Trilateral Project WM4
Comparative studies in new technologies
(biotechnology, business methods, etc.)

Report on comparative study on
Examination Practice Relating to Single Nucleotide Polymorphisms (SNPs) and Haplotypes

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Theme: Comparative Study on Examination Practice Relating to Single Nucleotide Polymorphisms (SNPs) and Haplotypes

1. Introduction

The promise of the development of designer therapeutics based upon genetic diversity has sparked great interest in patent protection on variations of genomic DNA including single nucleotide polymorphisms (SNPs) *[1]* and combinations of SNPs known as haplotypes. *[2]* Current technology allows laboratories to rapidly generate thousands of bits of genetic data in short order. Expanding SNP and haplotype technology has resulted in an increase in the number of patent applications claiming SNPs and haplotypes, as well as corresponding methods of use. Furthermore, patent applicants often file applications that disclose and claim hundreds or thousands of related nucleic acid molecules. Claims to SNPs and haplotypes are expected to present special search and examination challenges.

A comparative study of the challenges faced by the Trilateral Offices when examining claims directed to SNPs and haplotypes may help in generating greater mutual understanding and possible convergence of examination practices.

[1] "SNPs are single base pair positions in genomic DNA at which different sequence alternatives (alleles) exist in normal individuals in some population(s)." "SNPs: what they are & what they might they tell us," Anthony Brookes Research Group, available at http://www.cgr.ki.se/cgb/groups/brookes/snps.htm.

[2] "The term 'haplotype' refers to a combination of SNPs on a chromosome, usually within the context of a particular gene." "Haplotype Identification" at http://www.variagenics.com/articles/haplotypeid.html

2. Questions Common to All Cases

The answers to the following questions are intended to set forth the challenges faced by each Office regarding search strategies, analysis of the presence or absence of unity of invention, clarity, sufficiency of disclosure, industrial applicability/utility, and patentability over the prior art as related to each of the examples set forth below.

For each of the fact patterns set forth below, please provide comments regarding the following issues:

1. For each claim, identify the challenges to establishing a complete search, including any considerations regarding the extent to which the full scope of the invention can be searched using automated tools.

2. For each claim, identify the challenges faced in comparing the subject matter disclosed in the prior art with the claimed invention.

3. For each example, identify the challenges that are presented in determining whether unity of invention is present either within each claim or between claims both before and after a search has been conducted.

4. For each claim, identify the challenges that are presented regarding the determination of compliance with the clarity, sufficiency (enablement/written description) and industrial applicability/utility requirements.

For each of 1-4 above, where applicable please provide information regarding how your Office is addressing these challenges.

3. Cases

Example I- New SNPs, Old useful gene, Association with phenotype shown for some

Outline of the Specification:

The application describes the discovery of eight single nucleotide polymorphisms in a known gene (SEQ ID NO: 1) that is in a biological pathway. The polymorphisms are identified as polymorphisms 1-8. The specification provides table A, which gives the position of polymorphic sites 1-8 within SEQ ID NO: 1 and the possible nucleotides present at the polymorphic sites. Allele 1 of each SNP is the allele present in the known sequence, while Allele 2 is the newly discovered polymorphic allele. The application further demonstrates that the presence of allele 2 of polymorphisms 1-3 is associated with the presence of disease X. The specification provides data indicating that there is no association between the presence of either allele and disease X for polymorphisms 4-6. The specification is silent as to whether the presence of either allele of polymorphisms 7-8 is associated with the presence of disease X or any other disease.

Search Results:

SEQ ID NO: 1 is known in the prior art.
The prior art does not teach any single nucleotide polymorphisms of SEQ ID NO: 1.

Claims:

1. An isolated nucleic acid molecule comprising SEQ ID NO: 1 except for a single polymorphic change at one of the positions as shown below:

Polymorphism	Position	Change from the nucleotide in SEQ ID NO: 1 to
1	10	G
2	27	A
3	157	C
4	234	T
5	1528	G
6	3498	C
7	13524	T

2. A method for detecting the presence of disease X in a patient comprising the steps of:

a) isolating a nucleic acid from a sample that has been removed from the patient and
b) detecting the nucleotide present at one or more polymorphic sites within SEQ ID NO: 1 as listed in the Table of claim 1, wherein the presence of the nucleotide specified in the Table of claim 1 at the polymorphic site is indicative of the presence of the particular disease.

