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Datasheet for the decision of 25 March 2014

Case Number: T 2264/09 - 3.3.02

Application Number: 97929672.0

Publication Number: 960207

IPC: C12P19/34, C12Q1/68, C07H21/04

Language of the proceedings: EN

Title of invention:
MULTIPLEX AMPLIFICATION OF SHORT TANDEM REPEAT LOCI

Patent Proprietor:
PROMEGA CORPORATION

Opponent:
Qiagen GmbH

Headword:
Multiplex amplification of STRs/PROMEGA

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:

Catchword:

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Case Number: T 2264/09 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 25 March 2014

Appellant: (Patent Proprietor)	PROMEGA CORPORATION 2800 Words Hollow Road Madison, WI 53711-5399 (US)
Representative:	Walton, Seán Malcolm Mewburn Ellis LLP 33 Gutter Lane London EC2V 8AS (GB)
Respondent: (Opponent)	Qiagen GmbH Qiagen Str. 1 40724 Hilden (DE)
Representative:	Kilger, Christian Fanelli Haag & Kilger PLLC Fasanenstraße 29 10719 Berlin (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 18 September 2009 revoking European patent No. 960207 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: T. Sommerfeld
D. Prietzel-Funk

Summary of Facts and Submissions

I. European patent EP 960207, based on European application 97929672.0 entitled "Multiplex amplification of short tandem repeat loci" and published as international application WO 97/39138, was granted with 42 claims.

II. An opposition was filed against the granted patent, the opponent requesting revocation of the patent in its entirety on the grounds of lack of novelty and of inventive step (Articles 54(2) and 56 EPC, Article 100(a) EPC).

III. The documents cited during the proceedings before the opposition division and the board of appeal include the following:

D14 Fourney et al., "Evaluation of a new STR..." internet citation, not dated
D18 Urquhart et al. (1995), BioTechniques 18, No. 1, pp. 116-121
D19 Gill et al. (1995), Electrophoresis 16, pp. 1543-1552
D20 Oetting et al. (1995), Genomics 30, pp. 450-458
D25 WO 96/10648
D35 Budowle et al. (1998), 2nd European Symposium on Human Identification, pp. 73-88

IV. The opposition division revoked the patent under Article 101(2) EPC 1973 (Article 101(3)(b) EPC 2000).

The opposition division decided that the claim set according to the main request (claims as granted)

lacked novelty, the disclosure of D14 anticipating the subject-matter of claim 31, and that the first auxiliary request lacked inventive step, starting from D14 as the closest prior art.

As regards document D35, the opposition division was of the opinion that it had not been established beyond reasonable doubt that the meeting to which this document was related was public, and thus that the disclosure made in said meeting and described in D35 could not be considered as being part of the prior art.

V. The patent proprietor (appellant) lodged an appeal against that decision. With the statement of the grounds of appeal, the appellant requested that the impugned decision be set aside and that the patent be maintained as granted (main request) or alternatively according to one of auxiliary requests 1 to 7, all filed with the grounds of appeal. New documents D48 to D54 were submitted at the same time.

The **main request** corresponds to the claims as granted. Independent claim 1 reads:

"1. A method of simultaneously determining the alleles present in short tandem repeat loci from one or more DNA samples, comprising:

a. providing at least one DNA sample to be analyzed,
b. selecting a set of short tandem repeat loci of the DNA sample to be analyzed which can be amplified together, wherein the set of loci is selected from the group of sets of loci consisting of:

D3Sl539,D7S820,D13S317,D5S818;
D17S1298, D7S82O, D13S317, D5S818;

