Evidence for a Heritable Predisposition to Death Due to Influenza

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(See the editorial commentary by Mubareka and Palese, on pages 1–3.)

Animal model studies and human epidemiological studies have shown that some infectious diseases develop primarily in individuals with an inherited predisposition. A heritable contribution to the development of severe influenza virus infection (i.e., that which results in death) has not previously been hypothesized or tested. Evidence for a heritable contribution to death due to influenza was examined using a resource consisting of a genealogy of the Utah population linked to death certificates in Utah over a period of 100 years. The relative risks of death due to influenza were estimated for the relatives of 4855 individuals who died of influenza. Both close and distant relatives of individuals who died of influenza were shown to have a significantly increased risk of dying of influenza, consistent with a combination of shared exposure and genetic effects. These data provide strong support for a heritable contribution to predisposition to death due to influenza.

Seasonal influenza affects 10%–25% of the world’s population each year, resulting in 500,000–1,000,000 deaths. The flu pandemic of 1918 killed 20–100 million individuals [1], including >800,000 individuals in the United States [2]. Clinical manifestations of influenza virus infection vary from asymptomatic infection to fulminant disease and death. The incidence of and fatality rate associated with influenza virus infection are believed to be determined by viral virulence and acquired immunity. Familial clusters of infection are thought to be a consequence of shared exposure. Inherited host factors that also could account for the variability of illness and familial clustering include increased susceptibility to infection, decreased ability to control infection, and/or an ineffective immune response [3]. Demonstration of a heritable contribution to death due to influenza would provide a better understanding of the host genetics of virus susceptibility and also provide insights regarding risk assessment and improved prophylaxis and treatments that could lessen the impact of influenza epidemics.

Recognition of a genetic contribution to the acquisition and course of influenza is confounded by high rates of infectivity, variable morbidity, strong effects of co-morbid disease, and a low case-fatality rate. The existence of a population-based resource in Utah allowed the identification of individuals who died as a result of influenza infection in the past 100 years and enabled the determination of their genetic relationships. These data have been analyzed to examine the hypothesis of a heritable contribution to influenza mortality.

METHODS

Genealogical data. The Utah Population Data Base (UPDB) is a computerized genealogical resource derived from multiple computerized and record-linked data sources. This resource includes genealogical data for the original Utah pioneers (members of the Church of Jesus Christ of Latter-Day Saints, or Mormons) and their descendants [4]. These genealogical data have been record-linked to disease data for Utah, including death certificates dating from 1904. At the time of the present analysis, >2.2 million individuals in the UPDB be-
Table 1. *International Classification of Diseases (ICD)* codes used to identify influenza deaths in Utah.

<table>
<thead>
<tr>
<th>ICD revision</th>
<th>ICD code(s)</th>
<th>ICD definition, (cases, no.)</th>
<th>Total influenza deaths in Utah no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>480-483</td>
<td>Influenza with pneumonia (15), other respiratory (6), digestive (0), or nervous manifestations (0)</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>480-483</td>
<td>Influenza with pneumonia (41), other respiratory (44), digestive (4), or nervous manifestations (2)</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>470-474</td>
<td>Influenza (57); influenza with pneumonia (88), other respiratory (3), digestive (5), or nervous manifestations (1)</td>
<td>154</td>
</tr>
<tr>
<td>9</td>
<td>487</td>
<td>Influenza (113)</td>
<td>113</td>
</tr>
<tr>
<td>10</td>
<td>J10, J11</td>
<td>Influenza due to identified influenza virus (25); influenza, virus not identified (4451)</td>
<td>4476</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td>4855</td>
</tr>
</tbody>
</table>

* Nineteen of these codes were assigned to 1918 death certificates, obviously in error. We will pursue the suggestion of identified virus of the 6 J10-coded deaths from 2000 to 2004.

longed to genealogies with \( \geq 3 \) generations of data; some pedigrees extended to 10 generations. Within the population of individuals for whom genealogical data are available, there are 388,221 individuals with a death certificate. The genetic relationships among the 4855 individuals for whom influenza was a cause of death between 1904 and 2004 were analyzed to describe the familiality of death due to influenza.

