Technologies of similarities and differences: on the interdependence of nature and technology in the Human Genome Diversity Project

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Chapter 3

Ten Chimps in a Laboratory:
Or How a Human Genetic Marker May Become a Good Genetic Marker for Typing Chimps.

Introducing the Argument

This chapter deals with genetic markers. Genetic markers are pivotal categories in the field of population genetics. As was shown in the previous chapter, markers are the very object of comparison between individuals, or populations. The question in this chapter is, therefore, what is a genetic marker? To answer this I will not treat a marker as an entity or an autonomous category. Rather, I will “study around it,” and examine the socio-technical network of laboratory routines in which it is enacted. The argument carried out in this chapter is that genetic markers are technically and locally invested, and that this quality co-determines their ability to move from one locale to an other.

Genetic markers are often presented as innocent tools, as loci present on the DNA, which need only the keen eye of technology to make them emerge. Population geneticists have become increasingly aware of the lack of universality of these tools and of the embeddedness of markers in different populations and different laboratory practices. Nevertheless the dream of genetics is to find universal markers, through trial and error or through large-scale studies. In a way the latter is a quest for the unproblematic tool that will make it possible to focus more on populations and less on the technology at hand. One could call this dream the quest for an “unbiased eye” that can see without regard to populations or individual. The dream of good genetic markers is nowhere and everywhere at the same time. Yet genetic markers are tools in everyday laboratory practice, developed to meet the specific goals and needs of laboratories.

This chapter takes the practicalities of markers seriously and considers how laboratory work is involved in them. A case involving the typing of chimp DNA is studied in order to show that the DNA fragment, the technical means to visualise that fragment, and the goals for studying DNA all become constituent parts of a genetic marker. All these investments contribute to
markers and, hence, to what may count as a good genetic marker at the specific sites where markers are being crafted.

Markers: A Round-table Discussion

Let me take you to a round-table discussion that took place after three days of conferring on human genome diversity. The theme was genetic markers. To quote some remarks made by a number of participants:

- “A list of markers should be made, as an indication to newcomers in the field and in order to compare the different data” (Jaume Bertranpetit).
- “What are good genetic markers?” (Svante Pääbo)
- “We need to have some consent about the markers so as to compare the results” (Lucca Cavalli-Sforza).
- “We need markers that are selectively neutral to different population structures” (Sir Walter Bodmer).
- “Preferably markers that do not require use of radioactivity” (Svante Pääbo).
- “Criteria for markers should be that they show variation between populations” (Lucca Cavalli-Sforza).
- “What we need right now is a list of priority markers” (Jaume Bertranpetit).
- “What is the use of such a list if people aren’t working with it anyway?” (Brian Sykes)
- “One could recommend things now, but it would be preferable to choose a democratic procedure, such as people reacting from their own experience of research” (Svante Pääbo).

This discussion was part of the conference Human Genome Variation in Europe: DNA Markers held in Barcelona in 1995. The conference was aimed at fine-tuning a variety of laboratory practices, scientific goals, and criteria for population genetic research, by paying special attention to an important category to this field, namely genetic markers. A “list of priority markers” should do the job of fine-tuning. Particularly the last two remarks quoted, indicate that this is not an easy job. Moreover the round-table discussion revealed a tension between various local needs, interests, goals, and practices. The question raised by one of the participants, namely: “what are good genetic markers?” hints at a variety of practices and suggests that markers bear this tension as well.
In order to understand the tension, we will consider how markers are applied in daily laboratory practice and how they may become good genetic markers. A laboratory case will be analysed to examine the practicalities of markers and how they mediate the local and global goals of scientists aiming at developing a universal approach to genetic diversity. For this purpose we will enter a forensic laboratory concerned with identifying human individuals. This case, however, is not about humans but about chimpanzees. Let us first take a closer look at a definition of a marker.

**Markers: A Definition**

"Marker: an identifiable physical location on a chromosome whose inheritance can be monitored. Markers can be expressed regions of DNA (genes), a sequence of bases that can be identified by restriction enzymes, or a segment of DNA with no known coding function but whose pattern of inheritance can be determined [...]"  

A marker may thus be understood as a specified fragment of the DNA that is inherited *unchanged* from one individual by another. These fragments can be identified by their "physical location" on the DNA and can be monitored by geneticists.

**Not the DNA but a Marker**

Geneticists do not study the whole DNA of an individual or a population, but only small fragments. Why? The DNA molecule of a human being contains too much information to be studied as a whole. Consider the fact that geneticists all over the world have been constructing and mapping *one* human genome ever since 1989 and have "finished" doing so by the mid of the year 2000. To make the picture complete, consider also the fact that what is often referred to as the *genome* is the so-called coding region and makes up only 5% of the whole DNA molecule. The non-coding region is often referred to as "junk DNA" and is hardly ever considered as part of the *genome*. Thus scientists can only study small fragments of the molecule, either coding or non-coding DNA, defined by their interests and research questions. These fragments may be referred to as *markers*. Hence it is not the DNA but genetic markers which are objects of monitoring.
Monitoring and Markers

The definition emphasizes the “monitoring” of markers in individuals in terms of inheritance. This indicates that markers are objects of comparison. Markers cannot be studied in one individual but are dependent on comparisons between individuals. Conversely one could say that in genetics individuals are not related by blood or even by DNA but by genetic markers, and that monitoring these markers means studying how markers “behave” in different individuals.

Moreover the definition seems to suggest that a genetic marker is both the information encoded in the DNA, a “gene” or “some segment of DNA,” and also its “physical location,” namely a specified sequence and its location in the DNA molecule. Whereas the first is concerned with the functioning of DNA, namely how genes play a role or how DNA fragments are inherited, the second is concerned with where the sequence is and what it looks like in terms of nucleotide order. The definition embodies both accounts, but there seems to be a primacy of the first over the second when the importance of monitoring is being considered. A genetic marker is defined as “a physical location [...] whose inheritance can be monitored.” Thus the criterion of monitoring seems to be a precondition for the physical location to become a marker. As indicated, this chapter is concerned with how genetic markers are enacted in routine practices, and will therefore examine how “monitoring” is done in a laboratory context.

In the forensic laboratory, the site of the case investigated here, the Lab members would rather speak of typing than of monitoring markers. However, to capture the kind of work that is being done in laboratories, I consider monitoring instead. Since the interest of this chapter is to understand practices and how these practices are involved in genetic markers, it seems not a bad idea to analyse that in terms of monitoring. Monitoring not only highlights the socio-technical investments of “looking” but also underlines that “looking” implies changing an object, that these changes have to be taken into account in a laboratory setting.

Let us now enter the Forensic Laboratory for DNA Research in Leiden (Lab F). There we will have an encounter with how markers are monitored in such a place.

Markers: Laboratory Practice

On Monday 18th March 1996 the rail connection between Amsterdam Central Station and Leiden Station was bad. That morning, the Amsterdam station was a scene of people running from one platform to the other while
trying to listen to the information coming through the speakers about their next possible connection. As a result of this chaos I arrived late on my first day in the laboratory. After having made my way through a labyrinth of corridors, I was surprised to be welcomed by a group that had learned about my delay by listening to the radio.

My trip to Leiden was not without preparation. I had asked Lab F for a short training course in some of the basic tasks of a technician. After introducing me to the lab members, the head appointed a daily supervisor for me, explained the project I was going to work on and promised that before the end of the day I would have done my first DNA extraction. Indeed, in the afternoon we were extracting DNA from blood. Before I knew it, blood spots that belonged to ten male chimps known as Fauzi, Carl, Yoran, Zorro and their mates had been changed into DNA samples marked as TNO-CH1, TNO-CH2, TNO-CH3, TNO-CH4 and so forth.

But hold on! Wasn’t DNA supposed to look white? I asked my supervisor. I explained that I had seen Kenneth Kidd (a population geneticist) on TV, demonstrating a white wool-like substance to the viewer. What we had was a clear solution instead. He told me that we work with small amounts of blood and could not extract that much DNA from them. But the tiny bits of DNA would be sufficient because we would be able to copy them, using the PCR machines. Ha, I said, Polymerase Chain Reaction, the Nobel Prize-winning cloning technology I had read about. And we both tried to recall the name of its inventor, Kary Mullis. We placed the rack with the labelled cups containing DNA in the refrigerator and left the so-called pre-lab.

