

## GLOBAL GENETIC RESOURCES

# Marine Biodiversity and Gene Patents

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The October 2010 Nagoya conference of the United Nations (UN) Convention on Biological Diversity (CBD) saw establishment of the protocol for improved access to genetic resources and fair and equitable sharing of benefits arising from their utilization (1). This allows effective implementation of provisions in Article 15 of CBD regulating access to genetic resources through mutual agreements between countries of origin of resources and those acquiring them. Yet the principle of sovereign rights of states underlying the CBD does not apply to Marine Genetic Resources (MGRs) in Areas Beyond National Jurisdiction (ABNJs), international waters encompassing 65% of the ocean; thus, no consensus could be reached to include them in this new protocol.

Although recent CBD efforts tackled terrestrial genetic resources and those distributed in Exclusive Economic Zones (EEZs), where states hold rights over marine resources, the increasing industrial use of MGRs, particularly those extracted from ABNJs, occurs in a legal void because of the lack of an internationally accepted framework to ensure ethical and equitable access, and sharing of benefits (2–6). We describe imbalances in ownership of patent claims on MGRs and propose steps toward addressing gaps in governance.

## Ownership of Patent Claims

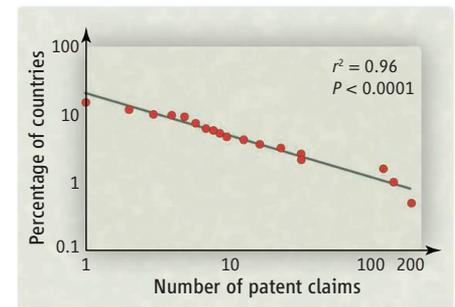
Marine biodiversity contains most phylogenetic and genomic diversity on Earth (e.g., 34 of 36 animal phyla hitherto described versus 17 on land). Progress in marine and molecular technologies has facilitated “bioprospecting,” with the number of patent claims associated with genes of marine organisms growing at 12% per year (2). Although patenting does not always result in effective exploitation, the existence or lack of patent claims and their relative distribution offer a rea-

sonable ranking of countries’ accessing of resources.

We screened records in the patent division of GenBank (7) to extract international claims valid in all countries subscribing to the World Trade Organization (WTO) agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and deposited in the World Intellectual Property Organization (WIPO). Among 677 international claims of marine gene patents deposited between 1991 and 2009, 8648 sequences from 520 species were found. Gene patent claims from marine organisms make up only 2% of the WIPO gene patents (table S1), whereas claims associated with human genes dominated (35%), closely followed by the most frequently raised cultivars (wheat, rice, maize, and barley).

Claims associated with marine genes originate from only 31 of the 194 countries in the world. Ten countries own 90% of the patents deposited with marine genes, with 70% belonging to the top three (see the table). These 10 nations represent only about 20% of the world’s coastline, but they benefit from access to advanced technologies required to explore the vast genetic reservoir of the oceans. The power law describing the distribution of “ownership” of MGRs across countries (see the figure) (table S1), fits the Pareto principle describing the “rich get richer” distribution of wealth in society (8–10). Benefits derived from application of MGR patents may fuel further investment

Ten countries account for 90% of patent claims associated with marine genes, including some from international waters.



**Patent claims associated with genes of marine origin.** Cumulative distribution of patent claims showing the proportion of countries (*y* axis) at the origin of *x* or more patent claims. See SOM.

in marine bioprospecting (11, 12), broadening the gap in oceanographic and biotechnological capacities among countries. A similar distribution for patent claims associated with human genes or key plant crops (table S1 and fig. S1) suggests differential access to molecular technologies as the main advantage. This inequality calls for policies targeting capacity-building in countries that lag behind and stresses the need for an internationally recognized framework governing MGRs.