The cause of death recorded on Utah death certificates was encoded using *International Classification of Diseases (ICD)* codes (from the sixth through the ninth revisions of the ICD and from the *International Statistical Classification of Diseases, 10th Revision (ICD-10)*). For deaths occurring before 1956, ICD-10 coding was assigned. The ICD codes used to identify individuals whose cause of death was influenza are shown in table 1, as are the corresponding sample sizes. We used ICD codes to identify influenza deaths; some influenza-type codes were not included because of their inappropriate bacterial (e.g., *Haemophilus influenzae*) or viral (e.g., parainfluenza virus) origins.

**Relative risk (RR) for relatives.** The analytical methods used in the present study have previously been applied to describe the familial and genetic contribution to multiple diseases [5–12]; a similar approach has been used for analysis in the an Icelandic genealogical resource [13]. To estimate the RR of influenza death among relatives, the observed rate of influenza death among relatives was compared with the expected rate of influenza death, as follows. All individuals in the UPDB who belong to \( \geq 3 \) generations (according to genealogical data) and who have a coded cause of death \(( n = 388,221 \) were assigned membership in 1 of 132 cohorts that were specific with regard to birth year (in 5-year groups), sex, and birthplace (Utah or not Utah). The rate of influenza death for each cohort was estimated to be the number of individuals in each cohort for whom influenza was reported as a cause of death, divided by the number of individuals in each cohort who had a death certificate reporting any cause of death.

The number of relatives expected to die of influenza was estimated by counting all relatives of probands (by cohort, with no duplication), multiplying the number of relatives (per cohort) by the cohort-specific rate of influenza deaths, and then summing the data over all cohorts. The RR estimated as the observed number of deaths/the expected number of deaths is an unbiased estimator of the RR (also known as the “standardized mortality rate”). One-sided probabilities for the alternative hypothesis test of RR > 1.0 were calculated under the null hypothesis of RR = 1.0, under the assumption that the number of observed deaths follows a Poisson distribution with mean equal to the expected number of deaths.

**Genealogical Index of Familiality (GIF).** The GIF statistic was developed specifically for the UPDB [14]. In contrast to the RR, which examines close relationships between cases, GIF analysis considers all genetic relationships between cases. The GIF statistic measures the average relatedness among all pairs within a set of individuals. The relatedness measure for a case-pair implements the Malécot coefficient of kinship [15], which is defined as the probability that randomly selected homologous genes from the 2 individuals are identical by descent from a common ancestor. For siblings, the coefficient is 0.25 \(( 1/2^2 \) ); for grandparent and grandchild, the coefficient is 0.125 \(( 1/2^3 \) ); and for first cousins, the coefficient is 0.0625 \(( 1/2^4 \) ). The contribution to the GIF statistic is smaller for pairs with a greater genetic distance between them. The “case GIF” is defined as the average of the coefficients of kinship between all possible pairs of cases \(( \times 10^5 \) ). To test the hypothesis of no excess relatedness among all individuals dying of influenza, the case GIF was compared with the empirical distribution of GIF statistics from 1000 sets of matched controls. In addition, we calculated a standardized normal z score for the case GIF, compared with the mean control GIF, estimating the SD of the mean control GIF from the 1000 control GIF analyses. Controls were randomly selected from all individuals for whom genealogical data and a death certificate were available, and they were matched with cases by birth cohort (in 5-year groups), sex, and birthplace (Utah or not Utah). The GIF statistic can also be estimated while ignoring all close relationships (relationships for which the length of the genetic path
is <3); this allows testing of the hypothesis that the excess relatedness that is observed has occurred not only among close relatives.

This research was limited to the analysis of unidentifiable data. There was no contact with subjects, and no informed consent was required.