The Second Day in the Lab

On my second day in the lab I had my first encounter with a genetic marker. We ran a PCR to test one of the human genetic marker on the chimps’ DNA, DYS 389 I-II. Even with the help of a protocol and a supervisor, “setting up” a PCR for the first time proved to be a complex procedure. It required using and distinguishing between three different pipettes, which look the same but pipette different volumes; distinguishing between the different chemicals; pipetting and mixing in the right order and adding different solutions to a specified volume of DNA. Undivided attention was crucial here, because you had to do this for various individuals simultaneously. With such small volumes, it was easy to make mistakes, such as forgetting to add a chemical to a sample, or adding a chemical twice. After having prepared the samples and being instructed about the storage of the different ingredients (DNA samples and various chemicals, also called
“reagents”), we moved from the pre-lab to the post-lab to load the samples into the PCR-machine.

While the PCR was running, my supervisor and I had a talk about what was happening to the DNA in there. He made some drawings to explain it. It became clear that the copying of DNA during PCR was a mimicking of nature. A prefabricated enzyme (a thermostable DNA polymerase), which was part of the solution, assisted this process. Due to a time-designated process of heating and cooling down (the so-called cycles), the double-stranded DNA is first straightened and pulled apart (the so-called denaturing of DNA) and then copied before it clings back together. The copies complement the single strands and are produced by using DNA building-blocks (nucleotides) and elongated by the polymerase, all added to the solution. Most important, not the whole DNA but only the marker fragment is copied. This is due to the so-called primers: short synthesised sequences matching the beginning and the end of the marker fragment. By attaching themselves to the target sequence they expedite the copying of that specific part of the sequence. In a way, the primers come in between the two pre-existing DNA strands and prevent their clings together. In the process of becoming a double strand, the primers force the single strand to use the DNA-building blocks and to produce a copy. Thus the single strand is forced to cling back using a copy instead of an existing single strand of the template DNA. The primers not only match the beginning and the end of the target fragment: they also mark this fragment. The primers are labelled with chemical groups (either radioactive, fluorescent, or biotin groups) which assist the visualisation of the marker fragment after PCR. Moreover, the process of copying is not linear but exponential; after one PCR cycle the double strands of such a fragment would be copied into four, after the next cycle, four would have become sixteen, sixteen turns into two hundred and fifty six, etc. Within less than two hours there might be a million copies. If the amplification works as expected, the marker fragment is available in prodigious amounts at the end of the PCR run.12

When the run was finished, I followed the instructions of my supervisor and loaded the PCR products (the copied template DNA) onto an agarose gel for electrophoresis.13 The agarose gel was placed in a bath containing a buffer (EDTA) and had a number of slots into which the PCR products had to be loaded. Before this is done the PCR products are taken up in a blue coloured solution (the loading mix), which renders visible to the naked eye how it “migrates” over the gel, once an electric current is applied. The gel itself plays a key role in the visualisation of the DNA fragments, which is not done with the naked eye but with the help of ultra violet rays. A chemical group (ethidium bromide) added to the solution before it sets in the form of gel is crucial to this process. Ethidium-bromide
binds to another additive in the PCR-product. This possibility was already provided during DNA extraction, a so called “chelex extraction.” When I asked my supervisor about chelex, he suggested to picture it like tiny pellets installing themselves in between the helix shaped DNA. The presence of these pellets in the PCR products allows for a chemical binding between chelex and the ethidium bromide in the gel substance, a bond through which the location of a DNA fragment, after electrophoresis, is revealed. The gel thus becomes part of the visualising technology.

When loading the gel, the first slot of the gel is usually reserved for the ladder. The ladder is a synthesised compound of DNA fragments whose sizes are known, such as 50bp, 100bp, 150bp and so on. Because the ladder starts to “migrate” together with the rest of the samples, it helps to determine the fragment length of those samples.

Once the samples had been loaded into the gel, the bath covered and the current set to 60V, the samples indeed started to move, leaving a faint blue trace behind. I was instructed to set the timer for twenty minutes. Consequently we had to wait that long to undertake the next step. I went out of the lab to have a short break. On my return I found that my supervisor had interrupted the run. He looked surprised and a bit embarrassed when I entered. He had been unable to wait the twenty minutes wanted to have a quick look at the results by exposing the gel to ultra-violet rays. At the same time he looked very excited and cried out: “They did it, it worked!” Since it was just my second day in the Laboratory, I did not altogether understand what he was trying to say. Was he trying to tell me that I had done a good pipetting job? A second technician had joined us and he started to point at the orange-coloured bands that had lit up under the ultra-violet rays. I slowly understood the nature of their excitement, and only a few days later did I understand the relevance of what we were looking at.

Before properly introducing the chimp case, let us have a brief look at the information contained in the previous sections. What did we learn about the monitoring of a marker and how is it enacted in laboratories?

**Monitoring Markers**

From the marker definition introduced above we have learned that markers are DNA fragments inherited by one individual from another and that these fragments can be monitored. The encounter with markers in Lab F illustrates the technological procedures involved in monitoring. There we learned that a marker involves not only the DNA fragment but also technical procedures crucial for its visualisation. Monitoring was seen to be a technical achievement through which the marker fragment was demarcated as
visualised. The fragment was defined as the target fragment by labelled primers. The primers together with other synthetic additives expedited the copying of that specific fragment and not other parts of the DNA. Hence to be able to monitor the fragment, the template DNA had to be made part of a technological system in which chemicals and gels, the marking of DNA and copying technologies, protocols and precise work are aligned.

Thus what can be monitored is that part of the DNA which has successfully become part of a technical network, facilitating its visualisation. In laboratories, therefore, a DNA fragment is never by itself: in order to be a marker, the fragment must successfully align itself with a number of technical procedures.¹⁶

Now why was the Forensic Laboratory developing an interest in chimpanzees, and why is it that one can find chimps in Lab F?

**Ten Chimps in the Laboratory**

Lab F had received blood samples from five different primates (ten male samples from each primate population) from The Biomedical Primate Research Centre: Dutch Primate Centre.¹⁷ This Primate Centre had asked Lab F to explore the possibility of developing genetic passports for primates. The passports would be supplied as chips and inserted into the primates’ bodies. In 1995 the Dutch government had announced its intention to “monitor” the international trade in primates and to restrict their import for scientific research as well as for zoos. The idea was to prohibit the import of primates into the Netherlands and to breed them as much as possible in the Primate Centre, especially primates that were meant for scientific research. It appeared to be common practice to mix up the identities of individual primates for financial or research reasons. Laboratories would claim to be experimenting with the same primate, when actually they would be experimenting with a second primate because the first had died. Identifying primates by their genes seemed to offer a solution to these problems. A “genetic passport” would also be of interest to the Primate Centre as a means of assessing the loyalty of their clients, i.e., to determine whether they would predominantly buy from the Centre or also from other primate suppliers in Europe.

Requesting Lab F in particular to conduct a pilot study is not that strange. As the name of the laboratory indicates, Lab F is a forensic laboratory and has therefore developed an expertise in identifying human individuals in forensic cases.¹⁸ Lab F supplies for the courts DNA evidence, based on DNA analysis, that confirms whether or not two genetic profiles of suspect and evidence material coincide. This individuality-producing
practice suggests that Lab F might be very appropriate to answer the question of the Primate Centre. If this lab can identify human individuals, might it not have the expertise to identify non-human individuals? This project was also of interest to Lab F for at least two reasons. If the answer to the question put by the Primate Centre proved to be positive, Lab F would have a fair chance of being asked to produce the genetic passports for all the primates at the Primate Centre. The second reason is connected to the Lab’s field of research. As noted above, the Primate Centre sent only male samples for this pilot study. This choice is not self-evident, given the goal of the Primate Centre, namely to develop genetic passports for all their primates, both male and female. Having just introduced a set of Y-chromosomal markers, Lab F had developed an interest in testing these markers for non-human primates. Since the markers are located on the Y-chromosome, a male-specific chromosome, the pilot did not aim at studying male and female primates equally, and was provisionally reduced to a male primates project.

To answer the question of the Primate Centre, namely whether it would be possible to identify individual primates on the basis of their genetic makeup, Lab F scheduled the typing of the chimpanzees first. The lab had practical reasons for doing this. It was not altogether clear whether these human genetic markers would work in primates under laboratory conditions. And since chimps are considered mankind’s next of kin, it made sense to start there, where the fewest genetic differences were to be expected.

Within the context of this pilot study, the Primate Centre’s question was whether the genetic material of Fouzi, Carl, and Zorro could indicate with certainty that Fouzi is neither Carl nor Zorro, and so on. Lab F set out to test this, using Y-chromosomal markers. In order to understand Lab F’s interest in these markers, let us take a closer look at the markers themselves.

Y-chromosomal Markers

In addition to forensic work, Lab F has also developed research projects in the field of population genetics. After attending a forensic meeting in Berlin in 1995, the head of the Lab established a joint project with another forensic lab in the former East Berlin. The laboratory in Berlin had a set of Y-chromosomal markers and was seeking joint projects with other (non-German) forensic labs to test these markers further and to evaluate their use for population studies and forensics. A set of seven markers had thus made the journey from Berlin to Leiden and was primarily being studied using the databases of these two labs. One of the results of the collaboration between Leiden and Berlin was a paper published in April 1996. Under the heading “Discussion” it stated:
We have demonstrated, for the first time, how sensitive PCR-based methods can be used to characterize highly informative haplotypes of Y-chromosomal microsatellite loci. With four out of seven microsatellites presented, samples of Y-chromosomes could readily be differentiated with respect to their Dutch or German origin on the basis of allele frequency alone [...], and as many as 77 haplotypes have been observed for these loci among the 159 males tested.23

By comparing males in Germany and the Netherlands, two neighbouring populations, and detecting variation between them, these scientists found a strong argument in favour of Y-chromosomal markers, also called microsatellites. According to the authors, Y-chromosomal markers are good genetic markers because they show differences between populations.24 Furthermore the paper also indicated that “the large within-population diversities noted for haplotypes of Y-chromosomal microsatellites will render them useful markers for forensic purposes.”25 Thus this set of Y-chromosomal markers allows studies to be made not only of the genetic differences between closely related populations but also of differences within these populations.

This paper was in preparation when the head of Lab F was invited to the conference Human Genome Variation Europe: DNA Markers. There he gave a talk about Y-chromosomal markers and made a similar argument presenting results based on a comparison between Dutch and Inuit (Eskimo) populations.26 Many geneticists showed an interest in these markers and a number of joint projects with other laboratories were initiated. The head of Lab F was also invited to contribute to a report about genetic markers based on the round-table discussion introduced earlier. In this report, which I will refer to as the “Marker Document,” the head contributed a section on Y-chromosomal markers.27 Furthermore two more papers were published in early 1997, co-written by 27 geneticists, reporting a large-scale study conducted in various laboratories, comparing Y-chromosomal markers for a large number of populations. Their use in the field of population genetics was recommended and conditions for forensic application were indicated.28

One could say that these Y-chromosomal markers have become good genetic markers. The markers meet the requirements of a number of geneticists since they can answer a variety of questions within different contexts. They have travelled from Berlin to Leiden, from Leiden to Barcelona, and have found their way into documents, papers, and various laboratories.29

Thus Lab F has developed good genetic markers. But what happens to their status if the Lab formulates a slightly different goal? What happens when the Lab decides not to type humans but chimpanzees - and were to show particular interest in the differences between individual chimps? Even
though the markers were co-developed and tested in Lab F, and although they have been shown to work in a variety of contexts, changing the goal implies that the markers would have to prove themselves anew, in the context of chimp DNA typing. The question - whether these markers are good genetic markers - again becomes important.

Typing Ten Chimps: How Far Can Y-Markers Go?

After we had tested the first Y-chromosomal marker, I had a talk with the head of the Lab about the results. He explained to me that the markers we were testing had never been tested before on chimpanzees, and that the alleles we had already found were thus far unknown.

Continuous experiments with these markers in chimps indicated indeed that none of the alleles we had found was of the same length as those found in human samples. We could conclude this now with more certainty because we ran another type of gel, an acryl-amide gel using the ALF™ sequencer. The Automated Laser Fluorescent sequencing machine detects the fluorescent-labelled DNA fragments (labelled by the primers) via a laser beam and gives more precise identification of the allele lengths. Also, unlike the visualisation on the agarose gel, the allele information is no longer physically visible, but is processed via a computer and displayed on the monitor as graphs, on which peaks representing the alleles can be depicted. It appeared that our interest in alleles was an interest in sequence lengths expressed by the distance between the primers. Our main objective was to compare the different allele lengths found in the different samples. Moreover visualisation of these alleles showed that they were not as “strong” as in humans (the bands were not as strong on agarose and the peaks were not as high on the ALF™). My supervisor explained that this could be due to differences between human and chimp DNA sequences. Additional experiments, the sequencing of the loci, confirmed this suggestion. Differences between the sequences resulted in a reduced alignment of the primers to the template DNA. Since the beginning and the ending of this region differed between humans and chimps, the primers that were designed on the basis of human DNA could not attach easily and hence did not show very “strong” bands. But although chimp DNA differed from that of humans, it was similar enough to be detected by the PCR-technology and to be visualised. This is not self-evident, and explains the exclamation uttered by my supervisor: “They did it. It worked!”
Monitoring Y-chromosomal Markers in Chimps

In previous sections I have suggested that a DNA fragment is never by itself a marker. The monitoring of markers involves a set of technological procedures to which the DNA fragment must align itself in order to become a marker. Let us see whether we can learn more from this part of the case about monitoring and therefore about markers.

Y-chromosomal markers worked for chimpanzees. It was possible to find and visualise the alleles in all individuals. Even though the visualisation of chimpanzee alleles indicated a reduced alignment (allele bands were not as “strong” as in humans), the technologies and methods were powerful or “universal” enough to type chimp DNA. Conversely, the chimp DNA fragments have successfully become part of the technological procedures and protocols. From this perspective we could say that all Y-chromosomal markers we tested in Lab F could be monitored in chimps. It was possible to visualise all alleles. Might these markers then be considered good genetic markers? What was the visualisation about? And what does monitoring aim to analyse?

The goal of the primate project was to identify individual primates by their genetic material. For this purpose, the laboratory sought to develop individualised data by tracing specific fragments of the DNA that in combination produce an individual genetic profile, the basis for a genetic passport. The central question was whether Y-chromosomal markers could do the job. Do individual chimps differ enough in these marker fragments to be identified? Could these markers be considered good genetic markers for typing chimps? The Y-chromosomal markers are not just any kind of marker: they are already part of the laboratory’s context and routines. Lab F has optimised their use in human populations, and studies of the markers for human forensic DNA typing were in progress. Furthermore the Lab as well as other geneticists have become enthusiastic about the potentials of this set of markers. Thus Lab F has become interested in how far these markers can go, how many different goals can be reached using them and whether they can be used for human and non-human profile typing equally. Let us see how the project continued and whether the goal of chimp individualisation could be attained.

Typing Ten Chimps: Are Y-chromosomal Markers Good Genetic Markers?

Once it appeared that the markers were working for chimps as well as for humans, the focus of the experiments started to shift. The goal of the Primate Centre now came to the fore. We were interested not only in what
the individual chimps looked like for these markers, but especially in how they differed from each other. This applied not only in visualising the alleles, but particularly in identifying the differences between the alleles. Since the difference between one allele and another is only a matter of length, our previous excitement started to wane. It became increasingly clear that for most markers the chimps have about the same allele. The high diversity, the so-called polymorphism, reported in human individuals seemed not to be present in chimps; they looked too much alike. Whereas four to seven different alleles could be detected in human populations, depending on which marker was typed, the chimps showed only two alleles per marker, which was not regarded as a significant variation.

