Gene Patents in India: Gauging Policy by an Analysis of the Grants made by the Indian Patent Office*

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Patentability of genes has been controversial in the recent past. While the Patents Act, 1970 in India prohibits patenting naturally occurring substances, patents covering genetic material and nucleotide sequences have been granted. Owing to a lack of case law, this paper studies the patents granted by the Indian Patent Office (IPO) in order to understand the standards adopted by it in granting patents for nucleotide sequences. The paper examines the claims of five different patents along with available file wrapper documents/prosecution history documents to gauge the IPO’s practice in granting such patents.

Keywords: Genes, patents, biotechnology, policy, DNA, cDNA, recombinant, Section 3(i), Section 3(c)

Technology has progressed to a great extent after the historic revelation of the structure of the DNA molecule.1 Scientists have, since then, engaged in efforts of identifying the sequences of these molecules, their function and also in manipulating them to achieve desired results.

Owing to their close association with nature and its use to achieve desired results, biotechnology patents often raise issues of patentability. Gene and nucleic acid based patents, specifically, have been in controversy in the recent years around the world.2 While case laws and directives in other jurisdictions indicate the positions taken by them, the Indian legal position on gene patents is not that evident. This paper, therefore, seeks to study the position adopted in India with respect to the standards applicable in ascertaining patentability of a nucleic acid sequence.

As there is a lack of decisions in the higher judiciary on this subject matter, this paper seeks to study patent grants related to nucleic acids by the Indian Patent Office (IPO) and other guidelines issued by them to gauge the rationale employed. The author has chosen five patents that have been granted by the IPO and the examination reports, if accessible. The purpose is to answer the following fundamental questions –

(i) Are genes patentable in India?
(ii) What are the standards applicable for patenting genes?

This paper is divided into three parts: Part I provides a brief background on genes, DNA and other key terms used in this paper. Part II provides an overview of the existing law and policy and lays down the framework of analysis of the patents and Part III analyses these granted patents to identify the standards used by the IPO in granting and if the new biotechnology guidelines are a step in the right direction in laying down those standards. The final part concludes the analysis.

DNA, Genes, mRNA, cDNA: What are They?

DNA is basically a long double-stranded molecule with a series of paired bases, with each strand being assembled on a sugar-phosphate backbone and oriented in opposite directions (denoted 5’ to 3’ and 3’ to 5’). The four recurring bases are A, G, C, and T (Adenine, Guanine, Cytosine and Thymine) and the strands are complementary to each other where A complements T and G complements C. A gene is a segment of DNA that encodes for a particular polypeptide. Whenever this corresponding protein has been created in a cell, that gene is said to be expressed.

The first step, i.e., the transcription process mainly involves conversion of the gene into a strand of mRNA. mRNA is similar to DNA except that it is single stranded, and has a Uracil base instead of the

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Thymine. The mRNA is then spliced (split) where the non coding portions are removed and subsequently undergoes a process called translation for creating polypeptides.

The mRNA undergoes a process called translation with the assistance of tRNA and enzymes to form a polypeptide strand. The mRNA strand acts as a code where three bases form a 'codon' and therefore, code for a particular amino acid. In this way, the entire mRNA codes for a polypeptide strand.

Often, the mRNA is reverse transcribed by researchers using an enzyme called Reverse Transcriptase to obtain a complementary sequence called cDNA which is a more workable form and devoid of the non coding portions. The same can be seen in several patent claims. cDNA is nothing but a complement of the mRNA and does not differ significantly in its informational content, though it does not exist as such in nature.


The Patents Act under Section 3(c) specifies that the mere discovery of a scientific principle or the formulation of an abstract theory, discovery of any living thing or non-living substance occurring in nature would not be patentable. Another section that is relevant is 3(i) which states that plants and animals, in whole or any part thereof, other than microorganisms but including seeds, varieties and species and essentially biological processes for production or propagation of plants and animals – cannot be patented.

