

# Profile of Alec J. Jeffreys

**A**s one of the great contributors to modern genetics, Sir Alec Jeffreys was born with curiosity in his genes as the son and grandson of prolific inventors. Jeffreys displayed an insatiable quest for knowledge, and his father fostered his son's budding scientific interests with gifts of a microscope and chemistry set, the latter of which produced one of Jeffreys' most memorable scientific ventures. "Those were back in the happy days of chemistry," Jeffreys points out, "where you could go down to your local pharmacist and get virtually everything you wanted." The end result of that chemistry experiment was the detonation of his aunt's apple tree and a set of scars that Jeffreys still bears today. "You learn science very fast that way," he says, "but it was quite fun."

Jeffreys' scientific curiosity only increased after the apple tree incident, and years later it would lead to one of the most widely used applications in genetics: DNA fingerprinting. Among other uses, the DNA fingerprinting technique has helped solve numerous criminal investigations, settle countless paternity disputes, and spark a resurgence of interest in the forensic sciences. That achievement alone is worthy of merit, contributing to Jeffreys' receiving three high distinctions in 2005: the Albert Lasker Clinical Research Award, induction into the National Inventors Hall of Fame, and election to the National Academy of Sciences as a Foreign Associate.

Aside from the invention of DNA fingerprinting, Jeffreys has made many other pioneering contributions to the field of human genetics. These accomplishments include the discovery of eukaryotic introns, further understanding of the evolution of gene families, and insight into the secrets of genetic recombination. Some of these secrets are documented in Jeffreys' Inaugural Article in this issue of PNAS (1), which looks at the mechanisms of ectopic recombination, in which locally similar DNA sequences are exchanged. This recombination process can generate variation in gene copy number and lead to inherited pathological disorders.

## Oxford to Introns

Born in 1950 in Oxford, England, Jeffreys grew up in the shadow of the University of Oxford, but he did not have any connections to the storied institution. "We were very much on the other side of the tracks," he says of his family. Thus, Jeffreys never gave much thought to attending Oxford University, but his high school headmaster, an Oxford alumnus, seemed determined that Jef-



Alec J. Jeffreys

freys go there, so Jeffreys entered the university in 1968. He was at first intent on pursuing a degree in biochemistry but soon decided to alter his course. "This was no criticism of the way it was taught," he says of biochemistry at Oxford, "but rather a reflection of the faculty's research, which leaned heavily to physical biochemistry." Jeffreys had become more interested in genetics and molecular evolution, so after he received his B.A. in biochemistry in 1972, he remained at Oxford to complete his D. Phil. in genetics in 1975.

Jeffreys then received an European Molecular Biology Organization (EMBO) research fellowship to work with Piet Borst at the University of Amsterdam in The Netherlands. His project was intended to study yeast transfer RNA genes, but then he met up with another researcher, Richard Flavell. Says Jeffreys, "[Flavell] said, 'We've got this crazy project attempting to isolate and purify mammalian genes, specifically the rabbit  $\beta$ -globin gene. Would you be interested?' I mean, at the time, nobody had ever detected or cloned or analyzed a single-copy mammalian gene. So I said, 'Yeah, bet your bottom dollar, I'm in.'"

Jeffreys and Flavell hoped to biochemically purify a vast amount of rabbit DNA via mRNA hybridization enrichment, but their plan ultimately did not work. In the process, however, Jeffreys, with the aid of the then-new technology of Southern blotting analysis, developed a way to probe and detect the globin gene. The probes led to the creation of the first physical map of a mammalian gene (2), which in

turn led to another groundbreaking finding about the composition of eukaryotic DNA: introns (3). "I was 27 at the time, so still a real rookie, with the ability to detect single-copy DNA by Southern blot hybridization and a nice paper on introns under my belt, which is, yeah, not a bad start," he says.

