European Journal of Human Genetics (2011) 19, 1114–1121

www.nature.com/ejhg

ARTICLE

Impact of gene patents on diagnostic testing: a new patent landscaping method applied to spinocerebellar ataxia

Nele Berthels[1], Gert Matthijs*[,2] and Geertrui Van Overwalle[1,3]

Recent reports in Europe and the United States raise concern about the potential negative impact of gene patents on the freedom to operate of diagnosticians and on the access of patients to genetic diagnostic services. Patents, historically seen as legal instruments to trigger innovation, could cause undesired side effects in the public health domain. Clear empirical evidence on the alleged hindering effect of gene patents is still scarce. We therefore developed a patent categorization method to determine which gene patents could indeed be problematic. The method is applied to patents relevant for genetic testing of spinocerebellar ataxia (SCA). The SCA test is probably the most widely used DNA test in (adult) neurology, as well as one of the most challenging due to the heterogeneity of the disease. Typically tested as a gene panel covering the five common SCA subtypes, we show that the patenting of *SCA* genes and testing methods and the associated licensing conditions could have far-reaching consequences on legitimate access to this gene panel. Moreover, with genetic testing being increasingly standardized, simply ignoring patents is unlikely to hold out indefinitely. This paper aims to differentiate among so-called 'gene patents' by lifting out the truly problematic ones. In doing so, awareness is raised among all stakeholders in the genetic diagnostics field who are not necessarily familiar with the ins and outs of patenting and licensing.
European Journal of Human Genetics (2011) **19,** 1114–1121; doi:10.1038/ejhg.2011.109; published online 3 August 2011

Keywords: gene patents, genetic testing, patent licensing, spinocerebellar ataxia

INTRODUCTION

Issues surrounding gene patents and access to health care services have been a subject of wide debate for quite some time.[1–8] With genetic testing moving into mainstream medicine[4,9,10] and with ongoing efforts to harmonize and to set standards for genetic testing in Europe and elsewhere,[11,12] patenting and licensing issues regarding genetic testing continue to spur further attention from all parties involved. Opponents still question the legitimacy of patents claiming genes, and further argue that the availability of alternative testing is squashed while costs of testing could increase without guaranteeing good quality. Gene patents are perceived as hampering both innovation and access of patients to adequate genetic testing.

At present, solid empirical data to support statements on the impact of gene patents on diagnostic testing services are still scarce. Previous studies mainly considered gene patent documents based on keyword search strategies, allowing the identification of patents actually claiming genetic material (eg, DNA). However, any interpretation of the real subject matter of the claims in the patent document is often lacking[13,14] and many of the listed patents are often more relevant to the development of therapeutics than to genetic diagnostics.

The exclusive right granted to a patentee entails a right to prevent or exclude others from making, using, selling, offering for sale or importing the claimed invention without authorization of the patentee,[15] during a limited period of time and within a certain territory. A patent does not impose an obligation to the patentee to enforce his rights. Rather, a patent offers an opportunity to the patentee to undertake action against infringers, ranging, for example, from sending cease-and-desist letters to starting a lawsuit, or to provide a permission or license to lawfully use the patented invention. The possible curtailing effect of patents on the use of a patented invention by third parties thus largely depends on the degree and way of enforcement of the patent by the patentee, and on the availability and terms of licensing deals. Patents not actively enforced, or patents licensed out under reasonable conditions, seldom cause great concern regarding the use of the patented technology. Recent studies discuss the effect of gene patent enforcement in the United States[1,8] and the attitude of clinical-genetic laboratories[2] on access and use in more depth.

The present study reports on patenting and licensing practices related to genetic diagnostics of spinocerebellar ataxias (SCAs), an important group of neurogenetic diseases affecting patients worldwide.[16] Within the autosomal, dominant SCAs, about 30 monogenic subtypes are currently distinguished through genetic mapping, with the causative gene being identified for 16 subtypes (Supplementary Table 1). The most accurate way to diagnose this genetic disease is molecular genetic testing, using a gene panel that typically includes individual assays for the five most prevalent SCA subtypes (SCA1, SCA2, SCA3, SCA6, SCA7) and aiming to detect the pathogenic CAG-repeat expansion in one of these genes.[17]

[1]Centre for Intellectual Property Rights, Faculty of Law, University of Leuven, Leuven, Belgium; [2]Centre for Human Genetics, Faculty of Medicine, University of Leuven, Leuven, Belgium; [3]Tilburg Institute for Law, Technology and Society, Faculty of Law, Tilburg University, Tilburg, The Netherlands
*Correspondence: Professor G Matthijs, Center for Human Genetics, University of Leuven, Herestraat 49, Leuven, 3000, Belgium. Tel: +32 16 346 070; Fax: 32 16 346 060; E-mail: gert.matthijs@uz.kuleuven.be
Received 1 April 2009; revised 13 April 2011; accepted 11 May 2011; published online 3 August 2011

We developed a patent categorization method to rank European and US patents according to their impact on SCA testing. Our method facilitates the assessment of actual hampering effects of granted patents towards products and methods used in diagnostic testing, and could similarly serve to assess freedom to operate in other fields of technology.

METHODS

Patent search

Patents related to *SCA* genes and genetic diagnostics were extensively searched in both public and commercial patent databases, largely as described earlier[18] As claims may change over time (between filing and granting), the patent information provided here was last updated on March 1, 2010.

Legal status of patents and patent applications

The legal status of European and international PCT (Patent Cooperation Treaty) patent documents was checked on the European Patent Offices's website (http://www.epoline.com). The legal status of US patent documents was checked on the US Patent and Trademark Office's website (http://www.uspto.gov) and its Patent Application Information Retrieval website (http://portal.uspto.gov/external/portal/pair).

Claim analysis

Claims were analyzed and interpreted in light of the patent specification. We evaluated the reasonable scope of the pending/granted claims based on the context (eg, the claim itself, other claims, the description, drawings, file wrapper). In Europe, Art. 69 of the European Patent Convention (EPC) and its Protocol form the basis for such interpretation, striving for a balance between a fair protection for the patentee and a reasonable degree of certainty for third parties. In the United States, basis for claim interpretation can be found in the US Utility Patent Act §112, asking for a 'clear written description' and the 'best mode for carrying out the invention'.

Licensing policy

Telephone interviews were made to unravel licensing policies of Athena Diagnostics (Boston, MA, USA), Baylor College of Medicine (Houston, TX, USA) and the Research Development Foundation (Carson City, NV, USA).

Patent thickets

In order to evaluate whether a patent thicket exists or could be emerging in the field of SCA genetic diagnostic testing in Europe or in the United States, all granted patents currently in force and all patent applications at present under examination in Europe and the United States, were listed in this study.

RESULTS

The patent categorization method

A patent categorization method has been developed to weigh the impact of patents on genetic diagnostic services for SCA (Figure 1). A patent is considered to be hampering access to a genetic diagnostic test if the relevant patent (step 1) is valid in the country of interest (step 2), claims an essential part of the genetic test (step 3) that cannot be circumvented (step 4), is actively enforced and is not licensed at a reasonable cost (step 5).

Patent search (step 1)

Keyword searches in the title, abstract, and claims of patents in relevant International Patent Classification (IPC) classes yielded over 100 patent documents per SCA subtype, identifying the respective SCA gene. Despite careful drafting of Boolean keyword strings, the occurrence of semantics as well as the obfuscation of claim language occasionally found in patent documents made it necessary to check each patent document individually for relevance to the study. Manual processing of the patent claims, as opposed to automated patent analyses, remains the most optimal albeit time-consuming approach.

