

# When two tribes go to war

Medical geneticists and isolated Native American communities afflicted by inherited diseases should have much to gain from working together. But the relationship can go sour, as Rex Dalton finds out.

South of the Grand Canyon in Arizona, in a valley that roads still don't reach, the Havasupai tribe has for centuries lived a cloistered existence in the high desert. Isolation in a geological wonderland has allowed the tribe's 600-plus current members to protect their ancient culture. But the flipside is a restricted gene pool that has given the Havasupai one of the highest incidences of type 2 diabetes anywhere in the world.

Such populations offer geneticists the chance to discover rare gene variants underlying disease that would be difficult to detect in more diverse groups. And in the early 1990s, with the tribe's blessing, a team from Arizona State University (ASU) in Tempe began searching for a genetic cause of the Havasupai's diabetes.

Instead of a genetic breakthrough, the research project has spawned lawsuits claiming \$75 million in damages, filed by tribal members who claim that their rights were infringed. The accused researchers strenuously deny any wrongdoing, and blame the dispute on a series of misunderstandings. These problems seem to have been inflamed by personal differences among the scientists involved. But the case illustrates the sensitivities associated with conducting genetic research on Native American populations — which, enriched by gambling revenues, are now in a position to assert their legal rights.

Medical geneticists are watching the lawsuits carefully, as some believe the results could cast doubt on the future of genetic studies being conducted on Native American populations across the United States. In the meantime, the Havasupai reservation, some

240 kilometres northwest of Flagstaff, is closed to researchers.

"What concerns me deeply is that the allegations have resulted in a moratorium on biomedical research on the Havasupai reservation, excluding this and other communities from discoveries with the potential to address their health concerns," says Therese Markow, who led the Havasupai project during her years at ASU, and is now at the University of Arizona in Tucson.

## Family roots

To investigate the genetics of disease in small, remote populations, it is important to determine just how genetically isolated a group really is. With modern molecular tools, researchers can examine a tribe's genetic history, revealing where tribal ancestors migrated from, and the degree to which they have interbred, over the years, with other groups — including Americans of European extraction.

These are sensitive subjects for Native Americans. Details about migration may challenge the received cultural wisdom about tribal origins, and the question of who is 'more native' can be particularly contentious.

In decades past, Native Americans feeling violated by intrusion into such territory would have had a hard time challenging researchers from a major university. But the balance of power is shifting. Gambling on reservations produces millions of dollars in

revenue, and has made native tribes a political force. Given their remote location, the Havasupai do not run a casino, but they share in revenue from those Arizona tribes that do. And the state's tribes work together on various issues, hiring well-connected lobbyists and high-powered attorneys to protect their collective interests.

The growing influence of Native American tribes has already been used to block the publication of studies deemed culturally offensive — a development that has split researchers working with native communities (see 'The heart of the matter', overleaf). Some see it as unacceptable censorship; others argue that the tribes' cultural sensitivities must come first.

Against this background, the Havasupai experience illustrates just how badly things can go awry. The project began with great promise — melding Markow's interests in genetics with the expertise in social anthropology of John Martin, an ASU colleague who had worked with the tribe for more than 40 years. Martin knew several generations of Havasupai and had created a genealogical history of tribal families.

At the beginning of the twentieth century, a combination of disease and natural disasters had reduced the Havasupai to about 165 members, with only about 40 men and 40 women of reproductive age. As the population recovered from this bottleneck,


**"Native American tribes are so understudied. If this litigation continues, all research is going to cease."**

— Daniel Garrigan



C. KARNOW/CORBIS





In dispute: the Havasupai tribe initially welcomed geneticists into its remote settlement (right), but subsequent research has led the Native Americans to file lawsuits for \$75 million in damages.



the rate of diabetes began to climb. In 1991, when Markow's study began, 55% of Havasupai women and 38% of the men were diabetic. Martin had also observed a mental condition that he suspected to be schizophrenia — and which his family charts indicated may have originated with a tribal shaman in the late nineteenth century.

### On the trail

Markow and Martin put together a proposal to study diabetes, schizophrenia and depression in the Havasupai, which was approved by ASU's human subjects committee in 1991. Initially, the study was conducted with university funds and a grant of some \$90,000 from the National Alliance for Research on Schizophrenia and Depression in New York. Later on, there would be small grants from the National Science Foundation and the National Institutes of Health.

Working with the Havasupai meant hiking, riding horseback or taking helicopters into the reservation. Tribal members who volunteered for the study signed a consent form in which they agreed to provide blood samples, plus hand and fingerprints, for genetic studies into behavioural and medical disorders.