## DNA's First Fingerprint

After these heady research achievements, Jeffreys was faced with the question of "What next?" In 1977, he returned to England to accept a Lecturer position in the Department of Genetics at the University of Leicester (Leicester, United Kingdom), where he remains today as a professor, but scientifically the decision of what to do next was problematic. The logical course seemed to be to study introns, but Jeffreys expected that a lot of major laboratories would move into this field. "And it was obvious to me that, being essentially by myself—I had just a part-time technician working for me—with no funding, and really having to start from scratch, that to carry on with the intron work would not be competitive," he says. Instead, Jeffreys sought to combine his recently acquired molecular biology experience with his interests in human genetics.

"The first question we asked was, 'If you can see DNA restriction fragments,

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can you see variation between people in those fragments?” says Jeffreys, who ultimately was able to, in the form of the second-ever description of restriction fragment length polymorphisms (RFLPs) (4). “We were beaten to the post by Y. W. Kan, bless him, he well deserved it,” says Jeffreys. Although RFLPs would help advance several areas of genetics research, Jeffreys was a bit frustrated with them. “They were hard work to detect at the time, and they weren’t very genetically informative. We felt that there must exist bits of DNA that are far more variable than standard RFLPs,” he says.

Three years and an assortment of unsuccessful approaches later, Jeffreys found a clue in a completely different project looking at the organization and evolution of globin genes, particularly the often-overlooked myoglobin. The trail began with a lump of seal meat donated by the British Antarctic Survey (Cambridge, United Kingdom). “Seals express myoglobin at very high levels in their muscle,” explains Jeffreys, “and that made the messenger RNA, and hence the gene, much easier to isolate.” Successful isolation of the seal myoglobin gene paved the way for the isolation of the human myoglobin gene, and within that gene Jeffreys found a short stretch of DNA with tandem repeats: a minisatellite (5, 6).

“At first, it was a little bit of ‘so what?’” recalls Jeffreys of the finding. “This wasn’t even variable.” But a few examples of variable minisatellites had emerged in recent literature, and they seemed to share some sequence similarity. To better define this similarity, Jeffreys hybridized the myoglobin minisatellite to a human genomic library and pulled up numerous cross-reacting clones, all sharing a 10- to 15-bp core sequence (7). “That told us that if you want to isolate minisatellites in large numbers, you use this motif. So we thought, ‘OK, we’ll just try a simple experiment of taking a Southern blot of various individuals and hybridizing it with a probe of these repeat motifs,’” he says. His laboratory even had an available blot lying around, which included DNA from his technician, Jenny Foxon, and her parents.

“And on the morning, 5 past 9, of Monday, the 10th of September 1984, we got our first truly awful DNA fingerprint purely by chance,” Jeffreys says. Yet as soon as he took a look at what he remembers being “a horrible, smudgy, blurry mess,” he could tell what was going on: he could spot the family group present in that blot and distinguish all three members by what appeared to be a simple pattern of inheritance (8). “We suddenly realized that we’d essentially stumbled upon a DNA-based method for biological

identification. My life completely changed at that point,” he says.

### The Boy from Ghana

After the discovery of the first DNA fingerprint, Jeffreys rushed out of the x-ray developing room and proclaimed to his group, “I think we’re onto something really exciting here.” Within a half-hour, he and his laboratory had written down a slew of potential applications, including forensics, paternity or twin testing, and conservation biology. “We were then faced with two challenges, really. The first was to improve the technology from that blurry mess to something that would actually be reliable enough for real casework. The second was whether anybody would pay a blind bit of notice,” he says. A few months of tinkering solved the first challenge to Jeffreys’ satisfaction, and an opportunity to meet the second arrived soon after.

## The first DNA fingerprint was “a horrible, smudgy, blurry mess.”

In April 1985, Jeffreys received a letter from Sheona York, a London lawyer. York had read about DNA fingerprinting in the newspaper and wondered whether this technique could help sort out a tricky immigration dispute involving a family from Ghana. The youngest boy had gone back to Ghana and returned with a United Kingdom passport that appeared tampered. Immigration authorities suspected that the boy was a noncitizen substitute, perhaps a cousin, trying to sneak into the country. Although the standard genetic tests at the time could prove a familial relationship, they could not determine specifically which relationship. Complicating matters, the mother was not exactly sure who the father of the boy was, and none of her sisters were available for testing.