A gene occurs in nature and should therefore, not be patentable as per Section 3(c). While that is true, it must be noted that there is considerable skill involved in identifying its function, location and isolation. As far as Section 3(i) is concerned, while plants and animals as a whole or in part are unpatentable, would genes be considered a part of a plant or an animal and therefore unpatentable? Secondly, what can make a gene patentable? These are questions that are not answered directly by the Act.

The exclusion of parts of animals or plants ought to be taken seriously as this exclusion is phrases different from the TRIPS provision which allows for exclusion of plants and animals as a whole or in part are unpatentable, would genes be considered a part of a plant or an animal and therefore unpatentable? Secondly, what can make a gene patentable? These are questions that are not answered directly by the Act.

The draft manual in 2005 had an annex specifically dedicated to biotechnological and pharmaceutical inventions. This draft stated that any living entity of artificial origin such as transgenic animals and plants and any part thereof are not patentable. The living entities of natural origin such as animals, plants, in whole or any parts thereof, plant varieties, seeds, species and genes are not considered patentable. Whereas, it also stated that recombinant DNA and plasmids are patentable if there is substantial human intervention.

In the subsequent draft in 2008, there was no such annexure as seen in the previous draft. The explanations under Section 3(j) only describe how microorganisms will be patentable, on the basis of the Dimminaco decision.

However, under the description of unity of an invention: the manual provides the following example -

(a) Gene sequence/amino acid sequence
(b) A method of expressing above sequence
(c) An antibody against that protein/sequence
(d) A kit made from the antibody/sequence

This does give us an impression that a gene is patentable only when it is recombinant and having inventive step and industrial application. The actual Manual of Patent Practice and Procedure which was released in 2011 (ref.10) does not provide any further elaboration on the subject matter. The only provisions that were retained were the ones pertaining to sequence listing that had to be provided by the patentee and the abovementioned bullet list under ‘unity of an invention’. The requirement of substantial human intervention did not find a place in the manual.

This paper thus seeks to examine patent grants where such nucleic acid molecules are involved and to understand, study the scope of the grants and the responses given by the patent office, if any. Subsequently, the paper seeks to analyse the findings in the context of the new guidelines for the examination of biotechnology patents.

Patents Granted by the IPO: Is There a Method in the Madness?

Genetically Stable JEV cDNA based on Japanese Encephalitis Virus

The title of the invention as originally filed states that it relates to the ‘novel genomic RNA’ of the JEV and an infectious cDNA from it. However,
the final granted patent’s title reads as follows ‘Genetically stable JEV cDNA based on Japanese encephalitis virus’. The first examination report does not object to the title of the invention or the first claim that originally read “A genomic RNA of Korean isolate consisting of the entire genome…” - which further went on to describe the nucleotide length and the actual non-translating regions and the regions coding for a peptide.12

This could possibly lead us to conclude that there might have been an objection (however, not to be found in the records accessible on the official website) that led to the amendment of the claims, the title, the abstract to cover the cDNA instead of the RNA. Therefore, it is possible to claim cDNA sequences as a part of a patent in India.

When one specifically examines the patent, the claims essentially cover the entire cDNA (obtained from the genomic RNA of the virus) and the subsequent modifications made to it to obtain a vector and the corresponding RNA transcript, the synthetic JEV obtained, etc. The field of the invention and the background on the other hand states that the invention discloses the full length nucleotide sequence of the JEV strain, the infectious JEV cDNA clones (which can be obtained from the genomic sequence) and the use as a vector after introducing the cDNA in a BAC vector. Here, the creation of the cDNA is a part of the larger process of creating a vector to further create RNA transcripts that can be used to infect other microbial cells, to further produce synthetic JEVs/use as an expression vector. Nevertheless, the patent covers all the nucleotide sequences13 involved in the course of creation of the end products that are of use. This does appear to be a wide coverage given to the patentee.