Pursuit of a genetic cause of schizophrenia was dropped early on, after a psychiatrist found no evidence of the disease among tribe members. And as the ASU researchers began to examine Havasupai DNA samples,

they also ran into trouble finding a genetic link to diabetes. Studies of another Arizona tribe, the Pima, had by then found that 81% of nearly 200 Pima diabetics carried a particular variant of a gene involved in immune recognition called *HLA-A2* (ref. 1). But Markow's team could find no association between this gene and diabetes in the Havasupai<sup>2</sup>.

The project looked set to yield nothing but results on the general biological consequences of the tribe's restricted gene pool<sup>3</sup> — especially after cell lines created from the Havasupai blood were damaged by a freezer failure in 1994. By the time that Markow moved to the University of Arizona in 1999, it seemed as if all momentum had been lost.

But in 2002, the project was reinvigorated after genetic material was salvaged from the damaged cell lines. Daniel Garrigan, a PhD student in another lab at ASU, was then able to analyse genetic markers called microsatellites — repeating sequences of two or more letters of the genetic code that vary in their length from person to person — to examine genetic variability among the Havasupai.

By early 2003, Garrigan had a manuscript accepted by the journal *Genetics* detailing markers in the Havasupai that were sufficiently variable to use in the search for genes predisposing to diabetes. This was also a major part of his doctoral thesis — until he walked to the podium at ASU on 4 March 2003 to deliver a lecture as part of the examination process.

The audience included Martin and an acquaintance of his from the Havasupai,

Carletta Tilousi. She publicly questioned Garrigan's authority to perform the study. "It was a bizarre event," recalls Garrigan. The day before the lecture, Garrigan says Martin had warned him that he viewed the Havasupai data as his intellectual property. "Stop, or there will be repercussions," Garrigan claims he was told. Martin agrees that he challenged Garrigan on his use of the samples, but denies that this was a threat.

### Culture clash

While he had made been aware of Martin's views on the ownership of the data, Garrigan was stunned by Tilousi's intervention at his lecture. Having worked among the Maya in Mexico before joining the Havasupai project, he thought that he was sensitive to Native American concerns. He also believed that his studies had put him on the trail of a genetic explanation for diabetes in the Havasupai.

When Martin and Tilousi objected to Garrigan's research, meetings were held at ASU. A decision was made to withdraw the manuscript from *Genetics*, and to remove the

microsatellite data from Garrigan's thesis. "It was disheartening," says Garrigan, who is now a postdoc at the University of Arizona.

After the thesis showdown, the conflict intensified. Martin first complained to ASU's human subjects committee, alleging that the research had strayed away from the topic of diabetes into areas that the tribe had not agreed to. When the committee investigated this and found no problem, Martin wrote to ASU president



Therese Markow sought a genetic cause for diabetes in the Havasupai.

## The heart of the matter

When it comes to genetic studies of Native Americans, anthropologist Robert Williams of Arizona State University in Tempe has learned that — in addition to passing scientific peer review — it may be necessary to pass a test of cultural sensitivity.

After eight years of laboratory work on blood samples taken from 5,000 individuals belonging to 12 tribes across the United States, Williams was in 1999 required to halt his attempt to investigate the growing incidence of cardiovascular disease among the tribes.

His project was part of the Strong Heart Study, a large epidemiological study that has received \$46 million over 15 years from the National Heart, Lung, and Blood Institute (NHLBI) in Bethesda,

Maryland. Williams suspected that the epidemic of heart disease among Native Americans was in part caused by gene flow from interbreeding with Americans of European origin. So he set about investigating this genetic 'admixture', an approach he had previously used in studies of diabetes among Arizona's Pima tribe<sup>4</sup>.

Every manuscript arising from the Strong Heart Study is submitted to tribal representatives for review. Williams' paper, dealing with the sensitive issue of interbreeding with non-Native Americans, was the first to be blocked. "I feel this is political censorship," Williams says. "This has never happened in my 30-year career."

Everett Rhoades, a Native American medical researcher at the University of Oklahoma who

was the chair of the ethics committee that recommended halting Williams' research, declined to comment for this article. But epidemiologist Barbara Howard of Georgetown University in Washington DC, who heads the Strong Heart Study, rejects Williams' complaints of censorship. "I know he is frustrated," says Howard. "He is a good researcher. But the concerns of Native American communities take precedence."

Peter Savage, the NHLBI's director of epidemiology, adds that Native American volunteers can withdraw from research and ask that their samples be destroyed at any time and for any reason. "This is the cost of doing research in special communities," he says.

Michael Crow and other university officials on 11 May 2003. In this letter, he alleged that Markow had misused tribal DNA samples by sending them for analysis of their *HLA* genes to two labs in California.

Martin had by then come to believe that the Havasupai's diabetes was caused by nutrition during fetal development, and his letter claimed: "no genetic research on diabetes genes was undertaken" by anyone. He now acknowledges that this statement was an error.

Regardless of its factual accuracy, Martin's letter came at an inopportune time for ASU. Newly installed as president, Crow was leading an ambitious plan to accelerate research at the university, including genetic studies of Native American tribes. A new state-funded research facility, the Translational Genomics Research Institute in Phoenix, was also developing collaborations with ASU researchers and Arizona tribes.

At the same time, the Havasupai were preparing to go public with a press conference, lambasting ASU over the research project. To head off an embarrassing public row, ASU opted to pay for an investigation into the project by an independent attorney.

In retrospect, that move seems to have been a monumental blunder on the part of the university — one that paved the way for the lawsuits now filed against ASU, the University of Arizona, the two institutions that performed the *HLA* gene analysis, and individual scientists including Martin and Markow.

The investigator was Stephen Hart, a lawyer in Phoenix who has represented tribal governments and formerly served as director of the Arizona Department of Gaming, overseeing Native American gambling operations. His report ran to nine volumes, and was delivered to ASU and the Havasupai late last year.

Hart's report is a compendium of interviews. It contains no firm findings of misconduct, but states that there are "issues"



Native Americans have become increasingly politically active — here they protest outside the football ground of the Washington Redskins.

with how the project was administered, the keeping of records, and whether the tribe realized the full extent of the research that would be undertaken. In March this year, a 150-page summary of the report was submitted to the state court in Flagstaff, in support of two lawsuits claiming that the Havasupai's civil rights were violated when their blood samples were used in the research.

### Deeply divided

The lead plaintiff on one of the lawsuits is Tilousi, who was elected last December to the tribe's governing council — the plaintiff on the other suit — as concerns grew about the research. Tilousi says she feels mentally "raped" by the project.

The accused researchers are disturbed by Hart's report. In particular, Markow argues that Hart gave too much credence to the testimony of Christopher Armstrong, formerly a researcher at ASU. Armstrong has since been convicted for dealing cocaine and was being treated for drug and alcohol abuse at the time he was interviewed by Hart.

Armstrong accused Markow of various improprieties, including hiding studies on schizophrenia from the Havasupai. Markow

denies the allegations. Far from exploiting the tribe, she argues that her group did extensive screening for diabetes among tribal members and provided health education.

Martin, whose complaints helped to trigger Hart's investigation, is similarly concerned about the report. Indeed, Martin's protests against Garrigan seem to have rebounded badly on him. His relationship with the Havasupai has been torn apart and the suspension of research on the tribe's reservation has halted Martin's work. "I'm bitterly disappointed," he says. ASU officials are now in the process of collecting any remaining stored blood and DNA so that they can be returned to the Havasupai.

Bartha Knoppers, an expert on informed consent in genetic studies at the University of Montreal in Canada, notes that standards have evolved since the Havasupai project began. But she feels that it is difficult to judge the conduct of the research by today's more explicit standards.

In some other cases, researchers have gone back with new consent forms when extending a project, but this is unusual. In the Havasupai case, ASU's human subjects committee accepted that Garrigan's research was an extension of the previously approved project.

Whatever the outcome of the lawsuits, the researchers at the centre of the storm fear that the publicity generated will threaten future genetic studies of Native American tribes. "They are so under-studied," says Garrigan. "If this litigation continues, all research is going to cease."

**Rex Dalton is Nature's US West Coast correspondent.**

1. Williams, R. C. *et al. Diabetologia* **21**, 460–463 (1981).
2. Markow, T. A. *et al. Am. J. Hum. Genet.* **53**, 943–952 (1993).
3. Markow, T. A. & Martin, J. F. *Ann. Hum. Biol.* **20**, 389–394 (1993).
4. Williams, R. C., Long, J. C., Hanson, R. L., Sievers, M. L. & Knowler, W. C. *Am. J. Hum. Genet.* **66**, 527–538 (2000).

For more news and analysis go to  
[news@nature.com](http://news@nature.com)  
[www.nature.com/news](http://www.nature.com/news)