’ generations are often observed in families segregating autosomal recessive characters, but the trait may then recur due to inbreeding (consanguinity), which increases the likelihood that parents have inherited the abnormal character and can then produce an affected homozygote child. Epidermolysis bullosa appeared in one family for example, in which the condition was quite unknown. But the parents had a common ancestor ten generations in the past, and several intermarriages had occurred since that time. Consanguinity can also play a role in families segregating dominant disorders. A gene for schizophrenia susceptibility has been found to recur over 12 generations in an inbred family from an isolated region in the Netherlands. The same pattern has been observed in Royal households. Edward I had symptoms of variegate porphyria as did his great grandson. Several generations of unaffected men were born until Henry V and Henry VI, who also may have been affected. This could represent an example of variable penetrance of the mutant gene, or the gene may have been lost in successive generations and then reintroduced into the family due to marriages with French cousins who may also have inherited the character from Edward I.

…but when this original intellectual deduction is confirmed point by point by quite a number of independent incidents, then the subjective becomes objective, and we can say confidently that we have reached our goal.
(Sherlock Holmes)
DNA ANALYSIS

The advent of DNA technology in the 1990s provided historians with the opportunity to confirm diagnostic analyses with genetic markers found in human tissues obtained from individuals of historic significance or their families. The precise identification of such diseases can now be accomplished. The case of Anna Anderson, who claimed to be Grand Duchess Anastasia and a survivor of the Romanov family, was resolved utilising such techniques. Her mitochondrial DNA (mtDNA) was extracted from histological tissue and hair roots, and then compared with mtDNA from a blood sample provided by Prince Philip, Duke of Edinburgh, who is a maternal great nephew of Tsarina Alexandra. The mtDNA did not match. Police investigations had suggested that Anna Anderson was really a Polish citizen. Her great nephew provided a blood sample which showed mtDNA that matched Anna, but not the royal line, indicating that she was an imposter.

One of the first studies to diagnose a historic genetic disorder involved the analysis of DNA extracted from dessicated fragments of the eyes of John Dalton, who suffered from colour blindness (sometimes referred to as Daltonism, because of his research in this area). The DNA demonstrated the specific type of the disorder that had affected the famous British chemist. The Romanov family died in the Russian Revolution. Bone fragments from their burial site of individual family members have now been identified, and DNA has been extracted. Mutated haemophilia B genes were isolated from the remains of the Tsarina Alexandra, the heir Alexei and one of his sisters. This investigation then confirmed the presence of the rare B form of haemophilia inherited from Queen Victoria’s royal line.

Another way to scrutinise families of historic figures who may have had a genetic disorder is to work with surviving relatives. Patient and family support groups for many of these diseases have developed in the past two decades. One index for such groups can be found at the University of Kansas (www.kumc.edu/gec/support). Members of affected families are often interested in their historical roots and have begun to investigate their genealogies. The porphyria group has focused their interest on seeking potential connections with members of the British Royal Family alleged to have had this type of inherited disease; they have accumulated records on more than 23,000 individuals. In a pilot study, a woman who is descended from Edward III provided a blood sample which was found to carry the R168L mutation in the PPOX gene for variegate porphyria. The mutation is unique and has not been observed among several hundred other PPOX mutations from families in various parts of the world. Finding the PPOX gene in the Romanov DNA could be a means of documenting a mutation in the gene for variegate porphyria.

...come, the game is afoot. (Sherlock Holmes)

CONCLUSION

The American medical geneticist Victor McKusick observed that physicians diagnosing suspected hereditary diseases had to be astute general practitioners of medicine, focusing on the totality of the patient, and not merely on the eyes, the skin or the kidneys. The same thing must be true of medical historians interested in determining the likelihood that a genetic disorder existed in a patient and his family. It is not good practice to focus solely on the subject’s mental state without reviewing the physical findings and family pedigree as well. It is important to remain skeptical in a questioning sense, but not dogmatic until all available data have been considered.

Once you eliminate the impossible, whatever remains, no matter how improbable, must be the truth. (Sherlock Holmes)

REFERENCES


J R Coll Physicians Edinb 2013; 43:11–14
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