One of the seven markers tested in chimps, DYS 393, showed four alleles and was therefore informative. A second marker, a curious one actually, was found interesting for another reason. Since most males have only one Y-chromosome, all marker fragments show one allele per individual. This is not the case for the DYS 389 marker. In both humans and chimps this specific marker shows two alleles per individual, one short and one long. This indicates that the primer set attaches at two different stretches of the DNA. Lab F has discovered that the primer set attached to both the marker fragment as a whole and to a smaller section in that same fragment. Lab F has developed a more specific primer set for this marker to identify each allele of the marker separately, indicated as: DYS 389 locus I and DYS 389 locus II. Beside this peculiar feature, the variation for this marker was also not high. Like most other markers it showed only two alleles per locus. But why was it informative? Why was it polymorphic? Another criterion for polymorphism is instructive here, namely the distribution of alleles among individuals. Unlike the other five markers for which the chimps also carried two alleles, DYS 389 had an equal distribution of its alleles among all chimps. To understand this, consider that a marker for which only one individual would have allele A, while the rest of the population would have allele B, is not as informative as a marker which shows allele A and B in a greater number of individuals. In the first case, the chance that two individuals would look alike for this marker is proportionally higher than in the second case. For this reason DYS 389 was found to be informative, despite the low frequency of alleles. Since this marker as a whole worked for chimps, and since it was found informative, we tried to type the alleles of each locus separately (DYS 389I and DYS 389II). This was, however, not an easy task. In fact the primer set did not work in chimps. After several attempts my supervisor explained that the chimp sequence may be quite different from that of humans, and that the primer set of the whole marker fragment may be strong enough to work for chimps, whereas primers designed for each locus separately would not
attach to the chimp DNA. Consequently, chimp-specific primers may have to be designed in the future to separate the alleles in each individual chimp.36

All together we had one marker that proved to be informative and ready to use in chimps. A second marker might become a candidate for future use, not because of a large number of alleles, but especially because of a more even spread of the alleles. All other Y-chromosomal markers were not informative for chimp DNA typing. But the identification of each chimp, i.e. producing a DNA profile based on an individual-specific combination of the alleles found for each marker, would require more genetic markers. What other markers would be appropriate to identify chimps?

Before addressing how the project developed and how the lab set out to answer the question about genetic passports, let us return to the monitoring of markers and consider how it affected the Y-chromosomal markers.

**Monitoring Variation in Chimps**

After the first excitement about the visualisation of the Y-chromosomal alleles, it became clear that visualisation was not the main aim of monitoring markers. Not the marker fragment as such was considered informative but, especially, its length. Having detected and determined the allele length, Lab F learned that they were all chimp-specific, i.e. not found in humans. This information could be an interesting means of differentiating between chimps and humans. But as we have seen, at least five of these markers were no longer considered for typing chimps. What does this mean in terms of monitoring? The lab and the Primate Centre wanted to learn about the possibility of differentiating each individual chimp, each individual macaque, or each individual baboon on the basis of its genetic makeup. This points to a more specific type of monitoring. Monitoring is a goal-directed activity, a purposeful visualisation. This indicates that a good genetic marker is also goal-invested. In our case it meant that it should work for all chimps equally and - most importantly - that it should show differences between individual chimps. Markers that bore these qualities were considered good genetic markers. One could say that markers that came with that specific message were considered good for monitoring.37 One of the markers (DYS 389), however, was considered a good genetic marker whereas five others were not. This was not because this marker suggested a higher variability, but because of the distribution of alleles; it was considered polymorphic, indicating that polymorphism as a quality of monitoring was not only about differences but also about similarities within a given group. An allele that can be found in only one member of a group does not contribute so much to
the criterion of polymorphism as an allele that can be found in – say – 50% of its members. Monitoring polymorphisms is monitoring ratios of difference and similarity within a specified group. As such it may contribute to the differentiation between individuals within this group.

Hence a good genetic marker should, at the same time, contribute to the analysis of what it reveals.\(^\text{38}\) It should produce a rate of similarity and difference according to criteria set for specific goals. From this we learn that monitoring is not only a technological achievement of a marker, i.e. a visualised DNA fragment; monitoring is also a methodological achievement, i.e. invested in terms of goals and criteria set forth in a specific practice.\(^\text{39}\) Only those markers that could be visualised and that met the criteria for similarities and differences were considered good genetic markers and could thus be monitored.

Taking this type of monitoring into account, how can we understand the question of the Lab regarding the general applicability of Y-chromosomal markers? We can conclude that Lab F has learned that these markers can be monitored in chimps as well as in humans for other purposes. The markers would enable Lab F to differentiate between humans and chimps, since the alleles in these species do not match. At the same time it became clear to the Lab that most of these markers could not answer other questions, such as the question of chimp identification. Most markers changed a difference-producing practice in humans into a similarity-producing practice in chimps, and therefore could not contribute to the production of chimp DNA profiles. Hence there are limitations to the applicability of these markers depending on the goals in question.\(^\text{40}\) Furthermore the experiments with DYS 389 indicate another feature of markers. Changing the primer set to separate the alleles in that locus was not successful in chimps. This result emphasises the technological components of markers. Whereas the first set of primers was powerful enough to type the chimp alleles, the second, more specific primer set no longer worked. It was not the chimps’ DNA that changed, but the technology to copy and visualise that fragment. This indicates that the success of technical procedures that assist the visualisation of a marker fragment is not self-evident. To know that a marker fragment can be monitored does not necessarily imply that it can be visualised under any kind of condition or in any kind of practice.

Since five out of seven markers were not found informative for chimp profile typing, because they did not show a significant variation, and since this feature of genetic markers was found particularly interesting, Lab F decided to look for other genetic markers.
Bring in Other Markers

Instead of testing other markers from the lab, my supervisor decided to select markers that have proved to be variable in chimps in other laboratory practices. He gave me a copy of a paper and asked me to have a look at it. It presented a large-scale study comparing human and non-human primates for 42 markers. The next day we went through the paper and he explained which markers would be interesting for the primate project. Provisionally he suggested three: FRAXA, DRPLA, SCAI, markers of so-called disease genes. These markers were promising because they showed variation in humans and chimps as well as in gorillas, baboons, macaques, rhesus monkeys, orang-utangs, and marmosets. Since our study was only a pilot study and given the fact that the same procedure would also have to be followed for other primates, choosing these markers would save a great deal of work in the future.

The paper gave some further information about the markers, namely the primer sequences and indications for the PCR programs. The suggested primer sequences had to be ordered from a pharmaceutical company. The ordering, a very precise procedure, is usually done via electronic mail. Typing into the computer the exact sequence order of the nucleotides of the primers involves checking and double-checking the sequences. We ordered the primers and awaited them eagerly. When they arrived we started typing the chimps based on the PCR conditions indicated in the paper. None of the markers worked! I could have made a pipetting or another mistake, so we tried again, but without any success. Again no alleles. The markers worked neither for chimp nor for human DNA. After having tried different samples it became clear that we had to change the “PCR conditions”, which consist of a number of variables: first the primers, but these we could not change since they were the most crucial piece of information in the paper; then the enzyme and the nucleotides, but they were standardised, supplied by a pharmaceutical company, and they had worked well, as we learned from other lab members who had also used them; next, “the salt solution” or the so-called buffer should preferably not be changed since there were too many variables in the solution itself. So the PCR programme was the only possibility left. My supervisor started rewriting the programmes based on the primer sequences.

A long period of trial and error started. The markers came to be labelled “the experimental primers” during laboratory discussions. At a certain point programmes for DRPLA and SCAI started to work - for humans, that is. Why not for chimpanzees then? Maybe the DNA we had extracted a month earlier had already started to deteriorate. It was suggested that we should test this possibility with a mitochondrial DNA marker. Mitochondria have a large number of small, circular DNA
molecules and their alleles are much easier to detect. The mitochondrial marker showed very strong alleles. So it was not the quality of the DNA. Again new PCR-programmes were suggested. I asked my supervisor: “Since the programmes worked for humans, why not keep them and change the salt solution instead?” Again he objected because he wanted to keep that standardised. 