Comparison of the first independent claim of India, US, Europe for genetically stable JEV cDNA patent is given in table 1.

When one compares this to the final publication by the EPO and the USPTO it can be seen that the scope there is limited to only the vector containing the cDNA sequence and its application as opposed to the cDNA sequence per se.16 While the independent claim is followed by some dependent claims that include other specifics about a vector, it has to be noted that independent claims are not restricted by the presence of the dependent claims.17 Thus, the IPO has, in this instance, given a wider protection than the one given by these other offices. The IPO has, in fact, granted protection to a cDNA sequence though it is not recombinant and a mere derivative of the existing sequence.

An Expression Vector or Cloning Vector Encoding Filarial Parasite Polypeptide

The abstract of this invention states that this is a cDNA sequence as per Sequence ID No. 1 or any functional equivalent, fragment, analogue, mutant or variant thereof. The original claim sought to cover the entire cDNA sequence under Seq. ID No. 1 or any other equivalent coding for a filarial parasite polypeptide, as mentioned in the abstract. The original claims were later narrowed down to an expression vector (i.e., a plasmid/carrier) containing the particular nucleotide sequence for the polypeptide (essentially making it recombinant).

In the first examination report19, the patent office had objected to several claims. This also seems to be a case where the original claims were objected to on the basis of Sections 3(c), 3(n) and even Section 3(j). The claims 1-6 and 17 (which specifically referred to a cDNA of a filarial parasite polypeptide and further delineated the sequences, the parasite, the conditions for hybridization etc.) were subject to a challenge under Section 3(c). This is relevant for our purpose as the patent office objected to a cDNA sequence stating that it was obtained from what was already existing in nature. Subsequent claims based on RNA and the polypeptides were also subject to the 3(c) objection.

<table>
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<tr>
<th>Indian patent</th>
<th>US patent14</th>
<th>European patent15</th>
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<tr>
<td>Genetically stable JEV cDNA based on Japanese encephalitis virus containing a promoter at the beginning of 5’ end of a JEV genomic RNA and a restriction endonuclease recognition sequence at the end of the 3’ end as a runoff site, wherein the cDNA is selected from a group consisting of sequences represented by Seq ID No. 43,44,45,46,47 and 48.</td>
<td>A full-length infectious and genetically stable cDNA clone of Japanese encephalitis virus (JEV), wherein a full-length cDNA of JEV is cloned into a bacterial artificial chromosome (BAC) and an infectious RNA transcript of JEV is transcribed directly from the cDNA clone; wherein the cDNA clone contains a promoter at the beginning of 5’ end of a DNA sequence corresponding to a JEV genomic RNA and a restriction endonuclease recognition sequence at the end of 3’ end of the DNA sequence as a runoff site; and wherein the restriction endonuclease recognition sequence is Xho I or Xba I.</td>
<td>A BAC plasmid comprising a genetically stable full-length cDNA clone of Japanese encephalitis virus (JEV) capable of producing an infectious JEV RNA transcript</td>
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</table>
All these claims were ultimately withdrawn; the grant was ultimately for expression vectors containing the particular sequence (Seq. ID 1) for the polypeptide. While these claims definitely fall outside the purview of Section 3(c), it is unclear if they are entirely non-obvious as ultimately, the particular nucleotide sequence is put inside a vector which is known recombinant DNA technology with no enhanced utility when compared to the prior art.

Polypeptides having Phytase Activity and Polynucleotides Encoding the Same

The invention, according to the abstract, pertains to phytases derived from the organism *Citrobacter gillenii*, the wild type, the recombinant ones and their use in animal feed.

The claims originally referred to an isolated polypeptide having phytase activity having an identity close to 75% with specific sequence IDs provided and the polynucleotide sequences encoding for the same. This was objected to by the IPO where the claims were challenged on the basis that they lacked an inventive step. The office contended that altering prior art to obtain the sequences can be envisaged by a person skilled in the art and that the sequences were in fact taken from a different species of *Citrobacter*. This might confer novelty but not non-obviousness as there are no enhanced properties. Therefore, on one hand, these were derived from a natural source and secondly, the patent office was stating that there were also no enhanced effects. The claims were subsequently amended to state that there was phytase activity and acid stability and having 80% identity with the sequence IDs provided in the claims.