D20S481, D7S820, Dl3S317, D5S818;
D9S930, D7S820, D13S317, D5S818;
D10S1239, D7S820, D13S317, D5S818;
D14S118, D7S820, D13S317, D5S818;
D14S562, D7S820, D13S317, D5S818;
D14S548, D7S820, D13S317, D5S818;
Dl6S490, D7S820, D13S317, D5S818;
D17S1299, D7S820, D13S317, D5S818;
D16S539, D7S820, D13S317, D5S818;
D22S683, D7S820, D13S317, D5S818;
D16S753, D7S820, D13S317, D5S818;
D3S1539, D19S253, D13S317, D20S481;
D3S1539, D19S253, D4S2368, D20S481;
D10S1239, D9S930, D4S2368, D20S481; and
D16S539, D7S820, D13S317, HUMvWFA31.

c. co-amplifying the set of loci in a multiplex amplification reaction, wherein the product of the reaction is a mixture of amplified alleles from each of the co-amplified loci in the set; and
d. evaluating the amplified alleles in the mixture to determine the alleles present at each of the loci analyzed in the set within the DNA sample."

Auxiliary request 1 differs from the main request in that claims 31 to 41 have been deleted.

Claim 1 of **auxiliary request 2** differs from claim 1 of the main request in that the set of loci is to be selected from only between two sets, namely those sets that contain the locus D16S539 and comprise at least 4 given STR loci.

Claim 1 of **auxiliary request 3** differs from claim 1 of auxiliary request 1 in that the set of loci is to be

selected from among sets which contain the locus D16S539 and comprise at least 6 given STR loci.

Claim 1 of **auxiliary request 4** differs from claim 1 of auxiliary request 1 in that the set of loci is to be selected from among 4 sets which contain the locus D16S539 and comprise 7 given STR loci.

Claim 1 of **auxiliary request 5** differs from claim 1 of auxiliary request 1 in that the set of loci is to be selected from between 2 sets which contain the locus D16S539 and comprise 8 given STR loci.

Claim 1 of **auxiliary request 6** differs from claim 1 of the main request in that the last set of loci has been deleted.

Claim of **auxiliary request 7** differs from claim 1 of the main request in that a further feature has been added "wherein the loci are amplifiable using..." followed by the indication of the SEQ ID NO for each primer of the primer pair for each specific locus.

VI. With letter of reply to the appellant's grounds of appeal, the opponent (respondent) requested that the appeal be dismissed and submitted new documents designated D55 to D63 and Annex IV. Apart from objections concerning novelty and inventive step, it also raised objections regarding clarity of auxiliary requests 2 to 5 and 7, and regarding added subject-matter in relation to auxiliary requests 3, 4 and 7.

VII. In reply to the respondent's letter, the appellant submitted documents designated D64 (in response to D58) and D65 (document referred to in D59).

VIII. Summons were issued for oral proceedings before the board to take place at 25 March 2014.

IX. With letter dated 19 February 2014, the appellant submitted corrected versions of auxiliary requests 3, 4 and 6, which mainly comprised corrections of claim dependencies, claim 1 remaining unchanged in relation to the corresponding previous versions.

X. Further letters followed, both from the respondent (letter of 21 February 2014, accompanied by new documents designated D66 to D71 and Annex II) and from the appellant (letter dated 13 March 2014).

XI. Oral proceedings before the board took place on 25 March 2014, as scheduled.

At the start of the oral proceedings, the board gave a preliminary opinion concerning the status as prior art of the poster corresponding to D14 and of the disclosure in the meeting mentioned in D35. In view of this preliminary opinion, both parties agreed to discuss first inventive step on the basis of documents which were undisputedly part of the prior art, and to recur later to the question of novelty, if needed.

XII. The appellant's submissions, in so far as relevant for the present decision, may be summarised as follows:

Main request and auxiliary request 1 - Inventive step

All claimed STR combinations, which had not previously been disclosed or even suggested, were experimentally demonstrated in the patent's 35 examples. More than 140 markers had indeed been tested, however the patent did not disclose the tests which had failed. While the

claimed loci stemmed from a publicly available depository, this was an incomplete and uncurated collection of genetic markers, comprising markers which were not polymorphic or which could not be amplified. Step d of claim 1 required that the claimed method makes it possible to identify all alleles within the DNA sample. However, simply amplifying a multiplex of markers did not necessarily achieve this purpose.

