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Response to "Pervasive Sequence Patents Cover the Entire Human Genome"

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LETTER TO THE EDITOR

Response to 'pervasive sequence patents cover the entire human genome'

Shine Tu^{1*}, Christopher Holman², Adam Mossoff³, Ted Sichelman⁴, Michael Risch⁵, Jorge L Conteras⁶, Yaniv Heled⁷, Greg Dolin⁸ and Lee Petherbridge⁹

See related Correspondence by Rosenfeld and Mason, <http://genomemedicine.com/content/5/3/27> and related letter by Rosenfeld and Mason, <http://genomemedicine.com/content/6/2/15>

Abstract

A response to Pervasive sequence patents cover the entire human genome by J Rosenfeld and C Mason. *Genome Med* 2013, **5**:27.

Letter to the editor

In the article by Jeffrey Rosenfeld and Christopher Mason published in *Genome Medicine* [1], significant misstatements were made, because the authors did not sufficiently review the claims - which define the legal scope of a patent - in the patents they analyzed. The authors contend that '41% of the genes in the human genome have been claimed' in US patents. Additionally, they suggest that claims to shorter sequences, specifically 15mers, in a patent held by Myriad Genetics (a litigant in the recent Supreme Court case involving the patentability of genes [2]) cover 91.5% of human genes. Their article has received wide attention in the press and industry (for example, in CNBC [3], Fox News [4] and CBS News [5]), and formed the basis for opinion articles by the authors in the *Washington Post* [6] and the *Huffington Post* [7].

We do not question the authors' assertion [1] that as k-mers become shorter, the likelihood that those k-mers appear in some gene increases substantially. However, the article does not accurately reflect the law behind gene patenting, because by failing to specifically analyze the claims of these patents, it overestimates the share of the human genome that is 'covered' by US patents. As an initial matter, unlike most articles in *Genome Medicine*, Rosenfeld and Mason's article [1] purports to make legal - rather than purely scientific - assertions. Our criticisms do not depend

on our viewpoint as patent lawyers or as patent law professors. As we describe below, the authors [1] make important legal assertions that are either misleading or simply incorrect.

More specifically, Rosenfeld and Mason [1] did not apply the legal standards required for patent infringement and, in turn, misinterpreted the scope of the CAMBIA patent sequence database [8] when performing their analysis. In order to arrive at a legitimate conclusion as to what subject matter is 'covered' by a patent claim, it is absolutely necessary to read and interpret every single limitation or element in the patent claim. The patent claim defines the patented invention, and infringement can occur only when every element of a claim is met by the accused product or process. Rosenfeld and Mason [1] identified patents that mention DNA sequences, but then fail to review the other terms and limitations required by the claims. Based on our review of some of these claims, they almost all included additional limitations and some simply mention the gene sequence without even making the sequence a limitation in the first place. For example, one patent they identify as 'covering' DNA sequences corresponding to human genes also requires testing on a bovine subject. But they ignore the required step of bovine testing when analyzing whether their claim covers gene sequences. In fact, because this claim requires testing, it is not a 'composition of matter' claim at all and cannot independently cover gene sequences.

The article by Rosenfeld and Mason [1] made an assumption that just because a patent mentions a gene sequence in a patent claim, any use or research of this gene would result in patent infringement. This is not the case. To directly infringe a claim that is directed to a composition of matter (such as DNA) that comprises elements 1, 2 and 3, one needs to make a composition that includes at least elements 1, 2 and 3. If only element 1 is present, then there is no direct infringement of the

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patent. For example, if a patent claims a bicycle with handlebars, wheels and gears, one would not directly infringe this patent by making only the handlebars.

For example, the authors [1] state that '15mer patent claims from one gene will always 'cross-match' and patent a portion of another gene as well.' From a legal standpoint, this statement is true only if the patent claim is directed only to the 15mer itself. However, as one of us (CH) has shown in his previous research, this is a rare occurrence - in fact, the only 15mer patent that he was able to find from searching hundreds of patents was the Myriad 5,747,282 patent ('the '282 patent') [9]. The authors' [1] analysis assumes that simply because a patent claim contains one limitation reciting a short nucleotide sequence, such as a 15mer, it is effectively the same as the 15mer claim in Myriad's '282 patent. We agree that if hypothetical 15mer (or shorter) human DNA composition of matter claims were routinely granted, this would be extremely problematic because they might cover a large percentage of genes. Such an assertion has been made before, and is not terribly controversial [10,11]. However, it is of little import, because there are few (perhaps one) patent that does so, and any such patent claim (such as the one in the '282 patent) would surely be invalid for lack of novelty.