Example II - Haplotypes, Association shown for some

Outline of Specification:

The specification provides 5 haplotypes for known gene X (SEQ ID NO: 1) that is 3,267 nucleotides in length and is known in the prior art. The set of variants (haplotypes 1-5) has been identified by the Human DNA Sequencing Project. Each haplotype represents a particular combination of 7 different polymorphic sites within the gene. The specification provides a Table that lists the identity of the nucleotide at each polymorphic site within each haplotype. The Table also indicates whether any or all of the polymorphisms result in an amino acid change within the protein encoded by gene X.

The specification provides data that illustrates that patients with disease X respond to treatment by drug Y which acts on disease X better if they have haplotype 1 or 5 than if they have haplotypes 2, 3, or 4. There is no association between disease X and haplotypes 2, 3, or 4.

Search Results:
The prior art shows that SEQ ID NO: 1 and Haplotype 1 are known in the art.

Claims:

1: An isolated nucleic acid molecule selected from the group consisting of haplotypes 1, 2, 3, 4, and 5 wherein each of haplotypes 1-5 comprises SEQ ID NO: 1 with the exception that the nucleotides specified in the table below for each haplotype are present at the corresponding position within SEQ ID NO: 1.:

Position	Haplotype 1	Haplotype 2	Haplotype 3	Haplotype 4	Haplotype 5
23	A	T	A	A	A
47	G	G	C	C	G
89	G	C	C	G	C
213	C	C	C	G	G
605	T	A	T	A	T
788	A	G	A	G	A
1592	G	G	G	G	C

2. A method for haplotyping gene X in an individual comprising the steps of:

(a) isolating a nucleic acid from a sample that has been removed from the individual
(b) determining the presence of the nucleotides present at positions 23, 47, 89, 213, 605, 788, and 1592 of the individual's copy of gene X, wherein the position numbers are determined by comparison to SEQ ID NO: 1,

(c) assigning the individual a particular haplotype by comparison of the nucleotides present at said positions to the nucleotides recited in the haplotypes of the table set forth in claim 1.

4. Summary of the Cases

Example I SNPs Reference SEQ ID NO. is not novel	SNP #	Association with Phenotype?	Novel?
	1-3	+ Correlation	Yes
	4-6	No Correlation	Yes
	7-8	Unknown	Yes

Example II Haplotypes Reference SEQ ID NO. is not novel	Haplotype #	Association with Phenotype?	Novel?
	1	+ Correlation	No
	2, 3, and 4	- Correlation	Unknown
	5	+ Correlation	Unknown

5. Summary of the Answers

5.1 Challenges to Establishing a Complete Search

The Trilateral Office identified the following challenges to establishing a complete search:

5.1.1 Example 1 (SNPs)

1. It is necessary to determine Unity of Invention a priori to make an initial determination of whether the scope of the search may be limited due to a lack of unity.
2. In addition to searching for the parent molecule by sequence (here, SEQ ID NO. 1), the examiner needs to search for each individual polymorphism within the parent sequence using both full-length sequence and oligomer searches.
3. While some databases are searchable via the Internet, these databases lack the necessary security to permit a complete search of the claimed invention(s).
4. Examiners need to conduct a sequence search as well as a keyword search.
5. A single nucleotide allele of a SNP site can be defined/disclosed in the prior art in different ways. Such an allele is in general defined/disclosed by either

- a gene sequence,
- a short sequence "identifier" or
- an indication of the position of the SNP site relative to a reference sequence and the nucleotide specifying the allele

6. The prior art lacks any standardized naming, numbering, or characterization schemes for any particular gene or protein, especially when it is newly or recently discovered.

7. Differences in the manner in which the prior art and the application at issue describe/define a polymorphic site and/or a reference sequence make it difficult to perform a comprehensive search using textual databases or sequence databases.
8. A parent sequence, such as SEQ ID NO: 1 may be present in a searchable listing while information about polymorphic variants is often embedded in the annotation fields of such databases, or within tables, charts, or figures of scientific literature.
9. Claim 2 requires text-based searching for associations between the parent sequence, the claimed SNPs, and the specified disease.