Document D25 was the closest prior art; it pursued the same aim as the patent but used different sets of STRs. D25's page 10 provided a list of multiplex combinations which were considered ideal; page 9 (last paragraph, from line 24 on) discussed criteria for the construction of multiplex systems, with its problems and difficulties. There was no reasonable expectation of success for any single combination, as confirmed by declarations from technical experts. In fact, thousands of STRs were known but not all of them were suitable as genetic markers and there was no pointer to try the claimed ones and no basis to expect that they would work. D25 could not be combined with any other document in order to arrive at the invention. Most documents relied on by the opponent merely demonstrated the theoretical availability of the techniques but the evidence on file demonstrated that the skilled person would not arrive at the invention in a trivial way.

The presence of advantages was not necessary for inventions which were alternative solutions. The claims were narrow, and the patent showed that the claimed combinations worked, and thus at least any question of lack of plausibility was overcome: there was no need to further restrict claims by providing the primers and other conditions.

Auxiliary requests 2 to 7 - Inventive step

Auxiliary request 2 was restricted to sets of loci comprising D16S539, a locus which had not been used in forensics before the priority date. While it was available from the CHLC database, this database was not curated and not all markers therein listed were polymorphic. Other documents referred to this marker but did so in different contexts, and thus could not be combined with D25 to arrive at the claimed subject-matter. Moreover, the conditions used in the patent's examples were not the same as in the CHLC database.

Auxiliary request 3 was further restricted to combinations comprising 6, 7 or 8 STRs, and thus increased the complexity of the system and provided a higher discriminatory power.

Auxiliary requests 4 and 5 were further restricted to combinations of 7 (auxiliary request 4) or 8 STRs (auxiliary requests 4 and 5), thus further increasing both complexity and discriminatory power.

Auxiliary request 6 on the other hand removed those STRs which were common with D25, and was thus further removed from this disclosure.

In relation to auxiliary request 7, this was further restricted by indication of the sequences of the primers to be used; otherwise, the same comments as for the main request applied.

XIII. The respondent's arguments, in so far as relevant for the present decision, may be summarised as follows:

Main request - Inventive step

There was no advantage in selecting the specific STR combinations. Even if time and diligence were needed to establish the claimed combinations, this did not account for inventive step; on the other hand, primer design and setting of PCR conditions were also not comprised in claim 1.

D25 shared large parts of content with the patent, the PCR conditions being more or less identical. It also related to a method of determining STR alleles by multiplex amplification; some of these STRs could also be found in the claims of the patent. The technical problem could thus be formulated as the provision of alternative sets of STR loci. The claimed sets of STR loci did not have a higher discriminatory power over those of D25.

Many of the STRs in the claimed combinations had already been multiplexed in the prior art. D16S539, for example, was part of multiplex set 26 in document D20 (page 455). Since the claimed alternative sets were clearly amplifiable and the creation of multiplex PCR was just a matter of diligence, the only way that the claim could be inventive was if there were advantages associated with the new subject-matter, which was not the case. The selection was thus arbitrary, just a juxtaposition of features. The effect of combining these groups was predictable and, in contrast to some documents of the prior art, there was actually no information in the patent concerning the discriminatory power of the claimed sets of STR loci.

Auxiliary requests 2 to 7 - Inventive step

Document D20 could also be considered the closest prior art for auxiliary request 2, see already its abstract. D5S818 was disclosed in set 11 in a pentaplex; the problem would thus be to provide alternatives to this pentaplex. D20 and D25 also provided the conditions and it was to be expected that the discriminatory power of a quadruplex as claimed would be worse than that of a pentaplex disclosed in the prior art. D19 furthermore showed that it was even possible to create octaplexes (page 1544 Table 1, second grouping) and D18 disclosed a heptaplex; there was thus a reasonable expectation of success and no beneficial effect. The same comments were also valid for auxiliary requests 3 to 5, while the same comments as for the main request were also valid for auxiliary requests 6 and 7. In relation to auxiliary request 7, not only had the primers also been disclosed in D25 but furthermore the added feature did not restrict the scope.

