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Case Number: T 0156/08 - 3.3.04

Application Number: 02006768.2

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Title of invention:
Chromosome 13-linked breast cancer susceptibility gene

Applicants:
The University of Utah Research Foundation, et al.

Headword:
BRCA2/UNIVERSITY OF UTAH

Relevant legal provisions:
EPC Art. 54, 87
EPC R. 103(1)(a)

Keyword:
"Main Request - reasons for refusal overcome (yes)"
"Remittal with the order to rectify decision to refuse (no)"
"Reimbursement of appeal fee (no)"

Decisions cited:
G 0001/03, G 0002/03, T 0080/05, T 0666/05

Catchword:
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Case Number: T 0156/08 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 14 January 2011

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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 11 June 2007 refusing European patent application No. 02006768.2 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: G. Alt
B. Claes

Summary of Facts and Submissions

I. This is an appeal against the decision of the examining division dated 11 June 2007 refusing European patent application No. 02 006 768.2 pursuant to Article 97(1) EPC 1973. The title of the application is "Chromosome 13-linked breast cancer susceptibility gene".

II. The decision was based on a main and two auxiliary requests.

III. Claim 1 of the main request read:

"1. A method for determining variation of the nucleotide sequence of a suspected mutant BRCA2 allele from a non-mutant wild-type BRCA2-encoding nucleotide sequence which comprises determining whether there is an alteration in the sequence of the BRCA2 gene in a tissue sample of a subject compared with nucleotides 229 to 10482 of SEQ ID No. 1 or a wild-type allelic variant thereof;

wherein one or more of the following procedures are carried out:

[procedures (a) to (m)]

with the proviso that said alteration is not an alteration in any one of the following nucleotide sequences or alleles thereof:

[sequences (i) to (xi)]

and with the proviso that said alteration is not an alteration at positions 2024, 4553, 4815, 5782-5789, 5841, 5972 and 8716 of SEQ ID No. 1." (unnecessary text omitted by the board).

Claims 4, 7, 10 and 11, 15 and 16 of the main request also recited the last-mentioned disclaimer.

IV. The examining division rejected the main request since it considered that the disclaimer in claims 1, 4, 7, 10 11, 15 and 16 "with the proviso that said alteration is not an alteration at positions 2024, 4553, 4815, 5782-5789, 5841, 5972 and 8716 of SEQ ID No. 1" was not in accordance with Article 123(2) EPC in view of decisions G 1/03 and G 2/03.

V. Claim 1 of the auxiliary request I was the same as claim 1 of the main request with the exceptions

(a) that claim 1 of the first auxiliary request read after "which comprises":

"determining in a tissue sample of a subject whether there is an alteration in the amino acid sequence encoded by the BRCA2 gene compared with the amino acid sequence set forth in SEQ ID NO: 2 or a wild-type allelic variant thereof, said alteration being a frameshift mutation or a point mutation in the coding region resulting in a stop codon;" and

(b) that the disclaimer present at the end of claim 1 of the main request was absent from claim 1 of the first auxiliary request.

Claim 3, relating to a method for determining variation of the nucleotide sequence of a suspected mutant BRCA2 allele from a non-mutant wild-type BRCA2-encoding nucleotide sequence, and claim 5, relating to a method for diagnosing a lesion in a human subject for neoplasia associated with the BRCA2 gene, also referred to determining whether there was an alteration in the amino acid sequence encoded by the BRCA2 gene compared with the amino acid sequence set forth in SEQ ID NO: 2 or a wild-type allelic variant thereof.

VI. The examining division did not allow auxiliary request I because its claims 1, 3 and 5 did not fulfil the requirements of Article 123(2) EPC since they referred to methods for determining whether there was an alteration in the **amino acid** sequence set forth in SEQ ID No. 2 whereas the application as filed only related to methods comprising the step of determining an alteration in the **nucleotide** sequence set forth in SEQ ID No. 1.

VII. Claim 1 of auxiliary request II read:

"1. A method for determining variation of the nucleotide sequence of a suspected mutant BRCA2 allele from a non-mutant wild-type BRCA2-encoding nucleotide sequence which comprises determining in a tissue sample of a subject whether there is an alteration in the sequence of the BRCA2 gene set forth in SEQ ID No. 1 that results in a shift of the reading frame defined by the amino acid sequence set forth in SEQ ID No. 2 or an allelic variant thereof;

wherein one or more of the following procedures are carried out:

[procedures (a) to (l)]

with the proviso that said alteration is not an alteration in any one of the following nucleotide sequences or alleles thereof:

[sequences (i) to (xi)]." (unnecessary text omitted by the board).

Claim 3, relating to a method for determining variation of the nucleotide sequence of a suspected mutant BRCA2 allele from a non-mutant wild-type BRCA2-encoding nucleotide sequence, and claim 5, relating to a method for diagnosing a lesion in a human subject for neoplasia associated with the BRCA2 gene, also referred to determining whether there was an alteration in the sequence of the BRCA2 gene set forth in SEQ ID No. 1 that resulted in the shift of the reading frame defined by the amino acid sequence set forth in SEQ ID No. 2.