While the change probably also indicates that the sequence had some enhanced effect, the claims are quite broadly termed as far as the 80% homology requirement is concerned. This leaves a wide range of sequences under the purview of the patent as long as they have phytase activity. A stricter, narrower disclosure requirement would make the claims clearer.

An Isolated Nucleic Acid Molecule Coding for Human Akt3

The patent here relates to an isolated nucleic acid coding for a human Akt3 protein (relevant in the process of cell death), the protein sequence and a method of producing it and expressing the sequence in mammalian cells. The expression of the protein prevents apoptotic cell death. The first claim specifically refers to an ‘isolated nucleic acid encoding a human Akt3 protein’ having a particular amino acid sequence as provided, ‘or a substantially similar sequence’. Here, instead of actually providing the sequence ID for the nucleotide sequence, the sequence of the protein is used. This is vague as there are several different nucleotide sequences that can code for one amino acid and it does not specifically pin down the actual sequence encoding the protein. Another important issue with this is that the patent actually covers isolated naturally occurring human Akt3 protein and the coding sequences amongst the other claims that envisage applying it, producing it etc. The first examination report does not object to these claims and it is indeed interesting to note that the fact that it has a human source also has not been objected to by the IPO. This leads to conclude that it is also possible to patent human genes in India.

Comparison between the US/European and Indian claims, is given in table 2.

It is evident that the Indian patent’s claims seem moderately wide or vague where the claims include even a ‘substantially similar’ sequence and other variants of a sequence so claimed. The US patent’s first claim is just for the sequence mentioned in the ID as opposed to covering a wide range of nucleic acids as seen in the European and the Indian patent where the protein sequence is used to define the nucleic acid sequence. While both these jurisdictions have made considerable headway in delineating their policy towards genes, the IPO has not made any open assertions regarding the same.
Table 2—Comparison of claim for an isolated nucleic acid encoding a human Akt3 protein

<table>
<thead>
<tr>
<th>Indian patent</th>
<th>US patent</th>
<th>European patent</th>
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<tr>
<td>An isolated nucleic acid encoding a human Akt3 protein comprising the C-terminal sequence Cys-Gln-Gln-Ser-Asp-Cys-Gly-Met-Leu-Gly-Asn-Trp-Lys-Lys, or a substantially similar sequence.</td>
<td>1. An isolated nucleic acid comprising the nucleotide sequence of SEQ ID NO:1.</td>
<td>An isolated nucleic acid encoding a human Akt3 protein comprising the C-terminal sequence Cys-Gln-Gln-Ser-Asp-Cys-Gly-Met-Leu-Gly-Asn-Trp-Lys-Lys, or a substantially similar sequence.</td>
</tr>
<tr>
<td></td>
<td>2. The isolated nucleic acid according to claim 1, which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. An isolated nucleic acid molecule that hybridizes under conditions of 2.times.SSC/0.1% SDS at 65.degree. C. to said isolated nucleic acid according to claim 1.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. The isolated nucleic acid according to claim 3, which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. The isolated nucleic acid according to claim 1, further comprising a sequence encoding a polypeptide tag.</td>
<td></td>
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**Analysis: Key Findings and the New Guidelines**

Owing to the lack of any guidance in the patent manual, the analysis of actual patents and the responses given by the examiners becomes necessary. The first patent was a situation where the claims that originally referred to genomic RNA were replaced with claims that covered the cDNA version. While the patent, in its subsequent claims describes incorporation of this sequence into a vector/plasmid, thereby making it recombinant – the patent also covers the cDNA sequence simpliciter.