XIV. The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted, or alternatively on the basis of the claims according to auxiliary requests 1 or 2 filed with the letter setting out the grounds of appeal, or auxiliary requests 3 or 4, filed with the letter dated 19 February 2014, or auxiliary request 5, filed with the letter setting out the grounds of appeal, or auxiliary request 6, filed with the letter dated 19 February 2014, or auxiliary request 7, filed with the letter setting out the grounds of appeal.

XV. The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. Main request

2.1 Novelty - claim 31

2.1.1 At first instance and in the appeal proceedings, objections were raised in respect of novelty against independent claim 31 of the main request. In this context, documents D14 and D35 were cited as post-published evidence of disclosures which had allegedly taken place before the priority date. At the oral proceedings, after the board expressed its preliminary opinion concerning the status of these disclosures as prior art, the parties agreed to discuss first inventive step on the basis of documents which were undisputedly part of the prior art.

2.1.2 In view of the findings of the board concerning inventive step of claim 1 (*infra*), novelty of claim 31 was not further discussed and for this reason the board refrains from giving a decision on this issue.

2.2 Inventive step - claim 1

2.2.1 The present patent discloses the simultaneous amplification of multiple distinct polymorphic genetic loci called polymorphic short tandem repeats (STRs). The abundance of STRs in the human genome and their high polymorphism render polymorphic STRs very useful genetic markers for human identification, paternity testing and genetic mapping (patent, paragraphs [0001] to [0005]). The methods disclosed in the patent have thus a specific use in the field of forensic analysis,

for which it is necessary to analyze multiple polymorphic loci of DNA in order to ensure that a match between two samples of tissue is statistically significant. For this purpose, the methods of the patent allow for the simultaneous amplification of three or more loci (multiplexes) using a single amplification reaction, instead of amplifying each locus independently (patent, paragraphs [0027] to [0029]).

2.2.2 Document D25 is also directed at the simultaneous amplification of polymorphic STRs, and also envisages the use of the method for forensic analysis (pages 1 to 3, page 5, lines 24 to 27). D25 is thus a suitable starting point for the discussion of inventive step.

2.2.3 The difference from the subject-matter of claim 1 is that document D25 does not disclose the specific combinations of STRs as claimed. The appellant agreed that there is no indication in the patent or elsewhere on file that the specific STR combinations encompassed in claim 1 present any advantages in relation to those of document D25, and thus the technical problem can be formulated as the provision of alternative methods of simultaneously determining alleles present in STRs from DNA samples.

2.2.4 The proposed solution is the method as claimed in claim 1. All claimed STR combinations of claim 1 have been experimentally shown in the examples of the patent to work in the methods of the invention. As such, the board is satisfied that the technical problem has indeed been solved. It thus has to be examined whether the skilled person would arrive at the claimed solution in an obvious way.

2.2.5 Starting on page 9, line 23, document D25 teaches how to construct a multiplex system, stating that an appropriate set of loci, primers and amplification protocols must be selected and that combinations of loci may be rejected for different reasons, such as that they are not compatible for use with a single amplification protocol, or that they do not provide an adequate product yield, or that they produce fragments that do not represent authentic alleles. This discussion continues on page 10 (lines 1 to 4), with the statement that "[s]uccessful combinations are generated by trial and error of locus combinations and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified".

2.2.6 Hence, from D25 alone the skilled person is taught how to proceed in the search for further combinations of STR loci. Motivated to provide further such STR combinations, the skilled person would thus follow the teachings of D25 to look for new combinations of known STRs. Then, by using routine testing methods for DNA multiplex amplifications - which were well known in the art, also for use in detection of STR loci, as is clear from both D25 (page 2, third paragraph) and the patent (paragraph [0007]) - the skilled person would arrive at the solution to the problem, which could be the claimed combinations or other equally suitable combinations. While the specific STR combinations as claimed were not disclosed in the available prior art, the single STRs were all known, as evidenced by a number of documents on file and not disputed by any of the parties.