The searches yielded 19 patent families related to SCA genetic testing (Table 1). The assignees thereof are geographically distributed, notably in Europe (FR, NL), the US and Asia (JP, IN, KR), reflecting the worldwide prevalence of SCA among all ethnic groups. Within each patent family, we considered the patent documents filed at the EPO, the USPTO and the World Intellectual Property Organisation (WIPO).

A set of 47 patent documents comprising 25 US, 9 EP and 13 PCT patent documents was selected for further study.

The majority of assignees (80%) are public institutions, at present the sole type of assignee in Europe, US and India. The remaining assignees (20%) are private entities in Japan and Korea (Supplementary Figure 1).

Legal status of patents and patent applications (step 2)

The duration and the territorial scope of patents are two essential elements often overlooked by non-patent practitioners. The relevance of a patent can therefore be largely misjudged. Patents can be withdrawn or lapse during or after prosecution, for example, through non-payment of maintenance fees. Checking whether a patent is in force in the country of interest is therefore a prerequisite to any freedom-to-operate analysis or patent landscaping effort assessing current patent obstacles.

Because of a different interpretation of the 'unity of invention' concept in the United States compared with Europe (Art. 82 EPC, 35 U.S.C. §121), product and method claims are usually split over different patents in the United States. As a result, patent families often contain more US patent documents. Therefore the relative number of patents is used to compare European and United States data, meaning that results have been averaged out to count one US patent per patent family (Figure 2).

In Europe, only one SCA patent has been granted and is still valid. This patent, EP 1.015.628 entitled 'Large scale genotyping of disease and a diagnostic test for spinocerebellar ataxia type 6' and owned by the Research Development Foundation (USA), is related to SCA6 testing (also see below). In the United States, a total of 22 SCA patents have been granted of which 20 are still in force. In patent family 9 related to SCA3, US patent 6.124.100 lapsed due to non-payment of maintenance fees, and in patent family 13 related to SCA6, US patent 6.825.332 expired for the same reason (Table 2, Supplementary Table 2).

Differences in patent strategies of applicants and examination approaches of the patent offices in Europe and the United States could explain the current legal status of SCA patent applications.[13] In Europe, eight patent applications were filed, which ended up 'dead': six patent applications are withdrawn or deemed to be withdrawn and two patent applications have been refused, namely EP 1.311.667 of patent family 7 related to SCA2, and EP 932.677 of patent family 13 related to SCA6 (Figure 2, Table 2, Supplementary Table 2). In the United States, three patent applications were filed, which have not led to a patent (yet): one application is still under examination, namely US 2003-0235841 (A) and two patent applications are abandoned, namely US 2005-0032083 (A) and US 2005-0090658 (A) (Figure 2, Table 2, Supplementary Table 2).

Claim analysis (step 3)

The third step in patent categorization involves a meticulous analysis of the claim scope in order to determine the relevance for genetic testing. The most subjective part of any patent analysis is probably the interpretation of the claims in light of the description of the invention, as neither a strict, literal reading of the claims, nor a loose interpretation of the claims as mere guidelines, is appropriate. Rather, a fair