RESULTS

Influenza deaths in Utah. In the UPDB, 4855 individuals for whom 3 generations of genealogical data were available had a death certificate that listed influenza as a cause of death between 1904 and 2004. The 1918 influenza pandemic was responsible for a noticeable increase in influenza deaths for several years after 1918. For the purpose of classifying Utah deaths as being caused by the 1918 strain of the influenza virus, influenza deaths (n = 1937) that occurred in the years 1918–1921 were considered. In the decade after the pandemic (1922–1932), an additional 1293 influenza deaths occurred. In the 1950s and 1960s, an average of 10 influenza deaths occurred in Utah per year, decreasing to 8 influenza deaths per year in the 1980s and to 4 such deaths per year in the 1990s. Similar to what has been reported worldwide, in 1918–1921 in Utah, an unusually high mortality rate occurred among young adults aged 20–39 years (54% of influenza deaths occurred in this age group). Before 1918 and after 1921, only 11% of influenza deaths occurred among young adults in that age group.

RRs. Table 2 shows the RR of death due to influenza for first-degree relatives of individuals whose death was attributed to influenza. The RR of death due to influenza was significantly elevated in all first-degree relatives, as well as in each category of first-degree relatives (siblings, parents, children) considered separately. The RR of fatal influenza among spouses who were married to individuals at the time of their death due to influenza was also significantly elevated. Of the 74 individuals who died of influenza and whose last spouse also died of influenza, 44 (59%) died within 3 weeks of each other, suggesting that the individuals were coinfected with the same virulent strain of virus and shared environmental and/or exposure factors. The remaining 30 individuals died 14 months to 69 years after their spouse, perhaps representing a mix of some sequelae of earlier exposure as well as random clustering.

Increased RRs for first-degree relatives cannot distinguish between the results of shared genetics or shared effects of environment and/or exposure, because first-degree relatives have these types of effects in common. Significantly elevated RRs in more distant relatives, however, provide strong support for a heritable contribution. Distant relatives share more genes but fewer effects of exposure and/or environment with each other than with do individuals in the general population. RRs of death due to influenza among second-degree relatives (e.g., grandparent/grandchild or avuncular relatives) and third-degree relatives (e.g., first cousins) of individuals dying of influenza are shown in

Table 2. Relative risk (RR) of death due to influenza among first-degree relatives and spouses of individuals dying of influenza.

<table>
<thead>
<tr>
<th>Relatives</th>
<th>Deaths due to influenza, no.</th>
<th>RR (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All first-degree</td>
<td>638</td>
<td>1.54 (1.42–1.67)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Siblings</td>
<td>376</td>
<td>1.74 (1.57–1.92)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Parents</td>
<td>148</td>
<td>1.37 (1.16–1.61)</td>
<td>.0002</td>
</tr>
<tr>
<td>Children</td>
<td>168</td>
<td>1.59 (1.36–1.86)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Spouse</td>
<td>74</td>
<td>1.98 (1.55–2.48)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval.

* One-sided significance for the test of the alternative hypothesis RR > 1.0.

Table 3. Relative risks (RRs) of death due to influenza in second- and third-degree relatives of individuals dying of influenza.

<table>
<thead>
<tr>
<th>Relative</th>
<th>Deaths due to influenza, no.</th>
<th>RR (95% CI)</th>
<th>P*</th>
<th>Relatives, b no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-degree</td>
<td>1090</td>
<td>1.22 (1.14–1.29)</td>
<td>&lt;.0001</td>
<td>64,363</td>
</tr>
<tr>
<td>Third-degree</td>
<td>1446</td>
<td>1.16 (1.11–1.23)</td>
<td>&lt;.0001</td>
<td>88,521</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval.

* One-sided significance for the test of the alternative hypothesis RR > 1.0.

b With a Utah death certificate.
excess relatedness was also observed when the GIF analysis was used to test for excess relatedness among individuals who died of influenza. As shown in table 5, the average relatedness of all 485 influenza deaths was significantly greater than expected (empirical $P < .001$). Significant excess relatedness was also observed when the GIF analysis was repeated with close relationships ignored ($P < .001$). These analyses provide strong support that individuals dying of influenza are significantly more related to each other than expected, and that this excess relatedness is represented by an excess of both close and distant relationships.