VIII. The examining division rejected auxiliary request II. It found that the methods, insofar as they related to the nucleotide sequence of the BRCA2 gene, could only enjoy the priority date of the fourth priority document since only the nucleotide sequence disclosed therein - and not that disclosed in the third priority document - was identical to that referred to in the claims of auxiliary request II. As a consequence, document D2 (Nature, vol. 378, December 1995, pages 789-792, Wooster R. et al.) was state of the art according to Article 54(2) EPC. Since it disclosed the

identification of frameshift mutations in the sequence of a specific BRCA2 gene - which was to be considered as a wild-type allelic variant of the BRCA2 defined by SEQ ID No. 1 referred to in the claims - the subject-matter of claims 1, 3 and 5 was not novel.

Moreover, the examining division held that the subject-matter of the claims of this request lacked an inventive step in view of document D2 in combination with standard methods.

IX. With the statement setting out the grounds of appeal the appellants filed a new main and a new auxiliary request. With a later submission the main request was replaced by a further new main request which was intended to bring the claims "in conformity with the recent case law formed in decisions T 666/05 and T 80/05". Both main requests differed in that the expression "or a point mutation resulting in a stop codon in said ORF" was absent from claims 1 and 3 of the new main request.

X. The latest main request had four claims. Its independent claims 1, 3 and 4 read:

"1. A method for determining variation in the open reading frame (ORF) defined by SEQ ID No. 1 which comprises determining in a tissue sample of a subject a frameshift mutation in said ORF, wherein said mutation causes protein truncation;

wherein one or more of the following procedures are carried out:

(a) amplifying all or part of said ORF from said sample to produce an amplified sequence and sequencing the amplified sequence; and
(b) molecularly cloning all or part of said ORF from said sample to produce a cloned sequence and sequencing the cloned sequence;

with the proviso that said mutation is not a mutation in any one of the following nucleotide sequences or alleles thereof

[sequences (i) to (xi)].

3. A method for diagnosing a lesion in a human subject for neoplasia which comprises determining in a tissue sample from said lesion a frameshift mutation in the open reading frame (ORF) defined by SEQ ID NO: 1, wherein said mutation causes protein truncation and is indicative of neoplasia;

wherein one or more of the following procedures are carried out:

(a) amplifying all or part of said ORF from said sample to produce an amplified sequence and sequencing the amplified sequence; and
(b) molecularly cloning all or part of said ORF from said sample to produce a cloned sequence and sequencing the cloned sequence.

4. Use of the mutation 6174delT in the BRCA2 gene for diagnosing in vitro a predisposition for breast cancer in a human subject being an Ashkenazi-Jewish woman." (unnecessary text omitted by the board).

XI. The appellants argued in particular with regard to the objections of lack of novelty and inventive step in relation to document D2 that the third priority date should be acknowledged for the method-claims of the main request in view of the rationale in decisions T 666/05 and T 80/05. Particularly in the latter decision the board considered the priority claim to be valid because the reading frame of the sequence referred to in the claim was the same in the priority document and the application as filed.

XII. In a communication the board informed the appellants of its view that neither the examining division's reason for refusing auxiliary request I nor any of its other objections applied to the claims of the main request. The board noted that the examining division should have rectified the contested decision according to Article 109(1) EPC. The appellants were further informed that, because the claims had been considerably amended, the board considered it appropriate to remit the case to the department of first instance for further prosecution rather than granting the appellants' procedural main request to set aside the decision of the first instance and to grant a patent.

XIII. In reply the appellants filed new procedural requests. They requested that "the present case be remitted to the first instance with the order to rectify the contested decision according to Article 109(1) EPC and to, accordingly, reimburse the appeal fee". As an auxiliary measure it was requested to remit the case to the department of first instance for further prosecution. The appellants moreover stated that a

decision on the requests could be taken without being heard at oral proceedings.

Reasons for the decision

1. In the decision under appeal the main request was refused because the disclaimer in its claims 1, 4, 7, 10 11, 15 and 16 "with the proviso that said alteration is not an alteration at positions 2014, 4553, 4815, 5782-5789, 5841, 5972 and 8716 of SEQ ID No. 1" was considered not to be in accordance with Article 123(2) EPC in view of decisions G 1/03 and G 2/03 (OJ EPO 2004, 413 and 448, respectively).

2. None of the present claims contains this disclaimer.

3. Moreover, the examining division held that claims 1, 3 and 5 of the first auxiliary request before it did not comply with the requirements of Article 123(2) EPC because the application as filed did not disclose methods comprising determining the alteration in the amino acid sequence set forth in SEQ ID No. 2, but only methods comprising determining an alteration of the nucleotide sequence set forth in SEQ ID No. 1.