## The Legal Gap

With 95% of claims filed after 2000, the growth of marine gene patents is a recent phenomenon, but it has matured well beyond “proof of concept.” The global market for marine biotechnology was estimated at U.S. \$2.4 billion in 2004, with estimated average growth of 5.9% per year from 1999 to 2007 (13). Marine molecules include cancer- and HIV-fighting agents representing \$1 billion and \$125 million, respectively, annual markets in 2005 (5). Most MGRs are derived from organisms sampled in territorial waters. However, source organisms can be shared by several different EEZs and/or may disperse across international waters during their life cycles. Exploration of extreme ecosystems, such as hydrothermal vents and polar oceans, mostly located in ABNJs, has disclosed a broad spectrum of molecules of biotechnological interest (2, 6). Examples include thermostable enzymes for molecular biology or the food industry (2, 5) and amylase isolated from a black smoker hydrothermal vent used for biofuel

PATENT CLAIMS FOR A GENE OF MARINE ORIGIN WITH SOURCE	
Country	Marine organism patent claims
USA	199
Germany	149
Japan	128
France	34
United Kingdom	33
Denmark	24
Belgium	17
Netherlands	13
Switzerland	11
Norway	9

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production with an annual market value of about \$150 million (5).

The scope for bioprospecting of MGRs surpasses national jurisdictions, a situation that does not apply to terrestrial resources. Frameworks in place for regulating the use of genetic resources (e.g., the UN Food and Agriculture Organization and CBD) were agreed on in the context of sovereign rights of states and therefore apply only to land areas and EEZs. The International Seabed Authority, a body within the UN Convention on the Law of the Sea (UNCLOS), manages activities linked to mineral resources in the seabed and subsoil in ABNJs. It is not clear why parties' agreement on mineral resource governance under UNCLOS was not extended to a similar framework for governance of genetic resources. Thus, lacking regulation, MGRs in ABNJs are accessed on a "first-come, first-served" basis (2, 5, 14).

The applications that MGRs offer to benefit humankind (2, 5, 15, 16) emphasize the need for an equitable solution. The issues of conservation and fair exploitation of oceans are increasingly present on the UN agenda to progress toward a governance framework for biodiversity in ABNJs (4). Although nations recognize the urgency of facilitating protection, the process is stalled by the lack of agreement regarding the status and governance of MGRs (4). One group of nations, including developing countries, proposes that MGRs in international waters should be considered common heritage of humankind, whereas another wishes to maintain the status quo of "freedom" of exploitation. These positions emerged in Nagoya where some states' proposal to include ABNJs was not retained in the final protocol.

### Prospects

The governance framework for MGRs in ABNJs will require a multifaceted approach to improve coordination of the protection of biodiversity and of intellectual property (IP) regimes to promote equity. Of the genes associated with WIPO patents, 17% are of unknown taxonomic origin, and almost none of the patent claims examined disclosed the geographic origin of material. Although states compromised in promoting establishment of sharing agreements under CBD, this is not a legally binding agreement and so does not imply that companies will necessarily comply. A sustainable CBD regime of access and benefit-sharing of genetic resources, terrestrial or marine, would profit from complementary efforts from the WTO to require geographic and taxonomic origin of resources associated with a patent under

TRIPS, allowing identification of the country (or countries) or geographical areas of origin of the genes involved. This would support application of Article 15 of CBD and the associated Nagoya Protocol for sharing between countries at the origin of resources and those exploiting them. This may also help ease constraints on bioprospecting for academic and environmental research that stem from national laws (e.g., Brazil) (17) protecting against "biopiracy" of resources.

Addressing inequality in exploitation of MGRs requires an international consensus over MGR status. The UN Universal Declaration on the Human Genome and Human Rights recognized that the human genome is a common heritage of humankind. Yet this has not prevented the patenting of human genes or given special status for sharing of benefits from those patents (18). But within the UNCLOS, there is specific meaning and significance of common heritage applied to mineral resources of the seabed. If this meaning could be applied to MGRs, they, too, could be managed by the International Seabed Authority. Alternatively, a new authority could be established that would benefit from the joint expertise of the CBD regarding conservation measures and access and benefit-sharing protocols and from the International Seabed Authority large-scale management of resources in vast areas beyond national jurisdictions, as well as the promotion of knowledge transfer.