In so far as the second patent is concerned, the claims were objected to, though they were cDNA (though granted in the case of the first patent), on the basis that they were derived from nature. The final claim covered a recombinant vector containing the cDNA with no clear indication of increased effects/utility. The fourth patent is a scenario where a naturally occurring sequence (not the cDNA or a recombinant version) is the subject matter of the first claim. The fifth patent happens to include an isolated human gene within its scope.

In addition to observations regarding the subject matter of the patent, it was also found that patents had phrases such as ‘or a substantially similar sequence’ or ‘75% similarity’ which significantly extends the scope of the patents and in the long run, will hinder innovation and growth.

When the IPO officials were generally asked about their practice with regard to gene patents – it was stated that genes that do occur in nature are not patentable. As far as non-naturally occurring genes are concerned, once there is a delineated function or utility specified, they will become patentable. Also, they mention that the exclusion referring to plants/animals or parts of plants or animals are not applicable at the molecular/cellular level where genes are involved. The latter statement has seen evidence as genes of pigs, human beings even have been subject to patenting. However, the former statement with regard to the exclusion of isolated naturally occurring genes has not been shown to be consistent with the actual practice of the office as isolated gene sequences have also been patented.

In this context, it is relevant to examine the new Guidelines for Examination of Biotechnology Applications for Patent (March 2013). The guidelines are a welcome step in the right direction as they IPO recognizes and states that there is a need to have uniform and consistent practices. However, it is also stated that these are not rules and that the Patents Act, 1970 and the Patents Rules, 2003 will supersede the guidelines.

The guidelines expressly state that sequences isolated directly from nature are not patentable subject matter which is the correct interpretation of
Section 3(c). However, now that the IPO has expressly stated the same, what happens to the previous patents granted that do cover isolated nucleic acid sequences?

Secondly, under the section on expressed sequence tags/gene probes, it is specified that if the use of these sequences is merely as a probe/chromosome marker, it would not be considered as an industrial application whereas if it is used as a probe to diagnose a specific disease, it would be a valid ‘use’ of the sequence. Contrary to this example, a diagnostic method using drug response markers/detection of a gene signature is completely barred under Section 3(i).

Finally, the larger question patenting of human genes, even if they are recombinant, has not been addressed. The illustrative examples also make references to human proteins and recombinant human nucleic acid sequences. This indicates that the IPO finds it acceptable to patent altered human genes. On the other hand, under the section on ‘Inventions contrary to morality…’ it is explained that if the subject matter involves modifying the germline of human beings or any process for preparing genetic materials comprising elements that could cause environmental impact, it would be a violation of Section 3(b).

Furthermore, it must be noted that a lot of human illness diagnosis can be done by gene markers which are complements and based on human genes. A clear stand on patentability of human genes or diagnostic methods using those genes is important for an industry that will choose to invest based on such considerations.

Conclusion

As observed by Judge Sweet in Myriad Genetics, most companies achieve remarkable results by identifying the actual functionality of a gene, the mutations that might cause a disease etc. However, these ought not to be subject to a monopoly as these are in existence in nature and are a discovery. Furthermore, the application of the discovery in the form of diagnostics (using probes), comparative analysis (as seen in the BRCA patents) and therapy is well known. Sequencing a particular sequence is very well known in the art and is regularly done. However, one must know the initial few nucleotides to sequence and scientists often try to identify a particular gene as opposed to random sequencing – and this requires ingenuity and effort. As observed, a lot of these patents cover an isolated sequence, it being placed in a vector and put into a host cell to express the desired characteristic or protein/to use the sequence to diagnose using a kit having a probe that is nothing but the complementary sequence, etc. Ultimately, their functionality is not radically different from that which is present in nature and, sometimes that is also the whole purpose of the invention – to diagnose the existence of a sequence and that requires one to use that which exists in nature/the complement.