4. The present claims do not contain the objected feature.

5. With regard to the second auxiliary request the examining division decided that the subject-matter of its claims 1, 3 and 5 was not novel over the disclosure in document D2. The document was considered as prior art pursuant to Article 54(2) EPC because the claims could enjoy priority only from the fourth priority

document. This was so because the nucleotide sequence of the BRCA2 gene referred to in the claims of the second auxiliary request, i.e. SEQ ID No. 1, was only identical to that disclosed in the fourth, but not to that disclosed in the third priority document.

6. Present claim 1 of the main request relates to "[a] method for determining variation in the open reading frame (ORF) defined by SEQ ID No. 1 which comprises determining in a tissue sample of a subject a frameshift mutation in said ORF, wherein said mutation causes protein truncation ...".

Present claim 3 of the main request relates to "[a] method for diagnosing a lesion in a human subject for neoplasia which comprises determining in a tissue sample from said lesion a frameshift mutation in the open reading frame (ORF) defined by SEQ ID No. 1 wherein said mutation causes protein truncation and is indicative of neoplasia ...".

7. Thus, in other words, the methods of claims 1 and 3 require determination of the open reading frame of the BRCA2 gene from the tissue sample and its comparison with the open reading frame "defined by SEQ ID No. 1" as the "reference" open reading frame. Consequently, the "open reading frame defined by SEQ ID No. 1" and not "SEQ ID No. 1" is a feature of the claimed methods.

8. Establishing a "reading frame" is a way of breaking a nucleotide sequence into portions of three nucleotides called triplets or codons. The "open reading frame" is the one that contains a start and a stop codon in the same frame. Also, it is the one supposed to be

translated into a protein. Each three-nucleotide codon is translated into one amino acid.

9. Hence, for determining any reading frame of a nucleotide sequence, including an "open reading frame", knowing the actual sequence of nucleotides, i.e. the kind of nucleotide at a given position, is not necessary.

10. The nucleotide sequence according to SEQ ID No. 1 as disclosed in the third priority document differs from that disclosed in the application in the kind of nucleotide at positions 2014, 4553, 4815, 5782-5789, 5841, 5972 and 8716. These alterations neither affect the length of the sequence to be translated nor the codon which "opens" the reading frame, i.e. the start codon. Therefore, despite the variations in the sequence, the open reading frame defined by SEQ ID No. 1 according to the third priority document and the application as filed remains the same. Thus, the feature at issue here, i.e. the "open reading frame defined by SEQ ID No. 1" is disclosed in the third priority document.

11. Consequently, in the board's view, the non-identity of the nucleotide sequence disclosed in SEQ ID No. 1 according to the third priority document and the application as filed is not a reason for denying the third priority date for the subject-matter of the present claims 1 to 3 and accordingly is also not a reason for considering document D2 as prior art pursuant to Article 54(2) EPC. Therefore, the examining division's objections of lack of novelty and inventive step are not tenable.

12. The finding in point 11 above, first half-sentence, is in line with the reasoning in two decisions issued after the decision under appeal was taken, i.e. decision T 80/05 of 19 November 2008 and decision T 666/05 of 13 November 2008 (see points 37 and 40 of the reasons, respectively). Also in the cases underlying these decisions the claims related to diagnostic methods involving the determination of frameshift mutations, the "reference open reading frame" was defined in relation to a specific sequence and the issue of the entitlement to priority arose because in both cases only the fifth priority document disclosed a sequence exactly corresponding to that referred to in the claims.

13. In summary, the board concludes from its observations in points 1 to 11 above that none of reasons given in the decision under appeal for refusing the present application applies to the present claims.

14. As regards the appellants' request to remit the case to the first instance with the order to rectify the decision under appeal and the related request to reimburse the appeal fee, Article 109(1) EPC stipulates that "if the department whose decision is contested considers the appeal to be admissible and well-founded, it shall rectify its decision." Thus, the decision to rectify or not the decision to refuse an application is at the examining division's discretion. Hence, by remitting the case with the order to rectify the decision under appeal according to Article 109(1) EPC the board would be acting beyond its competence. If at all, a decision not to rectify the decision to refuse

an application might only be appealable, if the examining division had exercised its discretion in a way which amounted to a substantial procedural violation. In the present case this has not been alleged by the appellants and also the board sees no substantial procedural violation in the examining division's refusal to rectify its decision in the light of the claims submitted with the statement of the grounds of appeal. It is moreover noted that the claims considered in the present decision are different to those submitted originally with the statement of the grounds of appeal (see section IX above).

15. In the absence of a procedural violation, Rule 103(1)(a) EPC which states that "[t]he appeal fee shall be reimbursed [...] where the Board of Appeal deems an appeal allowable, if such reimbursement is equitable by reason of a substantial procedural violation" does not apply.

16. The appellants accepted that a decision on either of their requests to remit the case to the first instance could be taken without oral proceedings (see section XIII above) and the board has proceeded accordingly.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution on the basis of claims 1 to 4 of the main request filed with the letter dated 15 September 2009.

3. The request for reimbursement of the appeal fee is refused.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith