

# How Does Genetics Influence Valley Fever? Research Underway Now To Answer This Question

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## **Introduction**

Of the roughly 150,000 new infections of coccidioidomycosis (Valley Fever) that occur each year, there is an enormous range of severity and outcomes. As depicted in Figure 1, approximately a third seek medical attention because of a significant illness and even fewer of these are accurately diagnosed and reported to state officials (1).

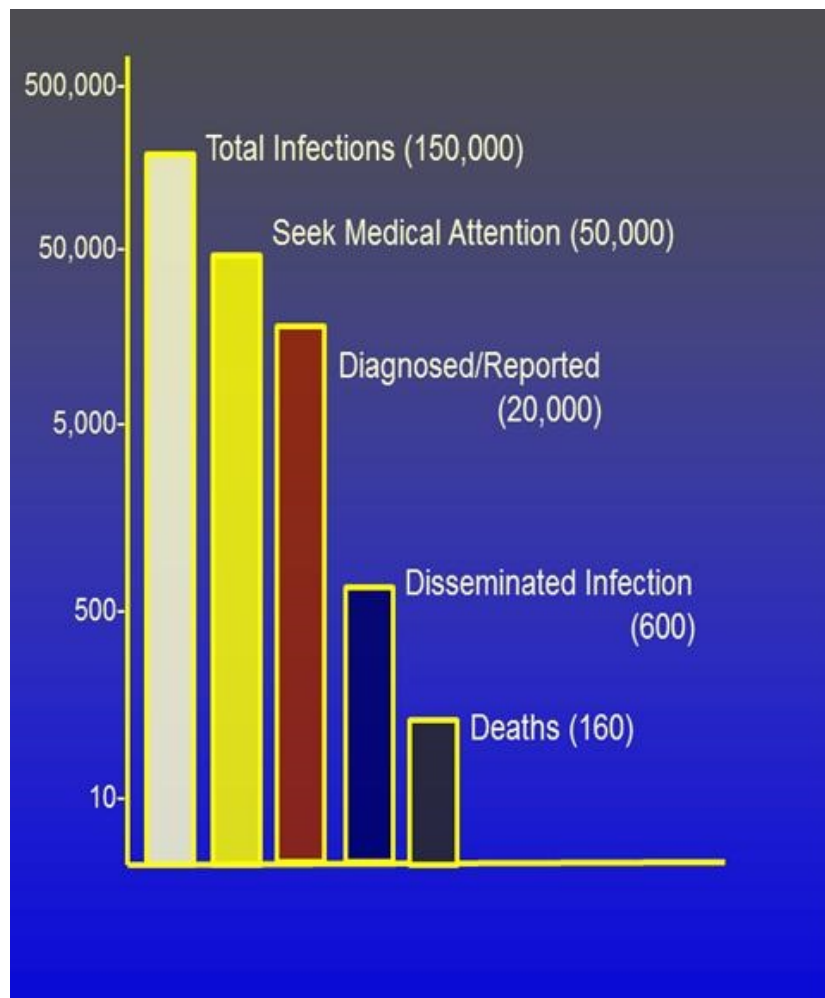


Figure 1. Severity and outcomes of coccidioidomycosis (Valley Fever).

The community-acquired pneumonia syndrome that most symptomatic patients experience often takes many weeks to many months to completely resolve and is anything but trivial (2). Even so, for most patients, the illness is eventually self-limited whether treated or not.

In contrast, a relatively small proportion of all infections result in the spread through the blood stream beyond the lungs (extrathoracic dissemination) to produce progressive tissue destruction in skin, bones, joints, the central nervous system, and almost any other part of the body. As a result, about 160 persons die of Valley Fever each year (3). What accounts for this striking spectrum of disease has been the subject of speculation for decades. Now two research programs have been initiated to try to answer this question.

