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Research Article

The Wright Brothers and their Genetic Susceptibility to Typhoid Fever

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Abstract

Importance: Typhoid fever gravely sickened Orville Wright in 1896 and the disease killed his older brother, Wilbur, in 1912. The occurrence of typhoid fever among other Wright family members has never been explored.

Objective: To investigate the number of cases of typhoid fever in the Wright brothers' family and determine if they had a predisposition to typhoid fever that might have had a genetic basis.

Methods: Biographical information concerning the Wright brothers was examined and a family tree was constructed. Using an estimated untreated case fatality rate of 20%, typhoid fever mortality data from decennial U.S. censuses (1850-1920) was converted to disease incidence rates from which individual and joint probabilities were determined. The medical literature was searched for genes associated with typhoid fever susceptibility.

Results: Nine Wright family members from three consecutive generations spanning 70 years were reported to have had typhoid fever. The joint probability that these nine separate cases could have occurred independently by chance alone was 8.57×10^{-25}. Multiple genes have been found in the medical literature which cause an increase in susceptibility to typhoid fever.

Conclusions and Relevance: The Wright brothers and their other family members who developed typhoid fever were highly likely to have had a genetic predisposition to this infection.

Keywords: *Wright Brothers; Typhoid Fever; Susceptibility; Genomics; Probability*

Introduction

During 1850 in the United States, typhoid fever caused 13,099 deaths with a mortality rate of 56 per 100,000 population [1]. Data from a half century later revealed only a slight improvement with 35,379 deaths for a mortality rate of 46 per 100,000 population [2]. Contaminated drinking water was the principal way that typhoid fever was then acquired [3]. However, there were other less common modes of transmission such as consuming raw oysters which were often "fattened" by osmosis from exposure to estuarial brackish water at the mouths of contaminated rivers [4].

In August of 1896, Orville Wright, a then 25-year-old bicycle mechanic and high school drop-out, fell ill with typhoid fever. The source of his infection was believed to have been a contaminated well at 22 South Williams Street on the west side of Dayton, Ohio. He and his older

brother and business partner, Wilbur, had rented this space for the Wright Cycle Company which was their bicycle sales, rental, repair, and manufacturing enterprise [5]. After a near-fatal six-week illness, Orville finally began to recover [6]. Seven years later, on December 17, 1903, Orville Wright made the world's first successful powered, sustained, and controlled flight in a heavier-than-air machine flying 120 feet in twelve seconds at Kill Devil Hills, a sandy spit of land just south of Kitty Hawk on the Outer Banks of North Carolina.

In late April of 1912, Wilbur, also a high school drop-out (yet world famous at the time), visited Boston for a legal deposition with their prominent patent litigation attorney, Frederick P. Fish. Shortly after returning to Dayton on April 30th, Wilbur began feeling ill. On May 2nd he was seen by his family physician, Dr. D.B. Conklin, who would subsequently diagnose his illness as typhoid fever [6]. As his malady progressed, he was also seen by Drs. Leon Spitler and William Conklin. Because of his continuing medical deterioration, Wilbur was seen in consultation on May 22nd by the renowned Cincinnati physician and medical author, Dr. Frederick Forchheimer [7], who confirmed the diagnosis, but was unable to recommend any beneficial therapy. On May 29th, Milton Wright, father of Wilbur and Orville, wrote: "Wilbur thought he contracted this fever, by eating schell-fish (sic) in Boston, two weeks before. It is often contracted in that way" [8]. Wilbur died at his home on May 30, 1912 at the age of 45 years. Albert E. Fey, an attorney with the Fish and Richardson law firm would later say: "A little known fact is that we dragged him to Boston for a deposition, where he became ill. He never recovered" [9].

In the past, familial occurrence of an infectious disease was typically attributed to a common source exposure or to person-to-person transmission. Yet, with the Wright brothers, this was not the case: their afflictions were separated by time (16 years), distance (850 miles from Dayton to Boston), and mode of acquisition (polluted well water and contaminated seafood, most likely end-of-season oysters). The ever-astute clinician, William Osler, wrote in his textbook chapter on typhoid fever: "Some families seem more susceptible than others" [3]. Beginning in the 1950's, medical scientists made a series of discoveries that indicated a familial predisposition to certain infectious diseases. It is now well-recognized that human genetics plays a major role in this process [10].

Objective of the Study

The objective of this study is to determine if the Wright brothers had a genetic susceptibility to typhoid fever.