MGRs should be regulated by an internationally negotiated regime that includes payment of fees to a common fund when exploiting resources, or any option promoting access and benefit-sharing. Such a regime may encompass other genetic resources, as inequality in the appropriation of biological resources through gene patents is not unique to MGRs but applies also to human genes and cultivars as well. Recent court cases in North America and the UK (19) involving human genes have challenged the legal basis for patenting genes that exist in nature. Also, patenting has been claimed to discourage rather than promote scientific progress (16, 20). Solutions are emerging, involving patent pools (21–23) to facilitate access to new technologies and more equitable use and benefits from IP rights. The idea of licensing all patents in a pool collectively, and sharing risks and royalties, such as was recently applied in HIV research (23), may save time and money for both claimers and users, and facilitate access to the information.

A patent pool for genetic resources managed by a UN authority could ensure fair reward of research efforts and equitable shar-

ing of benefits derived from resources that we believe should be considered a common good. In turn, coordination of instruments required to address governance of MGRs may inspire solutions for IP and access and benefit-sharing around other gene patenting, including human ones. We must pursue a framework in which exploration of marine life, and the biotechnological potentials it contains, serve to improve the lives of all humans rather than generate wealth for a few.

### References and Notes

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### Supporting Online Material

[www.sciencemag.org/cgi/content/full/331/6024/1521/DC1](http://www.sciencemag.org/cgi/content/full/331/6024/1521/DC1)

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Supporting Online Material for  
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Materials and Methods  
Fig. S1  
Table S1 References

**Other Supporting Online Material for this manuscript includes the following:**  
(available at [www.sciencemag.org/cgi/content/full/331/6024/1521/DC1](http://www.sciencemag.org/cgi/content/full/331/6024/1521/DC1))

Data file of patent list as an Excel file

## Supporting Online Material

### Materials and methods

#### *Data sources and processing*

Data on patented DNA sequences were obtained from the PAT division of GenBank (*S1*) available from NCBI's FTP site (<ftp://ftp.ncbi.nih.gov/genbank/>). All the files with names starting with "gbpat" were downloaded and decompressed in a local directory. GenBank formatted records are plain text files containing different fields as shown in this example:

```
LOCUS           A00001                   335 bp   DNA       linear   PAT 11-MAY-2001
DEFINITION     Cauliflower mosaic virus satellite cDNA.
ACCESSION     A00001
VERSION       A00001.1   GI:58418
KEYWORDS      .
SOURCE        Cauliflower mosaic virus
ORGANISM      Cauliflower mosaic virus
               Viruses; Retro-transcribing viruses; Caulimoviridae; Caulimovirus.
REFERENCE     1   (bases 1 to 335)
AUTHORS       Baulcombe,D.C., Mayo,M.A., Harrison,B.D. and Bevan,M.W.
TITLE         Modification of plant viruses or their effects
JOURNAL       Patent: EP 0242016-A 1 21-OCT-1987;
               AGRICULTURAL GENETICS COMPANY LIMITED
FEATURES      Location/Qualifiers
               source          1..335
                               /organism="Cauliflower mosaic virus"
                               /mol_type="unassigned DNA"
                               /db_xref="taxon:10641"
               misc_feature   1..335
                               /note="satellite DNA"
ORIGIN
      1 gttttgtttg atggagaatt gcgcagagg gttatatctg cgtgaggatc tgtcactcgg
      61 cgggtgggga tacctccctg ctaaggcggg ttgagtgatg ttccctcgga ctggggaccg
      121 ctggcttgcg agctatgtcc gctactctca gtactacact ctcatttgag cccccgctca
      181 gtttgctagc agaaccggc acatggttcg ccgataccat ggaatttcca aagaaacct
      241 ctgttaggtg gtatgagtc tgacgcacgc agggagaggc taaggcttat gctatgctga
      301 tctccgtgaa tgtctatcat tctacacag gacc
//
```