### ***Genetic Differences Among Persons Is The Prime Suspect***

For many infectious diseases, the size of the microbial inoculum determines whether disease will result. Indeed, there are very good examples of this when the exposure to coccidioidal spores is very high. For example, when archeologists or construction projects involve soil rich in spores of *Coccidioides* spp., infection rates are higher and symptomatic illness is more common than found in the general population within endemic regions (4-6). However, in such clusters, there is little or no evidence that high inoculum is more likely to result in extrathoracic dissemination.

Another possible source of differences in disease severity could be due to differences among strains of *Coccidioides* spp. While this cannot be entirely ruled out, the evidence that exists is not supportive. For example, in the clusters of infections cited above where likely most infections came from genetically similar spores, there is still a wide spectrum of illness. Similarly, in laboratory accidents where all persons are definitely exposed to the same strain, there are also diverse clinical manifestations (7).

In contrast to inoculum and fungal virulence, several lines of evidence implicate genetic differences among individuals as a factor responsible for disseminated infection. First and most apparent, normal control of coccidioidal infection is critically dependent on competent cellular immunity. When this is severely compromised either by an underlying disease such as AIDS (8, 9) or by immunosuppression for organ transplantation or treatment of autoimmune disorders (10-12), coccidioidal infections are very much more likely to result in extrathoracic dissemination. That broad immunosuppression is a major risk factor for disseminated Valley Fever opens up the possibility that more subtle differences in the immune response to coccidioidal infection could account for differences in disease severity.

Secondly, men are much more likely to develop disseminated coccidioidal infection than women. Evidence for this comes from the enrollment statistics for clinical trials conducted by the Mycoses Study Group for patients with disseminated coccidioidal

infection where between 1988 and 2007 three-quarters of 367 subjects were male (13-17). Similar results are apparent in other reports as well (18-20).

Thirdly, at least one specific genetic marker, that of B and AB blood groups, has been associated with disseminated infection (19, 21). This is not likely to be a causal relationship but does clearly suggest a genetic component.

Finally, numerous studies have implicated increased risk of certain ethnic groups for disseminated infection, most notably those of African and Filipino ancestry (22). Estimates of how much more susceptible African-Americans are to developing disseminated disease range as high as 41.9 times more than Caucasians (Table 1).

<b>Table 1. Relative risk of disseminated coccidioidomycosis in African-Americans as compared to Caucasians.</b>			
<b>Report</b>	<b>Year</b>	<b>Study type</b>	<b>Fold increased risk</b>
Smith et al (23)	1946	Retrospective	+14.0
Flynn et al (20)	1979	Outbreak, retrosp.	+9.5
Pappagianis (24)	1988	Outbreak, retrosp.	+9.1
Rosenstein et al (25)	2001	Retrospective	+ 7.0
Crum et al (26)	2004	Retrospective	+41.9
Drake et al (27)	2009	Retrospective	+11.0
Foley et al* (18)	2011	Prospective	+4.0

\* <https://www.vfce.arizona.edu/resources/pdf/csg/55Proceedings.pdf>

An Arizona Department of Health Services presentation in 2011 based upon chart review of reported cases found dissemination in Blacks was 25% compared to 6% in Whites, roughly a four-fold increase in incidence of dissemination. The denominator for these statistics was all cases reported to the state and therefore avoid referral bias and some other confounding factors in earlier studies.

Despite all of these associations suggesting a genetic component to a risk for disseminated infection, there have been essentially no observations as to which specific genes are involved and how genetic differences affect disease susceptibility. Dr. Stephen Holland, a physician scientist and his colleagues at the National Institutes for Health have recently identified in a small number of patients specific gene mutations which appear responsible for more severe infections. The mutated genes were the interferon-gamma receptor 1 (28), the interleukin-12 receptor beta (29), and STAT1 (30).