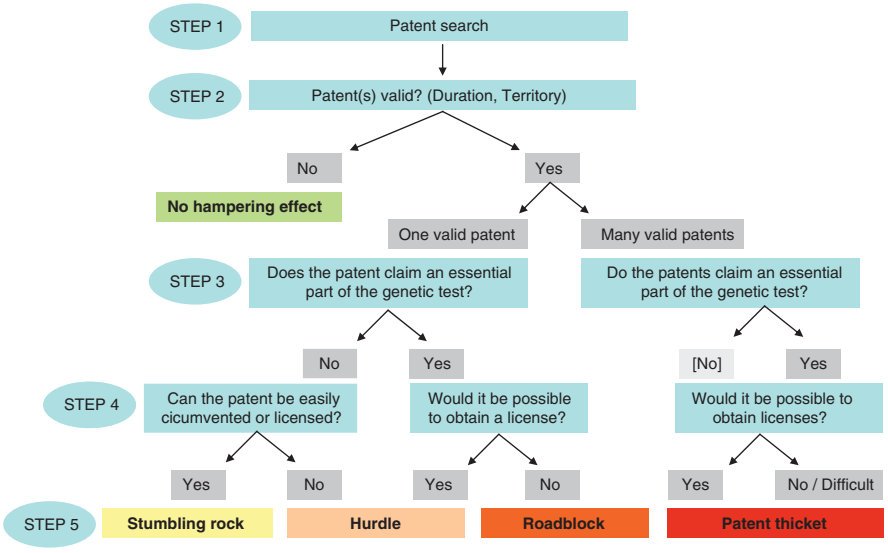

Figure 1 The patent categorization method for the assessment of hampering effects of patents related to genetic diagnostics. The metaphors of step 5 are modified from http://GenericsWeb.com.

Table 1 Overview of SCA patent families

SCA subtype	*Patent family*	*Patent assignee (nationality)*	*Title*
SCA1	1	Univ. Minnesota (Rochester, MN, USA)	Gene sequence for SCA1 and method for diagnosis
SCA2	2	SRL, Inc. (Tokyo, Japan)	Method for diagnosing SCA2 and primers therefore
	3	CNRS and INSERM (Paris, France)	Neurodegenerative disease treatment and diagnostic means
	4	Cedars Sinai Medical Center (Los Angeles, CA, USA)	Nucleic acid encoding SCA2 and products related thereto
	5	SRL, Inc. (Tokyo, Japan)	cDNA fragments of gene causative of SCA2
	6	CSIR (New Dehli, India)	Method of detecting of allelic variants of *SCA2* gene
	7	Cedars Sinai Medical Center (Los Angeles, CA, USA)	Transgenic mouse expressing a polynucleotide encoding a human ataxin-2 polypeptide
	8	Cedars Sinai Medical Center (Los Angeles, CA, USA)	SCA2 knockout animal and methods of use
SCA3	9	Samsung Fine Chemicals Co. (Ulsan, Korea)	Diagnostic method and kit for neuropsychiatric diseases using trinucleotide repeats sequence
	10	Ono Pharmaceutical Co (Kyoto, Japan)	DNA sequence encoding the Machado-Joseph disease gene and uses thereof
SCA5	11	Univ. Minnesota (Rochester, MN, USA)	Identification of a gene associated with SCA5 and methods of use
SCA6	12	RDF (Carson City, NV, USA)	Large scale genotyping of disease and a diagnostic test for SCA6
	13	Rijksuniversiteit Leiden (Leiden, the Netherlands)	A gene related to migraine in man
SCA7	14	Univ. Minnesota (Rochester, MN, USA)	*SCA7* gene and methods of use
SCA8	15	Univ. Minnesota (Rochester, MN, USA)	SCA8 and methods of detection
SCA10	16	Baylor College of Medicine (Houston, TX, USA)	DNA test for SCA10
SCA12	17	Johns Hopkins Univ. (Baltimore, MD, USA)	Expansion of a novel CAG repeat in 5′ region of PPP2R2Bβ is associated with SCA12
SCA13	18	Cedars Sinai Medical Center (Los Angeles, CA, USA)	Compositions and methods for SCA
SCA14	19	Univ. Washington (Seattle, WA, USA)	Methods for identifying subjects susceptible to ataxic neurological disease

protection for the patentee has to be balanced against a reasonable degree of certainty for third parties (Protocol on the Interpretation of Art. 69 EPC). All pending and granted claims were considered valid as it is not the purpose of this study to judge on the validity of the claims in terms of patentability requirements.[19]