The relevant fields, ACCESSION, DEFINITION, ORGANISM, AUTHORS, TITLE, and JOURNAL (which was parsed to yield different fields for Patent Application Number and patent date), as well as number of base pairs, were extracted from these files and translated into MySQL queries (*S2*) using Perl (*S3*) scripts written for this purpose (source code for non-commercial purposes is available from the author [txetxu@imedea.uib-csic.es](mailto:txetxu@imedea.uib-csic.es)). In addition to the fields mentioned above, a unique 32-bit cyclic redundancy check (CRC) signature was calculated for each sequence, which was used to filter out redundant sequences reported under different patent authorities through the database. The resulting MySQL equivalent of the record shown above was:

```
INSERT INTO gbpatents (definition, source, organism, taxonomy, authors, title,
patent, seqnum, patentdate, owner, patentyear, locus, length, type, unique_seq_id,
date) values ( "Cauliflower mosaic virus satellite cDNA. ", "Cauliflower mosaic
virus ", "Cauliflower mosaic virus", "Viruses; Retro-transcribing viruses;
Caulimoviridae; Caulimovirus. ", "Baulcombe,D.C., Mayo,M.A., Harrison,B.D. and
Bevan,M.W. ", "Modification of plant viruses or their effects", "EP 0242016-A", 1,
"21-OCT-1987", " AGRICULTURAL GENETICS COMPANY LIMITED ", 1987, "A00001", 335,
"DNAlinear", "4236116324", "11-MAY-2001");
```

The MySQL database corresponding to the PAT division of GenBank release 175 (December 2009) contained more than 11.8 million records of DNA. Identical sequences reported under different patent authorities were detected by means of the unique CRC code generated during

import in order to filter out redundancy in the database. Using this approach, a total of 6,722,681 sequences in the MySQL database were unique.

The list of named species in the MySQL database was extracted, and the resulting name list was sorted and cleaned up manually to eliminate obvious spelling variants, typos, strain names, or numbers. This “clean” list of names was imported into a new field of the MySQL database generated from the GenBank data, matching the “clean” names to the original names. Finally, the filtered list of species names was tagged to reflect the marine or terrestrial origin of each species. Information about the marine or terrestrial origin of each species was derived mainly from academic journals found in Google Scholar and the United Nations (UN) Educational, Scientific, and Cultural Organization–Intergovernmental Oceanographic Commission “UNESCO IOC Register of Marine Organisms” (URMO) available at (S4). A new field containing the information about the “marine” or “terrestrial” origin of each species was also added to the database. The resulting database allowed us to create specific lists of marine versus terrestrial patents and to extract patent information relevant to marine patents. It is worth noting that the same patent applications may encompass different sequences belonging to different organisms.

The initial MySQL database contained sequences belonging to 5120 named species, which had been declared in 122,658 patents deposited in patent offices worldwide. As our main propose was to infer the appropriation of genetic resources worldwide, the database was trimmed to retain only the international claims valid in all countries subscribing to the World Trade Office Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and deposited in the World International Property Organization (WIPO). This was performed by extracting a subset of the original database containing only those claims with patent number starting with “WO.” This subset, which we will call the PAT-WIPO database, contained only international claims and was used in all subsequent analyses. The PAT-WIPO database contained a total of 4,865,795 sequences included in 31,602 patents. A large fraction of these patent claims corresponded to sequences of synthetic constructs, viruses, viroids, plasmids, and transposons, whereas 17% of these claims did not disclose any information regarding the taxonomic origin of the sequences they were based on. Of the claims in the PAT-WIPO database (19,103), 60% could be related to 1,964,623 unique sequences belonging to 3901 named species of cellular organisms. Only a small fraction of the gene patents in the PAT-WIPO database corresponded to marine species, a total of 677 claims associated to 8648 sequences belonging to 520 marine species.