Says Jeffreys, “I first thought, ‘Well, forget it! This is a jigsaw puzzle with too many pieces missing!’” He decided to give it a try, however, and managed to reconstruct the DNA fingerprint of the missing father by using DNA from three other children. He then showed that every genetic character of the disputed boy matched the mother or father (9). As a result, the immigration tribunal dropped the case and allowed the boy back into the United Kingdom as a full citizen. “So that was a fabulous story to the start of

DNA fingerprinting. This was science, helping this poor family who got themselves in a bureaucratic tangle,” says Jeffreys. He dreads to think of what would have happened had he found the opposite result, but as it was, this heartwarming story made national headlines and helped open the floodgates for DNA fingerprinting technology.

### Forensic Crimefighting

In 1986, as Jeffreys and his small laboratory handled all the DNA test requests for issues regarding immigration, paternity, and the like, Jeffreys faced challenges for making DNA fingerprinting appropriate for use in forensics. Together with Peter Gill at the United Kingdom’s Home Office Forensic Science Service, he quickly established that DNA could survive in forensic samples, clearing one potential hurdle. Another obstacle was that DNA fingerprint blots were fairly complex and needed to be simplified. The solution for this problem came from Jeffreys’ work in cloning individual minisatellites from the fingerprints (10). “Once you get the cloned minisatellite, you can make the thing locus-specific,” he explains. These cloned probes could detect highly variable alleles of different lengths and produce easy-to-read two-band patterns, one for each copy of the allele. By sampling multiple loci on each sample, a “DNA profile” could be built.

In 1986, Jeffreys was contacted by local police regarding a murder case where two schoolgirls had been raped and murdered 3 years apart in an apparent copycat killing. The police had a suspect in custody, but although he confessed to the second murder, he denied the first. Jeffreys was asked to use DNA profiling to tie the suspect to both cases. The results were completely unexpected: both semen samples belonged to the same man but were not from the suspect (10). Jeffreys initially thought something was flawed with the DNA profile, because the police were sure they had their culprit, but repeated tests confirmed the discrepancy, and the suspect was eventually set free. “And that’s something a lot of people forget,” Jeffreys says. “They tend to see DNA as a powerful tool for the prosecution, but don’t realize it’s just as powerful for the defense.”

Says Jeffreys, “Then the police did something that I thought was fantastically brave. Rather than disbelieve DNA, they totally believed it and launched what proved to be the world’s first DNA-based manhunt, asking for blood samples from men from the entire local community.” In a Hollywood-like twist though, the perpetrator devised an elaborate deception wherein he forged his passport and had a friend stand in for him as a proxy. Fortu-

nately, the friend confessed to the ruse while at a pub one night, which allowed for the apprehension of the real murderer, who was positively profiled via DNA testing. “So that was the birth of forensic DNA in real casework,” says Jeffreys, “and this was DNA potentially saving the life of future victims, which was quite sobering stuff.”

### Launching Microsatellites

By the end of the 1980s, the word had spread about DNA fingerprinting, and DNA profiling had established itself as an international gold standard for genetic testing. Jeffreys realized, however, that limitations existed with the technique. “It was slow, not very sensitive, and the technology had to move on,” he says. That technology would soon arrive in the form of PCR, which had been invented in 1983 and advanced to a user-friendly form. Also, the identification of microsatellites, which are  $\approx 100$  bp long compared with several thousand base pairs for a typical minisatellite, provided variable loci that could be easily amplified and more resistant to degradation. “It was absolutely obvious to me that this was going to be the way forward,” says Jeffreys.

Jeffreys soon tested the power of microsatellite, or single tandem repeat (STR), typing. In 1990, he was contacted by a prosecutor in Frankfurt, Germany, who was seeking assistance in proving that some recovered skeletal remains belonged to Josef Mengele, the infamous Nazi German physician and officer. Together with Erika Hagelberg, an Oxford colleague with expertise in DNA extraction—“she can get DNA out of a stone, just about,” says Jeffreys—he developed microsatellite profiles from the bone samples. Comparing the DNA profiles with those of Mengele’s widow and son confirmed the authenticity of the skeletal remains (11) and helped close the book on a 40-year-old war-crimes investigation. Surprisingly, despite such noteworthy success with STR typing, several more years passed before this technique became the new standard for forensic science. Jeffreys believes this lag “was a testimony to just how good the old-fashioned Southern blot hybridization approach was.”