Similarly, Rosenfeld and Mason [1] state that 'we found 58 patents whose claims covered at least 10% of the bases of all human genes.' One of us (ST) has reviewed these 58 patents, and this is simply not the case. The claims of most of these patents contain many additional elements, and the fact that the claims contain reference to human genes does not mean that using nucleic acids directed to these sequences will necessarily result in patent infringement (Additional file 1: Table S1). As we stated earlier, it is essential to review every claim limitation to determine what a claim covers and what it does not.

Additionally, we note that some of the documents listed under the 58 'patents' examined by the authors [1] of the Pervasive sequence article are actually 'statutory invention registrations' (SIRs). SIRs are not patents and do not give the holder any exclusive rights; they are used purely as a defensive publication. In fact, SIRs require the registrant to affirmatively waive any right to receive a patent on the disclosed subject matter [12].

Rosenfeld and Mason [1] used the CAMBIA patent database [8], which simply identifies DNA sequences if they are mentioned anywhere in a patent claim. Yet, contrary to Rosenfeld and Mason's findings [1], the CAMBIA database fails to identify whether a DNA sequence that happens to be mentioned in a claim is standing alone encompassed - as a legal matter - under that patent claim. As noted above, additional elements may be required by the claim for a finding of infringement.

A manual review of patent claims to determine whether DNA sequences mentioned within the claims are in fact within the scope of the claims is more than feasible. First, one would only need to review the 3,945 patents that were matched from the CCDS gene sequence database [13] and the CAMBIA patent database [8] (not tens of thousands of patent claims). In fact, Graff et al. [14] show that there are only 11,868 gene patents, with 5,936 patents directed to humans. Second, one would only need to focus on the claims (usually only one to three pages at the end of a patent), and not necessarily read the entire patent. Finally, one could limit the analysis to only composition of matter claims. To do this quick first pass type of review, it took one of us (ST) less than 1 hour to review approximately 60 patents. Accordingly, for 3,000 to 4,000 patents, roughly 60 hours of work would be required - far under the amount of time spent preparing a typical article appearing in this journal. Interestingly, in a recent article, Jefferson et al. [15] describe tools for the CAMBIA database that begin to address this very issue.

We realize that Rosenfeld and Mason [1] are not patent lawyers. The field of patent law is one that can be both confusing and complex. However, we do not believe that readers could plausibly interpret the Rosenfeld and Mason [1] article as only making a statistical argument about coverage and not legal interpretations about patent law. Indeed, Rosenfeld and Mason [1] rely on their results to propose that 'the Supreme Court and Congress should limit the patenting of existing nucleotide sequences because of their broad scope and non-specificity in the human genome.'

We note that none of the above necessarily reflects on the position of the authors [1] in the ongoing debate regarding the patentability of 'gene patents'. Rather, we all believe that this vital debate should be tethered to legal reality. Also, since the publication of Rosenfeld and Mason [1], the US Supreme Court has issued an opinion regarding gene patents [2]. Specifically, the Court has drawn a line between isolated DNA (not patentable subject matter) and cDNA (patentable subject matter). According to the Court, '[the patentee] did not create or alter either the genetic information encoded [in the genes] or the genetic structure of the DNA. [The patentee] found an important and useful gene, but groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the [statutory patentable subject matter requirement].' However, the Court also ruled that cDNA is not a 'product of nature', and is thus patent-eligible [2].

It is well within our expertise as patent law professors to rebut such arguments. Additionally, we have the expertise to understand the science, as all but two of us have first degrees in biology or medicine and four of us have PhDs in biological subjects or MDs. Put simply, Rosenfeld and Mason [1] use their scientific results to

make a legal argument, and that legal argument is based on an incorrect view of the law. So it is to these legal conclusions, and not their scientific results, that we object. Specifically, the claims of the patent define the legal boundaries and the inventor's exclusionary rights. Accordingly, it is legally insignificant that the short nucleotide sequences statistically can be found in much of the human genome, unless many patent claims solely cover these short nucleotide sequences. Rosenfeld and Mason [1] have shown nothing of the sort, and our initial review of their patents indicates entirely otherwise.

Additional file

Additional file 1: Table S1. A brief analysis of the 58 patents referenced in Additional file 2 of the Rosenfeld and Mason article [1]. Analysis only includes review of the independent claims of the patent, and also a brief description of the elements necessary for patent infringement are given.

Competing interests

ST, CH, AM, JC and GD have written amicus briefs relevant to this publication. Amicus briefs are legal briefs written by someone who is not party to the lawsuit but who petitions the court to file a brief in the action because that person has a strong interest in the subject matter.

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