2.2.7 There is no special effect associated with the specific choice of locus combinations which could set them apart from all possible combinations of available STR loci or

even from those already disclosed in the same context by the closest prior art D25. As such, the presently claimed solution to the technical problem, which is an alternative to the solution of the closest prior art D25, is simply an arbitrary selection from a number of equally suitable alternatives. While alternatives to the prior art can also be an invention if they are not obvious, in the present case the skilled person was prompted by the prior art to follow a given path and there is no evidence on file that it would not be possible to arrive at suitable combinations of loci, including the specific combinations of claim 1, just by following the teachings of D25.

2.2.8 The board can accept the appellant's arguments that for each new combination of loci, appropriate primers have to be designed, amplification conditions have to be adapted and protocols modified in order to optimize the results and to avoid any possible artifacts. However this is considered as no more than the routine work, albeit laborious, that D25 refers to (*supra*). Even if there was a risk that some tested combinations would not work under standard conditions, this is not equivalent to a lack of reasonable expectation of success: the chances of arriving at suitable locus combinations were more than reasonable, in particular in view of the high number of known STRs which were available to the skilled person.

2.2.9 The board thus comes to the conclusion that claim 1 of the main request does not fulfil the requirements of Article 56 EPC.

3. Auxiliary request 1 - Inventive step

3.1 Claim 1 of this request is identical to claim 1 of the main request and thus also lacks an inventive step (Article 56 EPC).

4. Auxiliary request 2 to 6 - Inventive step

4.1 In auxiliary request 2, claim 1 has been restricted to two locus combinations, which both comprise locus D16S539. As argued by the appellant, this STR locus had not been used previously in forensics. However it had been used as part of a multiplex in D20, namely in set 26 of Table 2 on page 455. There would thus be no reason to doubt that this particular STR would work as part of a multiplex combination of STRs. In any case, in the absence of a special effect linked to the choice of this particular STR locus as part of an STR combination, again the claimed combinations are considered as a mere non-inventive choice from a myriad of possible, equally suitable alternatives.
Claim 1 of auxiliary request 2 is thus also considered to lack an inventive step (Article 56 EPC).

4.2 Claim 1 of auxiliary requests 3, 4, 5 and 6 differs from claim 1 of auxiliary request 2 in that it requires combinations of STR loci comprising 6, 7 or 8 loci (auxiliary request 3), 7 loci (auxiliary request 4) or 8 loci (auxiliary requests 4 and 5). According to the appellant, such larger combinations would increase both the complexity of the system as well as its discriminatory power. The board notes however that, while it may be assumed that it is indeed technically more difficult to provide multiplexes with more loci, it is still a matter of routine to develop the right conditions allowing such multiplexes to work: documents D18 (Title) as well as D19 (page 1544 Table 1) provide evidence that it was possible at the priority date to

attain working multiplexes of seven or even eight loci. That the discriminatory power might be increased when more loci are analysed - which is however not shown in the patent - would certainly be expected.
Claim 1 of auxiliary requests 3, 4, 5 and 6 is thus also considered to lack an inventive step (Article 56 EPC).

5. Auxiliary request 7 - Inventive step

5.1 In this request, claim 1 of the main request has been amended to further define the primer sequences used for each locus of the STR combinations.

5.2 The board concurs with the respondent that the further definition of the primer sequences to be used for each locus does not further restrict the claimed subject-matter. Indeed the term "amplifiable" just means that the loci can be amplified by using said specific primers but does not mean that the claim requires the necessary use of said primers. Since the claimed subject-matter has not been restricted in relation to the main request, it follows that claim 1 of this request does not involve an inventive step for the same reasons as for claim 1 of the main request. It is moreover noted that, even if it was considered that the use of the specific primers was a requirement of the claim, this would still not be sufficient to render the subject-matter inventive, since, as reasoned above, the provision of primers is *a priori* a matter of routine.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald

Decision electronically authenticated