5.1.2 Example II (Haplotypes):

In addition to the challenges set forth above with respect to Example I, the Trilateral Offices identified the following additional challenges to establishing a complete search for the haplotypes of Example II:

1. Selection of appropriate databases may be challenging, especially with respect to searching for an association between a haplotype and a patient's response to treatment by a drug.
2. The search for a haplotype is even more complex than the search for a SNP because it is necessary to search for the presence of multiple polymorphic nucleotide positions within a single molecule.

- However, given multiple positions that could be relied upon to distinguish over the prior art, once any particular position within a polymorphism is found to be sufficient to find a given haplotype novel and non-obvious (inventive), it is possible that no further search of any haplotype having the novel and nonobvious polymorphism would be required.

5.2 Challenges Faced in Comparing Claims with Prior Art

The challenges to establishing a complete search are also challenges faced in comparing claims with the prior art. The Trilateral Offices identified the following additional challenges faced in comparing claims with the prior art:

5.2.1 Example I (SNPs)

1. Variant numbering systems result in difficulty in aligning or directly comparing claimed sequences with sequences in the prior art.
2. Where the parent sequence is known in the art, a challenge is presented in determining whether the identification of any specific polymorphism thereof involves an inventive step.
3. In determining whether the claimed invention complies with the inventive step requirement, the examiner must consider any known association between a parent sequence and a particular disease.

5.2.2 Example II (Haplotypes):

In addition to the challenges set forth above with respect to Example I, the Trilateral Offices identified the following additional challenges faced in comparing claims with the prior art:

1. In determining whether the invention of Claim 2 involves an inventive step, the examiner must determine how much patentable weight should be given to the step of assigning a particular haplotype to an individual.
2. In determining whether the invention of Claim 2 involves an inventive step, a challenge is presented in determining whether the nucleic acid sequence information being compared in the claimed process would be sufficient to patentably distinguish the claims from a prior art process having the same basic steps, but comparing different nucleic acid sequence information.
3. In determining whether the invention of Claim 2 involves an inventive step, the examiner

must determine whether the person skilled in the art would have been motivated to seek haplotypes associated with disease X or drug metabolism.

5.3 Challenges Presented in Determining Compliance with Unity of Invention Requirement

The Trilateral Offices identified the following challenges presented in determining compliance with the Unity of Invention requirement:

5.3.1 Example I (SNPs)

- **Unity *a priori***

  1. In determining a priori whether there is a concept linking the 8 polymorphisms within a single invention, the following features could be taken into account:

  (a) the fact that the claimed polymorphisms are all to be found within SEQ ID NO: 1;
  (b) the fact that all of the claimed compounds comprise a single nucleotide polymorphism (SNP); or
  (c) whether the 8 polymorphisms are associated with the same particular disease.

  2. Here, association with disease X cannot play the role of the special technical feature to link all 8 polymorphic sites, because the description explicitly and unambiguously discloses that polymorphisms 4-6 are not associated with the disease and is completely silent as to any association of polymorphisms 7-8 with disease X.

- **Unity *a posteriori***

  3. Given the fact that SEQ ID NO: 1 is a known sequence, SEQ ID NO: 1 as such cannot represent a single general inventive concept linking the 8 polymorphisms in a single invention. In determining a posteriori whether there is a concept linking the 8 polymorphisms within a single invention, a challenge is presented in determining whether any of the following are sufficient single inventive concepts to establish unity of invention:

  (a) the fact that the 8 polymorphic sites of claims 1 and 2 are single nucleotide polymorphisms. The Trilateral Offices agree that this is not sufficient to establish a single inventive concept; or
  (b) the association of one or a group of SNPs with a particular phenotypic trait, such as the presence of a disease.

    - A challenge is presented in determining whether or not a "positive" association and/or a "negative" association (in contrast to the absence of any association) with a particular phenotypic trait may represent a single inventive concept.
    - If the association is inventive, unity of invention may exist for all SNPs associated with the trait in question.
      - SNPs not associated with this trait would not belong to the same invention as those showing the association.
    - If the association is not a contribution over the prior art (e.g., lacks novelty and/or inventive step), the association is not sufficient to establish unity of invention; or

  (c) the association of one or a group of SNPs with a particular phenotypic trait, such as the presence of a disease, and the presence of a common structure or significant structural element shared by all of the alternatives.

5.3.2 Example II (Haplotypes)

The challenges presented in determining unity of invention with respect to Example I, above, are equally applicable to the determination of unity of invention with respect to Example II. No additional challenges were identified.