Table 5 also shows the findings of GIF analysis for subsets of individuals dying of influenza. GIF analysis was performed for those dying of influenza in 1918–1921 (during which time infection was caused by the more virulent pandemic strain of influenza virus) and for individuals dying of influenza in all other years. Significant excess relatedness was observed for individuals dying of influenza during both time periods. GIF analysis was performed for individuals who died of influenza between the ages of 20 and 40 years (i.e., those thought to be most susceptible during the 1918 pandemic). Significant excess relatedness was observed among these young adults who died of influenza, even when close relationships were ignored.

Figure 2A illustrates the contribution to the GIF statistic for influenza death by genetic path length (or relationship, a measure of the probability of shared genes), for all individuals dying of influenza (case GIF, 3.83), and for the 1000 sets of matched controls (control GIF, 2.94). Figure 2A allows identification of the types of paired relationships that contribute to the excess relatedness observed; the sum of the contribution from each genetic path length (i.e., relationship) equals the GIF statistic. The distribution for the 1000 sets of matched controls represents the distribution of relationship pairs expected in a random set of matched individuals selected from the Utah population. A significant excess of case-pair relationships among individuals dying of influenza, compared with control-pair relationships, was observed for all genetic distances examined.

Table 4. Relative risk (RR) of death due to influenza for relatives dying of influenza and relatives of spouses dying of influenza.

<table>
<thead>
<tr>
<th>Relative</th>
<th>RR of death due to influenza (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibling</td>
<td>1.74 (1.57–1.94)</td>
</tr>
<tr>
<td>Parent</td>
<td>1.37 (1.16–1.61)</td>
</tr>
<tr>
<td>Grandparent</td>
<td>1.23 (1.03–1.45)</td>
</tr>
<tr>
<td>Third-degree</td>
<td>1.16 (1.11–1.23)</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval.

To elucidate whether effects of shared environment and/or exposure among distant relatives could be responsible for the significantly elevated RR observed for more-distant relatives, the correlation of the dates of death due to influenza between these pairs of relatives was estimated. The results are shown in figure 1. The correlation of the date of death in all third-degree relative pairs with influenza deaths was considered. Evidence for the increased RR of influenza death being due to shared environment and/or exposure would be supported if the date of death occurred within days—or weeks—for the paired relative deaths. Observations not lying directly on the diagonal line in figure 1 denote dates of death due to influenza for third-degree relative pairs that were at least 1 year apart. The bulk of the influenza deaths in Utah occurred during the period from 1918 to 1921, as can be seen by the crowding of data points in figure 1 for these years. Even with this crowding, it is clear that only a minority of the paired dates of death lie on or near the diagonal line in figure 1; this indicates that the majority of the third-degree relative pairs died years apart from each other. For third-degree relative pairs, the estimated Pearson product-moment correlation coefficient for the date of death was 0.0002 (i.e., not significant).

GIF. GIF analysis was used to test for excess relatedness among individuals who died of influenza. As shown in table 5, the average relatedness of all 485 influenza deaths was significantly greater than expected (empirical $P < .001$). Significant excess relatedness was also observed when the GIF analysis was repeated with close relationships ignored ($P < .001$). These analyses provide strong support that individuals dying of influenza are significantly more related to each other than expected, and that this excess relatedness is represented by an excess of both close and distant relationships.

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**Figure 1.** Scattergram of dates of death (DoD1 and DoD2) for all pairs of third-degree relatives dying of influenza, unordered. The diagonal line shown denotes DoD1 = DoD2 (the date of death for the 2 paired relatives was the same). Each axis denotes 100 years of deaths.
To provide comparison of the results for influenza with those for a contagious disease in which close contact and shared environment are risk factors, but for which a genetic predisposition is not suspected, deaths due to diphtheria in Utah were analyzed. Table 6 shows the results of GIF analysis of the 878 individuals dying of diphtheria in Utah. As can be seen, there is excess relatedness for all individuals dying of diphtheria considered together \(P < 0.001\), representing evidence for excess familial clustering. However, when close relationships are excluded, there is no evidence for excess relatedness of individuals dying of diphtheria \(P = 0.369\), demonstrating no evidence for any factors other than shared environment and/or exposure. Figure 2B shows the pattern of excess relatedness observed for diphtheria by relationship.

### Discussion

Influenza A viruses infect humans and spread as local outbreaks, yearly regional epidemics, and, intermittently, global pandemics. Previously identified factors associated with influenza morbidity and fatality include the infecting strain of virus and the age and comorbid conditions of the infected individual, but rarely is family history considered to be a factor. The highly infectious nature of influenza virus, ubiquitous exposure to the virus during epidemics and pandemics, and variation in the illness have hindered the clinical recognition of evidence for the heritable contribution to influenza mortality. The existence of a population-based genealogical resource in Utah, linked to 100 years of death certificate data for the state, has allowed testing of the hypothesis that there exists a heritable contribution to predisposition to death due to influenza.

A heritable contribution to cancer and other causes of death has previously been reported using this resource [5–12]. The previous descriptions of cancer heritability have subsequently been confirmed by the identification of multiple cancer predisposition genes in Utah pedigree studies [16–19]. The UPDB represents a geographically and culturally distinct population; however, the Utah population has been shown to be genetically representative of Northern Europe, with normal levels of inbreeding [20, 21].

It is difficult to separate effects of shared environment and/or exposure from shared genetics in relatives. This is most difficult among close relatives, and the difficulty is enhanced in the case of an infectious disease such as influenza. The significantly elevated RRs observed in spouses must be assigned entirely as resulting from shared exposure and/or environment, because
spouses in an outbred population typically do not share common genetics. Among relatives, however, shared exposure is unlikely to be the only contributor to the observed clustering of fatal cases of influenza virus infection. The significantly elevated RRs for influenza death observed for first-degree relatives suggest that there might be a genetic contribution to influenza death. The significantly elevated RRs for death due to influenza in second- and third-degree relatives confirm that this is so. Similarly, the GIF analysis excluding close genetic relationships confirms that distant relatives, who share a measurable percentage of their genome but have little chance for coinfection with the virus causing the fatal case, are at increased risk for fatal influenza. These results are further supported by the findings that the estimated RRs for relatives of spouses are lower than the estimated RRs for relatives of individuals dying of influenza. These composite results provide the definitive basis for a genetic predisposition to fatal influenza that is entirely distinct from shared exposure and environment. The recent observation that, in 15 documented family clusters of H5N1 infection, almost all infections occurred among blood relatives supports the hypothesis of a genetic effect on susceptibility to H5N1 infection [22, 23].

Much of our data on influenza mortality came from individuals who died between 1918 and 1921, when the population had no acquired immunity to the circulating virus and the fatality rate was markedly increased. Evidence for a genetic contribution to the familial patterns observed in this immunologically virgin population was significant, and the predisposition was confirmed even when the deaths occurring during these years of a pandemic were ignored. When analyzed separately, individuals who died of influenza during 1918–1921 had higher average relatedness than was observed for persons dying of influenza during all periods. This excess relatedness during the 1918 pandemic was observed in both close and distant relatives, and it was exhibited far in excess of the expected relatedness observed in random matched controls with comparable community exposure. The findings indicate that, even during this short period in which virtually the entire Utah population was exposed, a heritable predisposition to influenza death contributed to the patterns of influenza death observed. The results of analysis of all influenza deaths for the past 100 years show that the heritable predisposition that we have identified is independent of viral strain, the absence or presence of acquired immunity from natural exposure, and the age of the host.

We have also identified multiple Utah pedigrees in which at least 1 influenza death occurred (assuring exposure) but in which there was a significant deficit of influenza deaths among relatives. These pedigrees may simply represent families that remained relatively less exposed to influenza, but they might also represent pedigrees in which a heritable resistance to death from influenza is segregating. Study of the exposed—but surviving—relatives of individuals in these pedigrees may aid in the identification of influenza resistance genes. Such genes might include those that elicit more timely, more appropriate host response in controlling the infection.