Methods

Historical materials were examined concerning the Wright brothers for the purpose of constructing a family tree. These documents included the diaries of Milton Wright, biographies, historical websites, newspapers, and other miscellaneous items. From this data, further information was extracted regarding other close Wright family members who reportedly had typhoid fever. This data included the times and locations of the various typhoid infections, when this information was available.

Data concerning deaths from typhoid fever and the total population were collected from the decennial United States Censuses from 1850 to 1920 and were used to calculate typhoid fever mortality rates for those years. The medical literature was searched for information on typhoid fever case fatality rates (CFR) and a mean CFR was estimated for the years 1842 through 1912, the period of this study. This estimated CFR was then used to convert the decennial mortality rates to disease incidence rates. This conversion was necessary as data on the incidence of typhoid fever in the United States was not collected for the years encompassed by this study. Using this data, the typhoid fever disease incidence rates were estimated (disease incidence rate = mortality rate / case fatality rate) and then converted to probabilities for the years that the various Wright family members had each acquired their typhoid fever.

The medical literature was searched for publications concerning genes related to increased susceptibility to typhoid fever. Since these studies have only been possible since the relatively recent development of molecular genetics, the populations studied were from areas of the world with current high incidence rates for typhoid fever. No studies were found for United States residents for whom typhoid fever is now a rare occurrence. However, salmonella infections are still common in the United States, with the Centers for Disease Control and Prevention (CDC) estimating that, yearly: 1.35 million people are sickened from salmonellosis; 26,500 people are hospitalized; and 420 people die. Salmonellosis is the leading cause of hospitalizations and deaths from food poisoning.

Results

Cases of typhoid fever in the Wright family

Samuel Smith Wright, an older brother of Milton, was away from the family home in Indiana teaching school when he developed typhoid fever. He died on July 18, 1842 at the age of 23 years [11]. The records do not indicate his exact location at the time of his death.

Much of what is known about Milton Wright (a Bishop of the Church of the United Brethren in Christ) has been gleaned from his diaries. Fortunately, other sources of information concerning Bishop Milton exist because of his letters to Wright family members and his involvement with the United Brethren Church. "During 1865 Wright became ill with typhoid fever and was unable to attend the August session of the White River Conference" [12]. Information from the Wilbur Wright Birthplace Museum also documents that Milton was ill with typhoid fever in 1865 [13]. Bishop Milton and his wife Sarah had seven children, two of whom (fraternal twins) died shortly after birth. Of the remaining five children, Orville and Wilbur both contracted typhoid fever. Their illnesses have already been briefly summarized and, therefore, will not be additionally mentioned; however, it should be noted that neither Orville nor Wilbur ever married or had children.

William Wright married Lucinda Stevens in 1857 and they had three children: Flora, Sarah Katherine, and Ellis. These children all lived long lives of 88, 61, and 95 years, respectively. Their family home was in Orange Township, Fayette County, Indiana. "In October, Milton's younger brother William, also a minister in the United Brethren Church, contracted typhoid fever. Their sister Sarah Wright-Harris, then married twenty-five years and the mother of ten children, lived within a few miles of William, and she helped to nurse him through the illness. Despite the efforts of all who cared for him to get him through the illness, William succumbed on October 5, 1868. He was thirty-six years old" [14].

Harvey Wright was the oldest living brother of Bishop Milton. He and his wife, Delilah, had eleven children and three of these children died from typhoid [6,15]. Luella Grace Wright died from typhoid fever in 1893 at the age of 21 years. Rhoda Carrie Wright, Luella Grace's older sister, perished from typhoid in 1899 and an older brother, George Harvey Wright, M.D., expired from typhoid fever in Indianapolis, Indiana on September 9, 1903 after only 5 days of illness. He was 53 years old.

Lorin Wright, an older brother of Orville and Wilbur, and his wife Ivonette had four children. Their first child, Milton, was born on November 8, 1892. Young Milton lived with his parents at 1243 West Second Street in Dayton and developed typhoid fever on July 18, 1908 at the age of 15 years [6]. His illness was first considered to be mild after an initial assessment by the family doctor, Leon Spitler, M.D [6]. As his illness progressed, it became clear that he had a much more severe case of typhoid fever than originally thought and by August 2nd he was struggling to survive. However, his illness began to improve on August 11th and he went on to live a life of 69 years.

A family tree showing the three generations of Wrights reported to have had typhoid fever (with their outcomes) has been constructed (Figure 1). Data on the nine Wright family members with evidence of typhoid fever is summarized (Table 1).

Name of Wright	Relation to Wilbur	Year infected	Age when infected	Clinical outcome
Samuel Smith	Uncle	1842	23	Died
Bishop Milton	Father	1865	37	Survived
William	Uncle	1868	36	Died
Luella Grace	First Cousin	1893	21	Died
Orville	Brother	1896	25	Survived
Rhoda Carrie	First Cousin	1899	32	Died
George Harvey	First Cousin	1903	53	Died
"Young" Milton	Nephew	1908	15	Survived
Wilbur	-----	1912	45	Died

Table 1: *Data Concerning the nine wright family members with typhoid fever.*

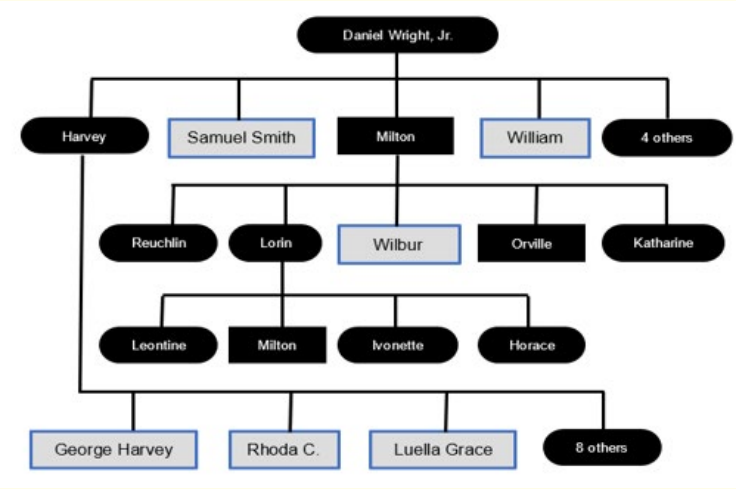

Figure 1: *The Wright family tree and typhoid fever.*

Obround ("stadium-shaped") black figures with white type represent Wright family members (WFM) without typhoid fever (TF); black rectangular figures with white type represent WFM who contracted TF and survived; and blue-surrounded gray rectangular figures with black type represent WFM who died because of TF.

Typhoid fever mortality and incidence in the United States

Typhoid fever mortality and population data from the decennial United States Censuses from 1850 to 1920 were used to calculate the mortality rate per 100,000 population (Table 2, Column 4).

Decennial year	# Typhoid deaths	United States population	Mortality rate*	Incidence rate*
1850	13,099	23,191,876	56	280
1860	19,236	31,443,521	61	305
1870	22,187	38,925,598	57	285
1880	22,854	50,189,209	46	230
1890	27,058	62,979,766	43	215
1900	35,379	76,094,000	46	230
1910	12,673+	53,843,896+	24	120
1920	6,805+	87,436,713+	8	40

Table 2: *Typhoid fever mortality rates and incidence rates in U.S. (1850-1920).*

**Per 100,000, +Registration Area (RA) only.*

Unfortunately, there were some inconsistencies in these census reports. In the reports of 1850 and 1860, cases of typhus were included with cases of typhoid. In 1870 the disease designation was changed to "typho-malarial fever". Typhoid or enteric fever were used for the category in 1880 and 1890. From 1900 to 1920 the reports finally used typhoid fever alone as the disease category.

The population of the entire United States was reported with respect to disease mortality in the census reports from 1850 through 1900. In 1902 Congress established a permanent United States Census Office and, with that new status, changes were made in the gathering of statistics. The decision was made to collect data from the areas considered to have the most reliable reporting capabilities and these areas were called "registration areas" [2]. Therefore, the mortality and population data in the 1910 and 1920 censuses are only for the registration areas (RA) rather than for the entire United States.

In a 1991 review of typhoid fever, Hornick estimated the CFR to have been between 12% and 30% in the years prior to antibiotic therapy [16]. The 2024 CDC Yellow Book states that the current untreated typhoid fever CFR is 10 - 30% [17]. We chose an intermediate value of 20% for the CFR to use in calculating a typhoid incidence rate from the typhoid mortality rate, yielding an incidence rate of five times the mortality rate (Table 2, Column 5).

Probabilities of the Wright family members contracting typhoid fever

Our interest was in determining the probability of each Wright family member acquiring typhoid fever in their particular year of infection. To yield a consistent methodology, we chose to use data from the closest decennial census to the date of the typhoid fever for all nine Wright family members. The incidence rates were then mathematically converted to probabilities of contracting typhoid fever (Table 3).

Name of Wright	Year infected	U.S. census year used	Incidence (Per 100,000)	Probability of typhoid
Samuel Smith	1842	1850^	280	2.80×10^{-3}
Bishop Milton	1865	1870	285	2.85×10^{-3}
William	1868	1870	285	2.85×10^{-3}
Luella Grace	1893	1890	215	2.15×10^{-3}
Orville	1896	1900	230	2.30×10^{-3}
Rhoda Carrie	1899	1900	230	2.30×10^{-3}
George Harvey	1903	1900	230	2.30×10^{-3}
Young Milton	1908	1910	120	1.20×10^{-3}
Wilbur	1912	1910	120	1.20×10^{-3}

Table 3: *Probabilities of the nine Wright family members contracting typhoid fever.*

^1850 was the first year that mortality data was presented.

Independent events

Because the nine cases of typhoid fever in the Wright family were separated by time and location, as well as having none of them being simultaneous or contagiously acquired from one another, these nine cases can be considered independent events (Table 4).

Joint probability

Two events are independent if the occurrence of one event does not affect the chances of the occurrence of the other. The mathematical formulation of the independence of two events is the probability of the occurrence of both events being equal to the product of their

Wright	Year	Location	State
Samuel Smith	1842	Unknown	Indiana
Bishop Milton	1865	Henry County	Indiana
William	1868	Fayette County	Indiana
Luella Grace	1893	Rush County	Indiana
Orville	1896	Dayton	Ohio
Rhoda Carrie	1899	Rush County	Indiana
George Harvey	1903	Indianapolis	Indiana
Young Milton	1908	Dayton	Ohio
Wilbur	1912	Boston	Massachusetts

Table 4: *Data documenting independence of the nine Wright family typhoid fever cases.*

individual probabilities. For N independent events, the joint probability would be the product of the probabilities of all N events. The estimated individual probabilities of each of the nine Wright family members acquiring typhoid fever in their given year were calculated (Table 3). The product of these nine individual probabilities is 8.57×10^{-25}.

Genetic susceptibility to typhoid fever

Recent advances in molecular biology and genomics have identified various specific genes that affect the susceptibility to typhoid fever [18]. The genes for the ABO blood group are present in all human beings and are located on chromosome 9 [19,20]. Clinical studies have shown that individuals with blood type O are more susceptible to both typhoid and paratyphoid disease [21,22]. The mechanism responsible for this increased susceptibility to *Salmonella* spp. infection for blood group O individuals has not yet been determined.

The sequencing and mapping of the human major histocompatibility complex (MHC) was reported in 1999 [23]. The MHC region is located on chromosome 6 and the genes are an essential component of the immune system. Three MHC genes (HLA-DRB1*0301/6/8, HLA-DQB1*0201-3, and TNF*2) were found to be associated with typhoid fever in Vietnam [24]. In England, human volunteers were challenged with *Salmonella enterica* serovars Typhi and Paratyphi A to determine their genetic susceptibility to enteric fever [25]. They found that the HLA-B*27:05 gene had the strongest association with the development of enteric fever.

Toll-like receptors (TLRs) are present on many cell types of the mammalian immune system. These receptors recognize numerous components of microbes thereby triggering an immune response [26]. A study in Malaysia found that two polymorphisms of the TLR4 gene were associated with susceptibility to typhoid infection [27]. The TLR4 gene is also located on chromosome 9 and has, as well, been shown to increase the susceptibility to *Salmonella typhimurium* in mice [28].

PARK2/PACRG is a gene cluster which codes for Parkin which has been linked to the development of juvenile Parkinsonism. Variants in the PARK2/PACRG region have been found to be risk factors for the development of leprosy. Since there is an overlap in the immune responses to intracellular salmonella and mycobacteria, investigators decided to study the role of this gene cluster in the susceptibility to typhoid. They found that polymorphisms of the PARK2 gene were associated with an increase in susceptibility to *S. typhi* and *S. paratyphi* [29]. The PARK2/PACRG gene cluster is also located on chromosome 6 [29].