5.4 Challenges Presented in Determining Compliance with Clarity, Sufficiency (Enablement/Written Description) and Industrial Applicability/Utility Requirements

The Trilateral Offices did not identify any challenges presented in determining whether the claims of each example complied with the clarity requirement, or with the written description requirement.

5.4.1 Example I (SNPs)

The Trilateral Offices identified different challenges presented in determining compliance with the support, enablement and industrial applicability/utility requirements as follows:

EPO

1. Claim 1 does not present any challenges with respect to the support requirement because the preparation of molecules such as those to which claim 1 relates is common practice for the skilled person. However, the application lacks support (Art. 84 EPC) for claim 2 because no experimental data of any kind are provided showing that the presence of disease X could be detected by detecting polymorphism 4-8 and the identification of the association between one or more SNPs and a specific trait is not a routine matter for the skilled person.
2. Unless the parent sequence on which a particular SNP resides is novel and inventive, uncharacterized SNPs, namely those SNPs for which no association with any phenotypic trait has been shown, are usually considered as lacking an inventive step. Therefore addressing the question of whether uncharacterized SNPs are susceptible of industrial application will usually not be necessary, because of their lack of inventive step.

JPO

3. A challenge exists regarding how to evaluate the scientific reliability of an asserted association between alleles containing SNPs and disease X. A challenge also exists in determining whether or not differences between the frequencies of various SNPs within a population are sufficient scientific proof of the association between gene X and disease X.
4. Allelic variants that have no disclosed association with the presence of a disease may lack industrial applicability and enablement.

USPTO

5. A challenge is presented by the need to determine whether claims 1 and 2 are enabled for their full scope, i.e., whether all of the claimed polymorphisms set forth in each of claims 1 and 2 have a specific, substantial, and credibility utility that could be practiced without undue experimentation.

5.4.2 Example II (Haplotypes)

The Trilateral Offices identified different challenges presented in determining compliance with the enablement and industrial applicability/utility requirements as follows:

EPO

1. Claim 1 does not present challenges with respect to the support requirement because it relates to nucleic acid sequences, which can be obtained by the skilled person by routine methods.
2. Claim 2 relates to a method for haplotying. It is deemed to meet the support requirements, because the application discloses 5 specific haplotypes characterised by the very polymorphic sites to which claim 2 relates and, having been provided with these haplotypes, the skilled person would only need commonplace methods for identifying the bases at the specific positions to which claim 2 relates.
3. The subject-matter of claims 1-2 is considered to be industrially applicable, because the nucleic acid sequences to which claim 1 relates can be used, for example in the method to which claim 2 relates.
4. With respect to example II, the greatest challenge for the EPO would be however to assess whether the subject-matter of the claims, insofar as novel, involves an inventive step.

JPO

5. As claim 1 does not involve an inventive step, clarity, enablement, and industrial applicability do not need to be examined.
6. The allele variants that have no disclosed association with the presence of disease may lack industrial applicability and enablement.
7. The claimed nucleotide presents a challenge with respect to the enablement requirement because it is doubtful that the claimed polynucleotides would be able to detect differences between haplotypes, because each polynucleotide is 3,267 nucleotides in length and too long to specifically hybridise to particular haplotypes.
8. If it is claimed that the response of patients with disease X to treatment by drug Y that acts on disease X correlates with a particular haplotype, a challenge exists regarding how to evaluate the scientific reliability of the asserted correlation.

USPTO

9. The principle challenge posed by Example II is the determination of whether all of the claimed haplotypes have a specific, substantial, and credibility utility that could be practiced without undue experimentation. The description states that the data present in these structures is useful in determining the sensitivity of an individual to drug Y. However, this is a use of the information content of the nucleic acids rather than a use of the nucleic acid molecules themselves.
10. Regarding the claimed method, the specification does not make an explicit statement asserting a specific, substantial and credible utility for the haplotype assignment method. However, the specification does disclose at least a potential use of the claimed molecules (see preceding paragraph) in designing a medical treatment regimen. A challenge is presented in determining whether using the haplotype assignment method as a basis for individualized drug prescription is implicitly disclosed, and if so, whether the data in the specification presents sufficient information to enable one skilled in the art to practice the claimed invention over the full scope of the claims.