With STR typing, Jeffreys and his group felt that the fundamental science of DNA fingerprinting had largely been solved. “So, it was time to let go of the baby’s hand and walk off in another direction,” he says, “although the baby has flourished quite well.” He has been pleased with the media attention that DNA fingerprinting has received, viewing it as a good platform to enthuse people about genetics. In fact, one of his fondest experiences was participating in a television program in 1990 where DNA fingerprinting showed that two sisters were in fact identical twins, a show viewed by nearly 18 million people. “Now, I’m a university teacher, so my typical class will be about 20 people. To reach out and hit 18 million in one go is phenomenal,” he says. If Jeffreys has any gripes about his “baby,” it’s only that some of the publicity has distorted its value, placing too much emphasis on the criminal context and not enough on the many other applications, such as for familial or immigration testing.

### Recombination and Globin’s Return

In recent years, Jeffreys has returned to basic questions about minisatellites and human genetic diversity. “Why were these bits of DNA so astonishingly variable between people?” he asks. Jeffreys has found that DNA recombination plays a crucial role as the driving force behind minisatellite mutation. “These bits of DNA were hooking into the meiotic recombination process and basically getting themselves in a mess,” he says. Looking at recombination events more closely, Jeffreys has found that recombination preferentially occurs at tightly controlled sequence elements, or hotspots (12). “And the picture that’s emerging is that these hotspots are likely quite dynamic features of the human genome,” he says, noting a study that found that despite nearly identical genomes, humans and chimpanzees have radically different haplotype structures (13, 14).

These dynamic hotspots are also puzzling, because Jeffreys observed that some single nucleotide polymorphisms (SNPs) inside hotspots could down-regulate activity but then engage in a bizarre process whereby they are overtransmitted into

progeny, creating a hotspot paradox (15). “In other words, any mutation that down-regulates a hotspot will be favored by the recombination process and should then wipe that hotspot out,” he says. More recently, Jeffreys has demonstrated that hotspots could come or go without any change whatsoever in the local DNA, such that two individuals could differ in the presence or absence of a particular hotspot but have the exact same DNA sequences for kilobases around that area (16).

In his PNAS Inaugural Article (1), Jeffreys and graduate student Kwan-Wood G. Lam examined another mysterious crossover event, ectopic recombination. Ectopic recombination occurs between segments of locally repeated DNA, such as in gene family clusters, and can result in gene duplications or deletions. Returning to the globin genes he had studied early in his career, Jeffreys used the  $\alpha$ -globin gene family as a model to investigate the rules governing ectopic recombination events. Jeffreys and Lam found that genetic exchanges involving  $\alpha$ -globin gene regions are surprisingly common, can occur in both sperm and blood, and can occur between short regions of sequence identity. Chromosomes with  $\alpha$ -globin gene deletions are prevalent in Asian and African populations and are likely maintained via malaria selection for  $\alpha$ -globin-deleted chromosomes (17, 18). Indeed, Jeffreys and Lam found that, despite high levels of instability, exchanged chromosomes are rare in geographic regions without malaria, suggesting strong selective pressure.

Of course, these recombination events still pose many unanswered questions, and like the detectives of the popular television show “CSI: Crime Scene Investigation,” Jeffreys is eager to tackle them and be surprised by the answers. For him, science has always been an exploration of the unknown, and the best experiments are those where one has no idea what is going to happen. “If someone had told me in 1980, ‘Alec, go away and figure out a way of identifying people with DNA,’ I would have sat there looking very stupid and got nowhere at all,” he says. “So, if I could tell you what I would be doing 5 years from now, I’d be very depressed, because that means I sort of know the answers.”

Nick Zagorski, *Science Writer*

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