In most fields of technology claims leave room for alternatives or to 'design around' the invention, hence triggering innovation. However, claims in genetic diagnostic testing often appear to be truly blocking because of the unique nature of the genetic code and the unique link between a mutation and an inherited disease.[20] Blocking claims are often very broad, not allowing for small modifications in molecular method steps to fall outside the scope of the claims. However, a claim towards an entire gene sequence, carrying a predisposing mutation, does not *a priori* cover the genetic diagnosis for the presence of the naturally occurring gene. Many claims are often directed towards the cDNA sequence or the genomic sequence of the isolated gene. But

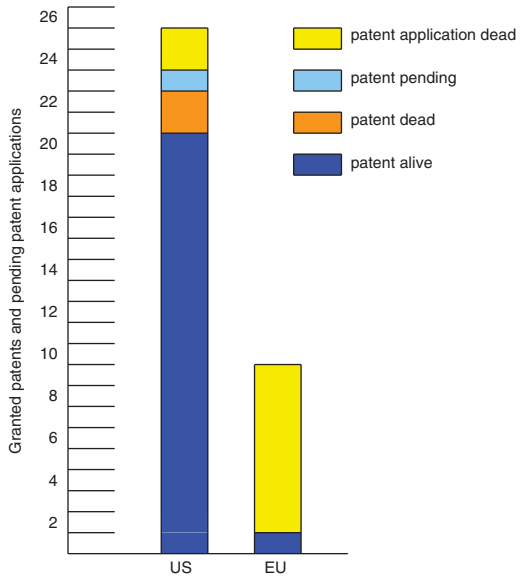

Figure 2 Legal status and relative numbers of patent documents within the SCA patent families, considering one United States patent per patent family. 'Patent application dead' means that the application is no longer under examination (abandoned, refused, withdrawn or deemed to be withdrawn). 'Patent pending' is a patent application that is currently being examined. 'Patent dead' means that a granted patent has either lapsed or been nullified. 'Patent alive' is a granted patent that is currently valid.

neither cDNA nor the entire gene is commonly used in genetic testing. Rather, a portion of a gene is isolated and hybridized (eg, to a microarray), or amplified from a larger template and subsequently analyzed for the presence of a pathogenic mutation.

The scope of a claim to a DNA sequence is prone to various interpretations by different national courts. The implementation of the Biotechnology Directive (98/44/EC) resulted in national laws specifying the scope of patents related to biotechnological inventions. However, the absence of relevant case law in most countries leaves the interpretation of these provisions unclear. Moreover, important differences may occur in claim interpretation between United States courts and European national courts.

The scope of claims towards a mutation-carrying gene fragment or preferentially used primers is usually more straightforward. These claims are likely to cause a blocking situation because they protect either a key element or a preferred tool of a genetic test. A license may thus be required. When patented primers are commercially sold, a license is generally provided upon purchase. To circumvent this type of claims, a truly different methodology may be necessary, for example, a non-molecular method (such as protein-based testing). Finding out whether a DNA claim is relevant for a particular genetic testing method cannot be generalized but requires an in-depth analysis on a case-by-case basis.[19] Within the SCA patents identified in this study, nucleotide sequences are claimed in 66% of the 47 patent documents. The entire, human SCA genes are claimed in 45% of the patent documents.

A claim to a diagnostic testing method is likely to hamper freedom to operate if it links a mutation to a disease without specifying how to establish this link. Among the (granted and pending) SCA patents investigated, genetic diagnostic testing methods are claimed most frequently (82%), followed by nucleotide sequences (50%), recombinant technology items such as vectors and host cells (41%) and diagnostic kits (27%) (Supplementary Figure 2). Protection for peptides and antibodies, and their use in a diagnostic context is also sought albeit to a lesser extent (Supplementary Figure 2). Accordingly, claims to diagnostic testing methods are not only most commonly envisaged by the applicants, they also appear to be relatively easy to patent. Several types of claims are discussed in further detail.