At the next lab meeting we reported on the problems we had encountered. One lab member suggested contacting the authors of the paper and asking them about their experiences: “They might have other lab conditions.” A discussion about lab conditions ensued. Another lab member, who was also working in a diagnostic lab, reported that they used different salt solutions for different markers (whereas our lab had a standard salt solution) and that they used standard PCR programmes (whereas we had marker-specific PCR programmes). During the meeting I asked about this difference. Laboratory practice was the key here. In a diagnostic lab, samples of individuals are kept strictly separate. Individuals are usually screened for a number of markers, and experiments are conducted on one individual at a time. The most efficient way to do this would be to run one PCR for all the markers at the same time. The variable in this kind of lab would be the salt solution. Our lab studied individuals and populations and compared these for one marker at a time. So an efficient PCR-run consists of as many samples as possible from different individuals to be typed for one marker. Therefore the lab has different PCR programmes for different markers. After this discussion I understood the lab’s general motivation and I stopped asking questions about salt solutions.

More PCR programmes were designed and tested. Making the markers work became an obsession. One lab member suggested that we conduct a search on the Genome Data Base (GDB) and look for other markers with more marker information. This was no option. They had been shown to work in the scientific paper so they should work here as well, we reasoned. After a while we started to have some results in DRPLA and SCAI, and as expected they proved to be variable for the chimps: six alleles were found for DRPLA and five for SCAI. For the third marker, FRAXA, my supervisor contacted colleagues at the neighbouring diagnostic lab, who had a great deal of experience with this marker. But it turned out that their primer sets were labelled by radioactive groups, whereas we were working with fluorescent groups. Consequently it did not make sense to use their protocols. Yet another lab in the Netherlands was contacted and they sent us different PCR programmes, but nevertheless advised us to drop this marker because it was too hard to type. It appeared that the problems we had with this marker were due to the sequence of the marker fragment. The intricacies of the fragment prohibited its amplification. Specific nucleotide repeats in
the sequence caused the fragment to fold in complex ways which made it difficult for the standardised PCR technologies and chemicals to copy the fragment. Their protocols suggested a special type of nucleotide to expedite the amplification. With some modifications in the PCR programme suggested and the addition of these special nucleotides, we started to have results with this marker. Finally we were also able to detect four alleles in the chimps.

Altogether we then had a set of five and perhaps six markers that were ready to use for chimp profile typing and to be tested on the rest of the primates. This set proved workable for chimps and it met the criteria for profile typing because it showed a considerable variability in each marker fragment.

In the meantime the highly organised lab, with clear-cut procedures and protocols, had changed dramatically. PCR machines as well as the ALF sequencer would be overbooked, colleagues would wish us good luck with breeding chimps, others received presents of the (unknown) trademark Monkey Jewellery Inc., and the previously well-organised and well-marked set of PCR programmes would include programmes such as: Sky (SCAI), Touch down (SCAI), amade1 (DRPLA) and Hot PCR (FRAXA).

Monitoring: Good Genetic Markers

Typing Y-chromosomal markers in chimps revealed monitoring problems for most of these markers. Although they were known as good genetic markers for human DNA typing, they did not meet the criteria of similarity and difference in chimps. To get round this problem, Lab F had chosen other markers. The Lab decided to look for markers that were guaranteed to be polymorphic in chimps and hence could contribute to their profile typing. The set of markers chosen could thus be termed good. But once introduced into Lab F, the markers faced other problems. The experiments that followed made clear that markers are more than just a DNA fragment or a variability found by comparing different individuals for that fragment. A good genetic marker is not dependent on the DNA fragment only. These experiments showed that the technical constituents of markers were not self-evident, “universal,” or problem-free. This feature had not become apparent in the Y-chromosomal markers because they were already operative in Lab F.

The newly introduced markers and the technologies and practices they embodied proved to have decisive consequences for their monitoring in the Lab. Taking this into account, it could be said that what makes a marker a marker, i.e. a DNA fragment that can be monitored, could just as well be a PCR programme, a salt solution (a buffer), a radioactive labelled primer, a fluorescent labelled primer, a complexity in the DNA fragment or a specific type of synthesised nucleotide in the reagent.
Whereas the problems with Y-chromosomal markers occurred on the DNA level, namely the absence of polymorphisms in chimps, the problems of the new markers could be located on the socio-technical level, namely in the practicalities of laboratory work and how these are embodied in markers. Consequently what makes a marker a good genetic marker is dependent on its eventual applicability in a variety of contexts. Monitoring these markers in Lab F could only be done by establishing alignments and links between the technicalities of these markers and Lab F’s practice. As has been shown, Lab F appeared to be more flexible in changing its PCR programmes and was reluctant to change the buffer (the salt solution). It became clear that markers might serve broader goals and become good genetic markers but to succeed in this they had to establish their qualities in a variety of contexts. This feature might be termed an “achievement” of markers which augments their practicability in various contexts.

Good genetic markers for typing chimps involved both the DNA and the successful enactment of a socio-technical practice. Hence criteria for similarities and differences should not be sought in the DNA only, but also in the practicalities that contribute to the monitoring of markers.

The chimp case made it clear that markers are “hybrids.” They are objects of study, methods and technologies to know that object, as well as the signs or visualisation of them. It was argued that a good genetic marker for one specific job or in a specific context may well lose its usefulness when transported to another practice or when the goal of the experiment changes. This might lead to the conclusion that since there are various ways of “knowing” DNA and genetic variation, and since different practices produce different knowledge, there is no privileged view in genetics. Should this lead to the claim that markers work and may become good genetic markers in isolated practices? Practices are never merely local. In fact the round-table discussion introduced at the beginning of this chapter illustrates the organised character of scientific work and of the traffic in markers. Let us consider the remarks quoted at the beginning once more, and see how the local and the global are negotiated and how this may affect knowledge assisted by genetic markers.53

A Roundtable Discussion

- “A list of markers should be made, as an indication to newcomers in the field and in order to compare the different data.”

This remark indicates that geneticists do not work alone but within a field. Even more, it indicates a need to exhibit the collective nature of scientific work, especially to newcomers, via a list of markers. Comparison of data and
genetic markers that might facilitate this are, like the geneticists themselves, crucial to the field and contribute to its existence.

- "We need to have some consent about the markers so as to compare the results."

Emphasising consent about which markers should be on the list suggests that knowledge, although a product of local practices, becomes meaningful only within communities. This indicates that local scientific practices are informed by criteria that transcend local contexts. Since the comparison of data is not self-evident, comparability should be built in at an early stage of experiments. This quality is delegated to markers. Hence the "global" aim of scientists, namely that of working together, is to be implemented in local practices to produce this possibility beforehand. A list of markers should do the job. But what about content? Does not a list of markers predefine what type of knowledge will gain pride of place? From the chimp case it became clear that markers are actively involved in what can be known about how individuals and populations relate to each other. For some markers chimp TNO-1 might as well have been chimp TNO-2 whereas for other markers they were distinguishable. Let us focus on the criteria suggested for markers and view their impact on the content of knowledge.

- "Preferably markers that do not require the use of radioactivity."

Choosing certain markers and not others for safety reasons, such as not using radioactive labelled primers, has an impact on the type of knowledge that is possible. Again the chimp case is instructive. Lab F could not learn from the practice of a neighbouring lab because they used radioactively labelled primers. So neither comparability of data nor safety measures is external to knowledge. They too determine which technologies become most favoured in learning about genetic lineage.

- "Criteria for markers should be that they show variation between populations."

This is an important criterion for population geneticists working on human variation. Such geneticists are interested not only in similarities of populations but also and especially in the differences between them. Something that easily escapes the eye, however, is how markers work together to produce similarities and differences. To make this point clear let us take the example of the differences between Dutch and German males, addressed in the paper discussed in the chimp case. The authors of the paper argued strongly in favour of Y-chromosomal markers since these markers allowed them to distinguish between Dutch and German males. The results were produced by combining marker information (alleles). These differences, however, were not based on combinations of alleles that belonged to actual individuals but on combinations of alleles, also called "haplotypes," belonging to actual and virtual individuals. Testing more
markers at the same time allowed these geneticists to produce "genetic profiles" (haplotypes) of more "individuals." Hence, in studies of similarities and differences, comparisons become more powerful when markers "work together" since it becomes feasible to compare more than the sampled individuals. In a way, markers are like scientists: they work best and produce more together. Thus knowledge about genetic variation and diversity is not only framed via the choice of markers but also via the arrangement of marker information.

• "We need markers that are selectively neutral to different population structures."

The suggestion made here is that markers should work for all populations in the same way and that they should provide information without respect to the populations studied. The problem raised is that within-population structures may be "reflected" in the markers studied. Hence marker fragments may be selected for and may not inherit at random. Comparing populations is then problematic because it is no longer clear what is being compared. However difficult it is for geneticists to know beforehand what they are comparing, in studies of diversity it is important to presuppose that marker fragments are inherited independently (without social or biological constraints) within a given population. This presupposition is called random mating. The markers suggested here presuppose random mating for particular DNA fragments in all populations studied. These criteria would turn those markers into "universal" markers.

• "What we need right now is a list of priority markers."

Prioritising some markers emphasises the variety in local practices and the need to attune these practices in order to work together and to reach certain goals. At the same time a list of priority markers indicates that there are tensions involved in doing so.

• "What is the use of such a list if people aren't working with it anyway?"

Whose markers will be on that list is crucial. As discussed above, a list will not only have consequences for the type of knowledge, i.e. the kinds of genetic diversity being produced, but also for the type of practice transported from one lab to the other. What if a lab is working successfully with radioactively labelled primers?

• "One could recommend things now, but it would be preferable to choose for a democratic procedure, such as people reacting from their own experience of research."

Markers involve practices and technologies and mobilise these when travelling from one lab to another. The comment quoted acknowledges this, and recognises the difficulties involved in changing existing practices. Some practices are more flexible than others, and introducing new markers may
mean changing laboratory work. But to take the experience of research into account indicates that both local and global aims should be negotiated in the list of markers itself.

- "What are good genetic markers?"

The round-table discussion shows that it is not easy for a genetic marker to go unnoticed under the umbrella of a priority list. *Good* genetic markers appear to be products of collaboration and comparison of data, of technical investments and safety measures, of practices and compatibility between different practices, but also products of decisions about which part of the DNA is to be studied and how many different parts of that DNA are to be studied and combined. All these criteria and qualities show that markers are neither merely local nor entirely global.

**To Conclude**

Genetic lineage and diversity are dependent on markers. The concern of this chapter was to investigate what a genetic marker is. In this investigation, the definition of a marker pointed in the direction of the DNA. Laboratory practice, however, suggested other sites for learning about markers. We learned that markers are enacted as a variety of things, such as protocols, PCR programmes, chemical solutions, and that aligning these turns a marker into a good genetic marker. A marker can thus be termed a socio-technical network, in which humans, technical devices, chemicals, DNA and procedures to handle it are linked in a specific way to produce it. Consequently enacting markers in a new context is dependent on the kind of world that *can* be introduced to a laboratory and the kind of alignments that *can* be established there.

This has implications for studies of diversity and lineage. This very quality of markers not only puts constraints on what *can* be standardised and how but also on our ways of learning about genetic diversity. Various technologies may be at hand in the field of genetics to do this, but making things work in a variety of practices equally evokes questions about which technologies will have pride of place in learning about diversity and lineage. It could be said that rather than a universal tool, a *good* genetic marker is a highly invested category in which genetic diversity resides.
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Notes to Chapter 3

1. For a similar narrative strategy, analysis and style, see Annemarie Mol and John Law, “Regions, Networks and Fluids: Anaemia and Social Topology,” *Social Studies of Science* 24 (1994): 641-71. Note that whereas Mol and Law’s elegant analysis contributes both to social theory and to an understanding of anaemia, the main objective of the case studied here is an analysis of a routine-like technology in laboratory practice.

2. These as well as other contributions to the discussion were elaborated in a document that should function as a guideline on the choice of markers, see Jaume Bertranpetit, “Recommendations on the Use of Genetic Markers in Human Genome Variation Studies” (Working document, 1996). This document will be referred to as the “Marker Document.” In the end the Marker Document was not issued but circulated, via e-mail correspondence, among a number of geneticists who contributed to the document and commented on it. Bertranpetit, the editor of the document, presented the results, in a way a list of priority markers, at a meeting of the *European Human Genome Diversity Project: Regional Committee*, which took place on 25th January 1996 in London. My references to this document are based on the copy that was distributed by Bertanpetit via e-mail on 3rd February 1996.

3. In the Book of Abstracts of this conference, under the heading “Presentation”, Bertranpetit states: “In the program, a large amount of time
has been reserved for discussion as consensus will be sought on the technical advantages and informativeness of the various marker technologies. It is our aim that presentations and discussion will mainly focus on DNA markers” (Book of Abstracts Euroconference Human Genome Variation in Europe: DNA Markers [Barcelona, 9-10 November 1995]), p. 1.

4. During The International Planning Workshop held in September 1993 in Porto Conte, Sardinia, the fine-tuning was on the side of population, such as the sampling procedures (criteria for sampling, how many individuals per population and how to inform the individuals about the goals of the scientists) and which populations should be studied first. The endeavour then was to produce a “priority list” for the populations, see The Human Genome Diversity (HGD) Project: Summary Document (HUGO Publication, 1993), pp. 12-33. The issue of population and the sample strategy of the Diversity Project was topic of a previously held workshop in October 1992 at Pennsylvania State University. Furthermore, in the Marker Document it is argued that: “Other crucial issues in genome variation analysis are not considered here, comprising the choice of populations, sampling strategy, availability of samples through central repositories (of DNA but plasma may be useful), fingerprinting of reference specimens, data bank results, numerical analysis of results and many others”, Bertranpetit, Marker Document (above, n. 2), p. 2.


6. In molecular biology, a “DNA marker” was originally a synthesised DNA fragment of known size, through which the molecular weight of target fragments could be determined,” see Daniel L. Hartl, Essential Genetics (Sudbury: Jones and Bartlett Publishers, 1995), p.379.

7. The complete human genome, coding and non-coding DNA, consists of 3, 500 million base-pairs and the percentage of coding DNA may differ depending on which literature is considered. The figure of 5% is based on, Daniel J. Kevles, “Out of eugenics: The Historical politics of the human genome,” in Kevles and Hood, Code of Codes (above, n. 5), pp. 3-36, at p. 24.

8. The significance of this difference can be seen in the criticism voiced about the (physical) mapping of the human genome. The critiques considered it too time-consuming and costly and not informative as such; the so-called large-scale sequencing without a directed interest in specific genes was seen
as a waste of effort. See for example, Daniel J. Kevles and Leroy Hood, “Reflection,” in Kevles and Hood, *Code of Codes* (above, n. 5), pp. 300-328, at pp. 300-301.


I apply the notion of performativity to make clear that “objects” do not exist in isolation, but are dependent on humans, materials and techniques. What these objects are made to be, which version of them is being performed, is thus dependent on practices. Moreover, this suggests that objects are not stable as such, and that their “existence” is dependent on the successful work of humans and non-humans, see also chapter 5 for references and an elaboration.

10. It seems that linguistic metaphors are privileged over visual metaphors in genetic work. The language metaphor produces, as it were, a “natural” fit between the accomplishment of the various actors in the lab. Lab members, technology as well as DNA, appear to be literate, capable of reading and writing. On the linguistic metaphor in genetics, see Evelyn Fox Keller, “Sense and Syntax: Metaphors of reading in the history of genetics” (paper presented at the ASCA conference *Come to Your Senses*, Amsterdam, 25-29 May 1998), Evelyn Fox Keller, *Refiguring Life: Metaphors of Twentieth-Century Biology* (New York: Colombia University Press, 1995); see also Lily Kay, “Ascent of the informational Gene” (paper presented at the conference *Postgenomics? Historical, Techno-Epistemic, and Cultural Aspects of Genetics*, Max Planck Institute for the History of Science, Berlin, July 1998). See on the limits of the linguistic and visual metaphor in genetics, Amâde M’charek, “Reply to Evelyn Fox Keller and Kaja Silverman” (paper presented the ASCA conference *Come to Your Senses*, Amsterdam, 25-29 May 1998).