As important as these findings are, all of the patients described in these reports are not typical of most patients who experience disseminated coccidioidomycosis. The patient with the interferon-gamma receptor 1 deficiency had two other opportunistic mycobacterial infections at other times in his life, and multiple opportunistic infections are not typical for patients with disseminated Valley Fever. The patients with the interleukin-12 beta deficiency were siblings from a consanguineous family. Disseminated coccidioidomycosis is very uncommon in multiple members of the same family. The two patients with the STAT1 mutation had a clinical presentation that included disseminated infection but also included a consumptive pulmonary process that was strikingly devoid of cavitation. However, Dr. Holland has identified additional patients who appear to have functional immunologic deficits, even though he and his team were unable to determine the genetic basis for those altered responses (31).

### ***Two Studies Now Underway Involving Arizonans To Better Understand The Genetics Of Disseminated Valley Fever***

Encouraged by his recent findings, Dr. Holland has written a clinical research protocol specifically addressing patients with disseminated coccidioidomycosis. The program, entitled "The Pathogenesis and Genetics of Disseminated Coccidioidomycosis," is open to any person over the age of 2 years who has culture or histologic proof of disseminated Valley Fever. Persons who have an already identified immunosuppressing condition or who have a medical or psychiatric condition that would interfere with providing informed consent would not be appropriate for this study. If informed consent is given, subjects will initially have blood specimens collected locally for shipment to the NIH. Then, depending upon initial results, subjects may be invited to visit the NIH for additional testing. After the initial visit, study related expenses, including travel and treatment of the disseminated Valley Fever infection, will be paid by the NIH (initial travel expenses may be covered for indigent subjects). Dr. Holland's study is open to patients throughout the United States. However, for those close enough to down town Phoenix, it will be possible to have the initial blood and urine specimens obtained and shipment arranged by the NIH laboratory located on the Indian Health Hospital campus. This protocol was initiated in the fall of 2014 and is currently active.

A second research initiative is investigating the increased susceptibility of those with African ancestry. Despite the findings shown in Table 1 above, an underlying problem with all estimates of increased frequency of disseminated coccidioidomycosis in African-Americans is that the relation of self-identified race/ethnicity (SIRE) is a poor surrogate for ancestral genetic origins. Genetic heterogeneity within each racial and ethnic grouping may bias associations in genetic association studies, generating both false-positive and false-negative results (32-36). Variations in the distribution of single nucleotide polymorphisms (SNPs), called ancestry informative markers (AIMs), have been found which describe the architecture of genome variations between populations (37). This discovery has led to an approach which circumvents the genetic ambiguity of SIRE categorizations. One of the benefits of AIMs is that relatively few markers are required (about 1,500 AIMs for African-Americans) to effectively screen the entire

genome. As such, we expect it to identify large chromosomal regions of differential ethnic ancestry in clinical samples.

For this second study, anyone who is self-declared of African ancestry who has laboratory confirmed coccidioidal infection is eligible. For those who have not experienced disseminated infection, an adequate length of time off antifungal therapy is necessary (nominally two years (38)) to determine if disseminated infection is not likely to occur. Consenting subjects will be asked for a sample of saliva for genetic testing. They may also be asked for a blood specimen in the future for laboratory studies of their leukocyte response to coccidioidal antigens. Collaborators for this study are in both Phoenix and in Tucson.

Any Arizona clinician interested in referring a patient for potential inclusion in either study can contact the Valley Fever Center for Excellence at the Arizona Health Sciences Center in Tucson or the Valley Fever Center in Phoenix located at St. Joseph's Hospital and Medical Center at their respective phone or FAX contact numbers:

	<b>Phone</b>	<b>FAX</b>
Valley Fever Center for Excellence, Tucson	520-626-4968	520-626-4971
Valley Fever Center in Phoenix	602-406-VALE	602-406-4272

### ***Summary***

After decades of interest and speculation about what possible genetic influences are involved in determining the severity of Valley Fever infections, there are now two separate studies underway to address this question, each taking a different and complementary approach. At the very least, such information would be valuable for risk stratification, either for persons wanting that information before travelling to the coccidioidal endemic area or early in the course of a new coccidioidal infection. However, depending upon the success of this research, understanding the genetics could possibly suggest new therapeutic options. Most helped by this work will be Arizonans where two-thirds of all Valley Fever infections in the United States occur.

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