Treatment of this area of technology probably requires greater thought than what is being employed currently. Identification, after careful effort, (if it was not obvious to identify) of the function of an existing gene should be rewarded with something other than a monopoly. As a monopolization of a nucleotide sequence will only affect research and innovation surrounding the usage of that sequence, alternative incentive mechanisms must be in place for such innovations. An example of such an incentive mechanism is that suggested by Thomas Pogge where an international fund is used to reward inventors on the basis of the effect, benefits of the drug/invention on the people.

There is a need to ensure that there is a consistency in granting patents. Expansive patents, incorrectly granted will only hinder development and innovation.

As far as the specific issue surrounding human genes is concerned, one ought to understand that patenting human genes will only restrict better diagnoses, health care and development. In the event that a patent has to be granted, it ought to be for a sequence (non-natural) showing enhanced effects or benefits when compared to that in nature or for a sequence having a novel application. The law must, therefore, better delineate the scope of the exclusions and also the standards for patenting a biotechnological invention. If patenting human genes is still deemed absolutely necessary, one must also be stringent with regard to the scope of the claims being granted in order to ensure that the monopoly is not extended beyond reasonable limits.

Acknowledgment

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References


3 The parts of the sequence that do not code for any particular protein.

4 A polypeptide strand is essentially a sequence of amino acids bound together. Multiple strands often form a protein molecule (with or without other additions).


6 Article 27.3 of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) treaty - Members may also exclude from patentability: (b) plants and animals other than microorganisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes. However, Members shall provide for the protection of plant varieties either by patents or by an effective sui generis system or by any combination thereof. The provisions of this subparagraph shall be reviewed four years after the date of entry into force of the WTO Agreement.


8 This particular sentence has a very similar wording to that of Section 3(ii) which also leads us to wonder whether the Office implied that genes were actually part of a plant and therefore, unpatentable?


12 A genomic RNA of the Korean JEV Isolate consisted of full length RNA genome in 10,968 nucleotide length, in which the genomic RNA are composed of 95-nucleotide 5’ non translated region (NTR) followed by a 10,299-nucleotide single polypeptide coding region and terminated by a 574- nucleotide 3’ NTR.

13 Including the ones derived directly from the natural occurring genome without any modifications.


17 Kahrl R C, Patent Claim Construction (Aspen Publishers Online, 2001), p. 4-40.2. ‘The independent claim is not whittled down by the dependent claims and can stand alone even if the dependent claims are struck down. Any infringement of the independent claim is sufficient and one need not look to the dependent claims to verify the same. Therefore, the scope of the independent claim is very relevant while examining the scope of the invention.


20 None mentioned specifically in the specification to that effect.


23 Cirera S et al., An isolated nucleic acid (na) molecule comprising an allele of a genetic polymorphism linked to resistance to enterotoxigenic Escherichia Coli (ETEC), Indian Patent No. 244118 (University of Copenhagen) (18 November 2010).


26 First Examination Report 17/10/06 in Appl IN/IPC/2001/1388/CHE.


29 The US position on genes was clear till very recently where the decision in Myriad questioned the patentability of isolated genes. The Article 5.2 EU Directive on Biotechnology expressly permits patents on genes isolated from nature as long as it is isolated by a technical process; Kamstra G et al., Special Report on Patents on Technological Invention – The EC Directive (London: Sweet &Maxwell), 2002, p. 36.

30 Interview with a Deputy Controller of Patents.

31 Interview with Examiners of Patents. The interviewees were asked a series of questions concerning 1. Patentability of genes in India 2. Patentability of isolated genes/DNA 3. Scope of Section 3(1) and whether genes are covered in that exclusion 4. If answer to 1 is in the affirmative, what has to be established by a patentee.

32 Association of Molecular Pathology v Myriad Genetics, US SDNY 09 Civ. 4515, http://www.aclu.org/files/assets/2010-3-29-AMPvUSPTO-Opinion.pdf. It must be noted that this decision was overturned in appeal before the Federal Circuit.