11. Trying to find out a little more about where the idea of monitor comes from, I came across some amazing, yet familiar stories. First of all, there is the “Monitorial System”, also called the *Lancaster System*, after its initiator. Introduced in the nineteenth century, this British educational system was based on the tutoring of younger or weaker pupils by older and better scholars. Secondly, a monitor turned out to be a special class of lizard, the *varanus*. Represented by thirty species, some of them up to three metres they are long, fork-tongued and gluttonous, with a long neck and heavy scales. A monitor is also a special kind of warship, specially designed for the
American Navy with many technical novelties, good for 40 basic patents. Operative at the end of the nineteenth and the beginning of the twentieth century, the monitor was a heavily armoured ship with shallow draught, thus able to sail in shallow waters and rivers where large vessels could not enter. Since it also had a low free-board, the monitor was difficult for other ships to hit. But the monitor's heavy and far-reaching cannons, positioned on a rotating tower, could easily damage large ships at a distance (Encyclopedia Britannica, 1987, 258-9). This brief history shows that monitoring, just like other technologies of vision, is historically charged and technologically invested. Hence the technologies of vision cannot be considered innocent or unproblematic. Rather than looking for another metaphor or category of analysis, I have chosen to examine the category of monitoring and explore it for the purpose of my argument. My interest in monitoring comes close to Haraway's theorisation of what she calls "the metaphor of vision." She argues that: "the visual metaphor allows one to go beyond fixed appearances, which are only the end products. The metaphor invites us to investigate the varied apparatuses of visual production, including the prosthetic technologies interfaced with our biological eyes and brains" (Donna J. Haraway, "Situated Knowledges: The Science Question in Feminism and the Privilege of Partial Perspective," in Simians, Cyborgs, and Women: The Reinvention of Nature, Donna J. Haraway [London: Free Association Books, 1991], 183-201), at p. 195.


13. In the laboratory this is the first and most practical method of visualising the DNA fragment; it takes less time than the ALF sequencer and is less expensive. The detection of alleles via the ALF sequencer is also based on electrophoresis; instead of ultraviolet it requires laser light for visualisation. Thanks to the computerised approach, the ALF sequencer produces not only raw but also processed data. One could say that with this feature the ALF™ fuses what Amann and Knorr Cetina have "identified" as "data" and "evidence", which are defined by the different practices they involve; the ALF sequencer produces both data and evidence simultaneously; see Klaus Amann and Karin Knorr Cetina, "The Fixation of (Visual) Evidence," in Representation in Scientific Practice, ed. Steve Woolgar and Michael Lynch (Cambridge, Massachusetts: The MIT Press, 1990), 85-121.

14. These ladders, also called sizers, serve as molecular weight "markers"; see Hartl, Essential Genetics (above, n. 6), p. 379.

15. See Amann and Knorr Cetina for an elaboration on gatherings of laboratory members around visual objects, depicting what is visualised in the process of talking about this. Emphasising the interconnectedness between
the laboratory talk and the (visual) object of research. Amann and Knorr-Cetina refer to “the talk” as “the machinery of seeing”, Amann and Knorr-Cetina, “The Fixation of (Visual) Evidence” (above, n. 13), p. 92.

16. Analogously, Annemarie Mol argues that the “thickening of the intima” in cases of “atherosclerosis is not all alone” either, but is dependent on visualisations, chemicals and tools added to the tissue to be analysed as well as the skilled eye of a technician; see Annemarie Mol, “Pathology and the Clinic: An Ethnography of two Atheroscleroses,” in Intersections: Living and Working with the New Medical Technologies, ed. M. Lock and Alberto Cambrsio (Cambridge: Cambridge University Press, 2000). Also Hans-Jörg Rheinberger argues that the tools of molecular biology are involved in the object of research, so that they become macromolecules themselves: “Die Scheren und die Nadeln, mit denen Gene geschnitten und gespleißt werden und die Träger, mit denen man sie transportiert, sind selbst Makromoleküle” (Hans-Jörg. Rheinberger, “Von der Zelle zum Gen: Repräsentationen der Molekularbiologie,” in Räume des Wissens: Repräsentation, Codierung, Spur, ed. H-J. Rheinberger, M. Hagner, and B. Währig-Schmidt [Berlin: Akademie Verlag, 1997], 265-279), p. 275. My use of alignment is akin to that of Joan Fujimura’s. Whereas Fujimura takes the broader context of laboratory work and social interactions into account, I focus more on technologies and their practicalities in this context, see Joan H. Fujimura, “Constructing ‘Do-able’ Problems in Cancer Research: Articulating Alignment,” Social Studies of Science 17 (1987): 257-93.

17. This is the former TNO-Dutch Primate Centre. TNO is the Dutch Organisation for Applied Scientific Research (Nederlandse Organisatie voor Toegepast-Natuurwetenschappelijk Onderzoek). In the mid-1990s the Primate Centre became a semi-private organisation aiming at becoming the world’s largest primate centre. This endeavour may guarantee considerable financing from the Dutch government.

18. Furthermore the head of the Lab used to hold a position in the Leiden TNO, where he conducted and guided research into heart disease.

19. The Y-chromosome is one of the so-called sex chromosomes which are normally inherited by men only. Daniel Hartl defines Polymorphism as follows: “The presence in a population of two or more relatively common forms of a gene, chromosome, or genetically determined trait” (Hartl, Essential Genetics [above, n. 6], p. 445; emphasis added).

20. In June that year, when we had a meeting with the chairman of the primate centre, he seemed to be somewhat disappointed that we had started with the chimps. He would have liked us to start with the macaques instead, for they are the most frequently used in laboratory research and thus the most interesting object of trade.
21. This is the "Institut für Gerichtliche Medizin" at the Humboldt University, Berlin.
22. The Y-chromosome was insufficiently studied by population geneticists, but interest in this chromosome has been growing. In the small amount of publications during the early 1990s it was argued that the Y-chromosome did not show considerable polymorphism (genetic variation). It was only towards the middle of that decade that some work provided evidence for polymorphisms on the Y-chromosome. At the 1995 conference *Human Genome Variation in Europe: DNA Markers* in Barcelona, a group of young population geneticists (Mark Jobling, Peter de Knijff, Chris Tyler-Smith and Antti Sajantila) working on Y-chromosome variation, was highly appreciated for its "pioneer work" on the Y-chromosome. They all participated in the panel for the conference's round table discussion and were all invited to participate as co-writers of the report about genetic markers, Bertranpetit, "Marker Document" (above, n. 2).
23. L. Roewer et al., "Analysis of Molecular Variance (AMOVA) of Y-chromosome-specific microsatellites in two closely related human populations," *Human Molecular Genetics* 5, no. April 19 (1996): 1029-1033, at p. 1031. An allele should here be understood as a term expressing different sequence lengths, found for one marker in different individuals and measured by the distance between the primers. See also footnote 31. A Microsatellite is an alternative name for short tandem repeats in a marker region. For example the nucleotide sequence ACTACTACT would be a tandem repeat consisting of three nucleotides ACT. The tandem may vary between two and five nucleotides, see W.S. Watkins, M. Bamshad, and L. B. Jorde M., "Population Genetics of Trinucleotide Repeat Polymorphisms," *Human Molecular Genetics* 4, no. June 2 (1995): 1485-1491.
24. See chapter 2 for an elaboration of the interdependence of markers and population.
25. Roewer et al. "Analysis of Molecular Variance" (above, n. 23), p. 1032. Haplotype, as referred to in this paper, are conceptual genetic profiles (a combination of alleles of different loci for one individual) used as a statistically informative measure to compare population similarities and differences.
27. Section 8 of "The Marker Document" addresses Y-chromosomal markers based on a collaboration between P. de Knijff (Leiden) and M. Jobling (Lancaster), see Bertranpetit, "Marker Document" (above, n. 2).