Recent paleopathological genetic analyses of human remains derived out of mass graves from the 14th century in the northern German city of Lübeck exhibited evidence of paratyphoid fever which is thought to have caused many deaths there following an epidemic of that disease [30]. Additional studies revealed the presence of the HLA-DRB1*03 gene in a higher percentage in these human remains than

in modern German controls [31]. Lübeck was once part of Denmark and the ancestors of the Wright family were Saxon Vikings that came from northern Germany and the Danish portion of the Jutland peninsula. Some Saxon Vikings had migrated to Normandy, France before they invaded England along with William the Conqueror [32]. This migration has been confirmed by genomic studies which have identified "a substantial increase of continental northern European ancestry in early medieval England, which is closely related to the early medieval and present day inhabitants of Germany and Denmark, implying large-scale substantial migration across the North Sea into Britain during the Early Middle Ages" [33]. These analyses found that individuals from eastern England derived up to 76% of their genetic ancestry from the continental North Sea zone [33]. This HLA-DRB1*03 gene has also been shown to increase the susceptibility to typhoid fever in the Vietnamese population [24].

Discussion

When Pierre Charles Alexandre Louis first described typhoid fever in 1829, he believed it was a complication of typhus [34]. It was not until 1837 that William Wood Gerhard, a pupil of Louis, differentiated typhus from typhoid fever in the wake of an outbreak of typhus in Philadelphia the previous year [35].

At that time, the diagnosis of typhoid fever was made based on clinical criteria and during the first few days of a febrile illness it was often difficult to distinguish typhoid fever from malaria. This resulted in the term "typho-malarial fever" which was used in the 1870 census. A bacterial etiology for typhoid fever was not discovered until 1880 and the bacterium was finally cultured four years later [36]. The terms enteric fever and typhoid fever were recorded as the same disease in both the 1880 and 1890 censuses. If the additional infectious diseases (typhus, malaria, and non-typhoidal enteric fever) had been eliminated from the 1850-1890 census data, the actual typhoid fever mortality rates would have been less than reported, which would have decreased those actual typhoid fever probabilities further, thus making it even less probable that the nine Wright family members would have independently contracted typhoid fever.

The epidemiology of typhoid fever was first elucidated by William Budd in 1873 when he reported a number of typhoid fever outbreaks including one in Clifton, England where water from a well utilized by 13 families with infected members was found to be "tainted with sewage" [37]. In the United States, contaminated well water was the most common source of typhoid fever and the disease did not decline until private and public companies began to provide customers with clean, filtered water [38,39]. While these new waterworks resulted in a nearly 70% decline in U.S. typhoid fever mortality from 1900 to 1920, rural inhabitants with wells still remained at risk. Contaminated food and milk continued to be risk factors for typhoid fever even after the quality of public water improved [40].

Oysters were first recognized as a source of typhoid fever in Ireland in 1880 [41] and in the United States after an outbreak at Wesleyan University in 1894 [42]. A Boston physician wrote: "the danger of infection arises wholly from the presence of sewage in the water where the oysters are planted or stored" [43]. This medical knowledge did not affect the public consumption of oysters as oyster production in the United States reached staggering amounts of up to 27 million bushels a year from 1880 to 1910 [44]. "Late in the winter of 1924, simultaneous outbreaks of typhoid fever were reported in Chicago, New York, Washington, D.C., and several other cities" [45]. Approximately 1500 cases of typhoid with 150 deaths were attributed to this outbreak which was traced to oysters harvested from Raritan Bay just south of New York City [44]. The widespread publicity of this large outbreak resulted in a dramatic drop in oyster consumption with a concomitant 50% to 80% fall in production [44].

We do not know the details surrounding the acquisition of typhoid fever for several Wrights, and even for those that have some available information, the source of their infection is not specifically proven by modern methods and standards. Most cases of typhoid fever are produced by ingesting contaminated food (including milk) and water (well or spring) with person-to-person transmission being rare [3,16,40]. It is possible that the Wright family members who became infected ate or drank more of a contaminated source than other consumers and exceeded the minimum infecting dose of *Salmonella typhi* [46]. However, it is much more likely that these family members who became ill with typhoid fever had an increased susceptibility to the typhoid bacillus.

Conclusion

In 1870, Louis Pasteur wrote: "It is not the microbe that is transmitted from the parents to the offspring, but the predisposition to disease" [47]. Multiple genes which increase the susceptibility to typhoid fever have been identified. The HLA-DRB1*03 gene has been found in the remains of 14th century inhabitants of Lübeck, Germany who might have been Wright family ancestors. We have performed calculations demonstrating that it is extremely unlikely that the nine Wright family members independently became infected by chance alone; this would seem to favor their genetic predisposition to typhoid fever.

Author Contributions

Both authors performed the research as well as the writing of the manuscript. JB performed the probability calculations.

Conflicts of Interest

The authors have none to report.

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Disclaimer

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