In addition to marine organisms, additional sets of patent claims were also retained for comparative analysis, including sequences from human (*Homo sapiens*, 11,146 claims) and the main cultivars wheat (232 claims), rice (447 claims), maize (489 claims), and barley (146 claims) (Table S1). These cultivars represent about 90% of worldwide grain production according to the UN Food and Agriculture Organization (FAO) (S5):. The estimates, for tons produced in 2009, are as follows: wheat–*Triticum* spp. (682); ric –*Oryza sativa* (679); maize–*Zea mays* (817); and barley–*Hordeum vulgare* (150) (S5).

The list of WIPO codes identifying each patent claim was then used to extract statistics from the WIPO database Patenscope (S6) as to the country of origin of patent claims. Briefly, lists

of patent numbers were generated by querying our PAT-WIPO database, the resulting list was reformatted in a text editor as one line containing all the patent numbers separated by OR (WO/2006029735 OR WO/2005063971 OR WO/02070674...) and subsequently submitted to Patentscope by using the Web form at (S7). Although the initial form admits up to 500 patent codes, subsequent statistical analyses are limited to handle queries no longer than about 250 to 300 claims per query. Thus, longer queries were split into two or three separate queries. In addition to marine gene patents, we extracted the country of origin of patents related to wheat, rice, maize, and barley and a subset of 500 randomly sampled claims from the listing of the ~11,000 claims associated with human genes.

The simple distribution of the number of patents per country was extremely skewed; the log-scale inverse cumulative distribution (Fig. S1) resulted for marine organisms, humans and the four crops studied, in typical power law distributions.

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**Table S1.** Country of origin and number of patent claims associated with sequences from marine organisms, humans, or crops (wheat, rice, maize, or barley). Numbers in red indicate the top 10 countries for each class of patent.

Countries	Marine organisms	Human*	Wheat ( <i>Triticum</i> )	Rice ( <i>Oryza</i> )	Maize ( <i>Zea</i> )	Barley ( <i>Hordeum</i> )	Total
USA	199	156	64	114	239	24	796
Germany	149	106	73	96	95	62	581
Japan	128	82	12	89	11	16	338
Belgium	17	15	25	62	51	14	184
United Kingdom	33	39	15	23	28	13	151
France	34	28	12	9	27	2	112
Switzerland	11	17	12	17	13	3	73
Denmark	24	10	3	2	1	5	45
Netherland	13	7	1	8	4	2	35
Canada	6	7	7	5	4	1	30
Israël	6	10	2	3	3	2	26
Sweden	5	7		3	3	1	19
Italy	7	3	1	5	1		17
Spain	5		4	2	5		16
Norway	9	3					12
India	8			3	1		12
Austria	5	1		1	1		8
Iceland	4	3				1	8
Australia	1	2		2	1		6
China	1			1	1		3
Ireland	1	2					3
Cuba	2						2
Russian Federation	2						2
Argentina				1			1
Chile	1						1
Czech Republic	1						1
Finland	1						1
Hungary			1				1
Cayman Islands		1					1
Lithuania		1					1
Monaco	1						1
Madagascar	1						1
Singapore	1			1			2
Turkey	1						1
Total	677	500	232	447	489	146	2491
Percentage of countries (of 194 total on Earth) accounting for ~90% of patent claims	4.64	4.64	4.64	3.09	3.61	3.61	3.61

\*A subsample of 500 patent claims was randomly extracted from the subset of 11,146 claims associated with human sequences to be analyzed in Patentscope.

**Figure S1.** Inverse cumulative distributions of patent claims associated with genes (on a log-log scale with  $y$  being the proportion of countries (out of 194 total recognized on Earth) at the origin of  $x$  or more patent claims) depicting power law with significant correlation coefficients ( $r^2$  ranging from 0.90 to 0.97,  $P < 10^{-3}$  in all cases) for claims with marine organisms, humans, wheat, rice, maize and barley genes. Regressions and figures were derived from numbers detailed in Table S1.