30. Reading the information produced on the ALF™ does definitely require training. An unskilled viewer may see a broad range of peaks in complex graphs, where a trained eye would locate the actual allele-peaks within a couple of seconds. Also, the ALF™ comes with a software program, the ALF manager, which allows practitioners to determine the allele length and to “polish” the graphic representations by homing in on the target peaks and amplifying them on monitor and printouts. In accord with Michael Lynch’s treatment of scientific visual object (specifically of photographic images and diagrams), one could term this conduct an “upgrading” of the visual object genetic marker; Michael Lynch, “The External Retina: Selection and Mathematisation in the Visual Documentation of Objects in the Life Sciences,” in Lynch and Woolgar, *Representation in Scientific Practice* (above, n. 29), pp. 161ff. For an elaboration on how the visualisation of genetic markers assisted by the ALF can be understood in terms of Michael Lynch’s analyses of the photo-diagram pairs, see Amâde M’charek, “Mediation” (above, n. 10).

31. Hence for Lab F the difference between the one allele and the other is a difference in length. But an allele may mean different things in different contexts. For evolutionary studies an allele may refer to the sequence proper, and differences between alleles may be categorised according to differences in nucleotides, e.g. by mutations in the sequence. Hence not the length but the sequence order is relevant here. In disease studies the genetic code, namely the triplet of nucleotides coding for an amino acid or a protein, is
more relevant in determining alleles. From this perspective, the difference between one allele and the other may be a difference in triplets that code for the same acid or protein, e.g. both GAA and GAG code for the amino acid Glutamine. Furthermore, a frequently used definition of an allele states the following: “One of several alternative forms of a gene occupying a given locus on the chromosome. A single allele for each locus is inherited separately from each parent, so every individual has two alleles for each gene” (Kevles and Hood, “Glossary” [above, n.5], p. 375). Note that this definition contains a bias. First of all, alleles on the Y-chromosome are inherited from the father only, so the individual does not have two. Secondly, there is a bias for coding DNA in this definition: the definition refers to genes, so the largest amount of DNA, the so-called “junk DNA,” is not included here. Thirdly, there is a bias for nuclear DNA: chromosomal DNA is exclusively nuclear DNA. Mitochondrial DNA which is outside the nucleus, on the mitochondria, is excluded.


33. The Forensic Laboratory is in the process of having more and more of these Y-chromosomal markers accredited by the Dutch Board of Accreditation. This will allow the Lab to apply these markers for all forensic DNA cases.

34. Since males usually have only one Y-chromosome, it is strange to find two alleles for a marker in an individual. For this marker it appears that the primer set (the synthesised sequence indicating the beginning and the end of the marker fragment) matches two loci on this chromosome, and therefore shows two alleles per individual.

35. This is because profile typing is based on a rate of difference rather than on absolute differences, also called matching likelihood estimations. Combined with statistical analysis a rate of difference will allow the lab to identify individual chimps, see chapter 2 for the individualisation of genetic profiles and matching likelihood estimates.

36. Provisionally, for the purpose of sequencing, we diluted the two allele fragments from the agarose gel. After electrophoresis, the specific allele fragments are “physically” locatable on different parts of the gel, and by cutting the gel into pieces we could retrieve the fragments separately for further experiments.

37. It is interesting to note that are there are two categories of markers, referred to as mini- and micro-satellites, emphasising the transmission of information involved. The types of markers discussed in this chapter are also called micro-satellites.
38. This is comparable to Lynch’s argument about diagrams. Diagrams not only represent what can be seen but also what can be claimed about a biochemical structure; Lynch, “The External Retina” (above, n. 30), pp.163-168.


40. Also Roewer et al. indicate that these markers may work for certain forensic tasks but not for others, Roewer et al. “Analysis of Molecular Variance” (above, n. 23), p.1032. Even though the variation found in humans is high, it was not possible to identify all individuals studied on the basis of these markers only. Thus markers lose their usefulness when the set goals change.


42. Disease genes are studied extensively because they are correlated to a specific disease. The abbreviations stand for the diseases they are associated with. FRAXA stands for a type of the fragile X syndrome, SCAI is associated with the spino-cerebellar ataxia type 1 and DRPLA stands for dentatorubral-pallidoluysian atrophy; see Watkins et al., “Population Genetics” (above, n. 23), p. 1485.

43. The paper indicated only the so-called annealing temperature. On this basis the PCR programmes could be deduced. The PCR programmes are based on different numbers of cycles expressed in time and temperature of denaturing and annealing. Primers attach at different temperatures to the DNA fragment according to their sequences. These annealing temperatures have to be optimal for an adequate copying of the DNA. “Denaturing” of the DNA means that the double-stranded and helix-shaped DNA is pulled apart into two single straight strands. This optimises the possibility for the primers to attach at the beginning and the end of the target sequence and thus the copying of the DNA. “Annealing” is the movement of two single strands of DNA to form one double-stranded DNA. Just before doing so the primers attach to the single strands, preventing them from clinging to one another and forcing the single strands (or better the enzyme polymerase) to use the “free floating” nucleotides in the solution in order to become a double strand again.
44. This indicates that genetic markers cannot entirely be understood as immutable mobiles, as I suggested earlier (above, n. 29); once moved to another context they prove to be mutable. See also Mol and Law, “Regions, Networks, and Fluids” (above, n. 1).

45. With Jordan and Lynch, one could term this a kind of “practical conservatism.” If things have proved to work in previous experiments, laboratory members tend to be “superstitious” about changing their mode of working; how the number of variables work together cannot be understood in rational ways only: Jordan and Lynch, “The Sociology of a Genetic Engineering Technique” (above, n. 9), pp. 93-4.

46. In chapter 2 I have shown that Lab F cannot “know” an individual without a concept of population. Thus individual genetic makeup and that of a population are mutually dependent.

47. Although the forensic work of Lab F can be categorised as routine work rather than fundamental science, the experiments I describe here echo Karin Knorr Cetina’s claim that laboratory action is about making things work; see Karin Knorr-Cetina, The Manufacture of Knowledge: An Essay on the Constructivist and Contextual Nature of Science (Oxford, New York: Pergamon Press, 1981). Moreover the argument that the markers introduced to Lab F should work since they have been shown to work in another and a presumably similar context, underlines that scientific work may rely on a variety of previous practices, as long as a kind of similarity can be presupposed between these practices, even at the risk of failure and the loss of time and resources, Ibid. at 57-63. For a variety of stories about making a routine-like technology work - such as the plasmid prep (a cloning technology), see Jordan and Lynch, “The Sociology of a Genetic Engineering Technique” (above, n. 9).

48. The so-called secondary structure of the DNA makes it difficult for the fragment to denature. Therefore the whole PCR procedure was inhibited, the marker fragment could not be copied and consequently it was not possible to detect the alleles.

49. FRAXA contains a CGG repeat. The nucleotides C and G also complement each other in the fragment, producing between the two strands the base-pair C-G. The large number of C-G bonds in this fragment introduces so-called secondary structures to the DNA. The double helix structure of the DNA is known as the primary structure. Due to the secondary structure of the sequence, the PCR method which is based on the denaturing (the straightening and pulling apart) of the DNA fragment is inhibited, since it now has a double task: the denaturing of two structures at same time.
50. This set consists of FRAXA, DRPLA, SCAI, 1mtDNA marker, DYS 393 and perhaps DYS 389 I and II.
51. For how concepts as well as laboratory practice are involved in genetic objects such as “probes,” see for example Jordan and Lynch, “The Sociology of a Genetic Engineering Technique” (above, n. 9); Fujimura, “Crafting Science” (above, n. 29). Moreover, Fujimura argues that standardisation increases “the doability” of laboratory experiments and that it conversely reduces laboratory uncertainties and time investments. In a way the newly-introduced primers obliged Lab F to open its “standardised packages” of doing PCR, see Fujimura, “Constructing ‘Do-able’ Problems in Cancer Research” (above, n. 16).
52. See Mol, “Pathology and the Clinic” (above, n. 16); Rheinberger, “Von der Zelle zum Gen” (above, n. 16). I would like to emphasise that the DNA cannot be viewed as “resource” that allows for any kind of representation: it is actively involved and co-determines the tools of representation as well as the way it is represented (as in the case of FRAXA). Representations are thus best understood as configurations of traces of “the epistemic thing,” the DNA, as well as the tools and practices of representation; see Rheinberger, ibid., p. 274.
53. For the sake of this argument I have changed the order of the statements.