There are limits to the evidence and interpretations provided by this analysis. Only those individuals whose Utah death certificate indicated influenza as a cause of death could be analyzed; death certificate data can be nonspecific. Influenza is most often a clinical, rather than a virologic, diagnosis, and virologic confirmation of influenza was not available during much of the past century. Influenza deaths may have been censored through incorrect reporting on death certificates. Similarly, some deaths, especially those of close relatives, may reflect a halo effect and may have been incorrectly ascribed to influenza, perhaps more so during epidemics or pandemics. We considered both close and distant relationships in this analysis, to avoid the effects of such a bias. Other potential confounders, such as geographic location, poverty, and patterns of shared behavior, could be risk factors that span distant genetic relationships. We are analyzing the risks for other heritable predisposing conditions in cases and relatives. Although data for these other factors are currently unavailable, future studies will gather information on shared risk factors in relatives.

Demonstration of a significant heritable contribution to the fatal outcome of influenza adds a new dimension to understanding the nature of the disease. Death is a finite objective event at the end of the spectrum of variation in clinical influenza. The nature of the UPDB data available for this analysis does not permit a determination of the mechanism(s) that produce the predisposition to a fatal outcome of influenza. Recent data on the pathogenesis of death due to influenza virus H5N1 infections found that high pharyngeal viral loads, viral RNA in the blood, and a host response with high levels of immunocytes and cytokines were the determinants of death [24]. The degree of control of these factors is likely to differentiate severe illnesses from fatal ones. Death is probably the least sensitive indicator of the im-

<table>
<thead>
<tr>
<th>Cases</th>
<th>Deaths, no.</th>
<th>Case GIF</th>
<th>Mean control GIF (range)</th>
<th>Empirical P</th>
<th>z scorea for case GIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>878</td>
<td>5.13</td>
<td>3.33 (2.55–4.22)</td>
<td>&lt;.001</td>
<td>6.5</td>
</tr>
<tr>
<td>Ignoring close relationships</td>
<td>2.63</td>
<td>2.56</td>
<td>1.96–3.10</td>
<td>.369</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* Standardized normal z score.
portance of genetic factors in the course and outcome of influenza. Genetic variation in the innate and adaptive immune system has been associated with severe disease due to respiratory syncytial virus, but not with death [25]. Further analyses will consider other phenotypes of severe influenza in the high-risk pedigrees identified, including nonfatal infections and postinfluenza sequelae, such as myocarditis, encephalitis, persistent respiratory symptoms, or postinfectious fatigue.

The more we learn about human predisposition to, as well as resistance to, the deadly effects of influenza virus, the more prepared we will be for the next influenza pandemic. Current defense strategies center on prophylactic vaccination of individuals who are at the most risk for serious complications of influenza, including only those aged ≥65 years and those with chronic respiratory, cardiac, or metabolic disease. Priorities based on the remaining lifespan have been proposed; global rationing issues further complicate strategies [26]. Our results suggest that a family history of a severe influenza response is another index to target appropriate populations for vaccination, quarantine, and early treatment. Identification of the gene(s) responsible will allow more accurate estimation of individual risk, as well as better individualized screening and care.

These results provide a strong rationale for pursuing efforts to map genes associated with severe or otherwise inappropriate responses to influenza virus infection, but they need to be confirmed in individuals with virologically confirmed influenza. Using Utah genealogical resources linked to hospital and clinic data, we will be able to identify individuals with virologically confirmed influenza, as well as identify outcomes for high-risk individuals in high-risk pedigrees who have been vaccinated. Recruitment and study of surviving members of these pedigrees at high risk for influenza death will allow identification and understanding of the predisposition gene(s) responsible. It will be also be important to identify those genes associated with the ability to respond with protective immunity after natural or vaccine challenge. Identifying the genes responsible for an acute response to influenza virus infection and gaining an understanding of the molecular basis for individual differences in the host response will provide insight into the development of improved vaccines and into new interventions during influenza epidemics and pandemics.

References