Claims to human genes

In case the invention comprises the identification of a human gene and the occurrence of predisposing mutations therein, the entire gene is likely to be claimed, and the sequence is often specified. Alternatively, a claim towards a short gene sequence, if open ended, can be interpreted to cover a polynucleotide of any length comprising the claimed sequence, including the entire gene. Claim 10 of US 5.834.183 claims a nucleic acid fragment, defined by the protein it encodes, which could encompass the entire *SCA1* gene. Moreover, due to the degenerative character of the genetic code, all sequences that encode the specified SCA1 protein are protected by this claim.

Genetic testing based on PCR amplification of the CAG repeat region is unlikely to infringe this claim because the claimed fragment is neither used nor produced. Firstly, the claimed fragment is unlikely to be used as a PCR template. Secondly, the claimed fragment is more than 580 bp in size and it is unlikely that a PCR amplicon of that size is generated. However, it should be noted that claim interpretation is subject to high variability across various jurisdictions. In the United States, a broader interpretation in the light of the US's strong commercial focus is typically expected. In addition, other claims in this patent may probably infringe PCR methods.

US 5.834.183 'Gene sequence for spinocerebellar ataxia type 1 and method for diagnosis'

Applicant
Regents of the University of Minnesota (US)
Claim
10. An isolated nucleic acid fragment encoding the polypeptide for spinocerebellar ataxia type 1, wherein the polypeptide comprises amino acids 1 to 196 of SEQ ID NO:9 followed by a polyglutamine repeat region.

Blocking claims

Claims on the gene sequence, on a common pathogenic mutation, or on the fundamental method to determine the association between a gene and an inherited disease could be blocking in the sense that it would be very difficult to find an alternative product or to invent around the method. In Europe, the single granted SCA patent, EP 1.015.628 of Research Development Foundation (RDF, USA), appears to have a blocking claim affecting SCA6 diagnosis. This claim is drawn towards a method in which the CAG repeat length is first determined and subsequently assessed on its pathogenesis. By claiming the fundamental method of the SCA6 genetic test, it appears to be very difficult to circumvent the patent when performing SCA6 genetic diagnosis. Filed in 1998 as a PCT application, the patent was eventually granted after an examination procedure of about 8 years and validated in 16 countries.

Table 2 SCA patent landscape using the patent landscaping method of Figure 1. Status on March 1 2010

						Blocking claims	
Type	*Status*	*SCA subtype*	*Application number*	*Family number*	*Filing year*	*Claim(s) on entire gene*	*Claim(s) on essential method*
US	Granted	SCA1	US 5834183	1	1994	Yes	Yes
			US 5741645	1	1995	Yes	Yes
		SCA2	US 6251589	2	1998	—[a]	No
			US 6673535	4	1998	—	Yes
			US 6844431	4	1998	Yes	—
			US 6623927	6	2000	No	No
			US 6515197	7	2000	No	—
			US 7446239	8	2002	No	—
		SCA3	US 5840491	10	1995	—	Yes
		SCA5	US 7527931	11	2006	Yes	Yes
		SCA6	US 5853995	12	1997	—	No
			US 6303307	12	1999	—	Yes
			US 7329487	12	2003	—	No
		SCA7	US 6280938	14	1998	—	Yes
			US 6514755	14	2000	Yes	—
			US 7118893	14	2003	—	Yes
		SCA8	US 6524791	15	1998	No	Yes
		SCA10	US 6855497	16	2001	—	Yes
		SCA13	US 7585629	18	2006	—	Yes
		SCA14	US 7655401	19	2003	Yes	Yes
	Pending	SCA8	US 2003-0235841 (A)	15	2003	Yes	Yes
	Dead[b]	SCA2	US 2005-0032083 (A)	4	2003	Yes	Yes
		SCA3	US 6124100	3	1999	—	No
		SCA6	US 6825332	13	1999	Yes	—
			US 2005-0090658 (A)	13	2003	Yes	Yes
EU[c]	Granted	SCA6	EP 1015628	12	1998	—	Yes
	Dead[b]	SCA1	EP 707647 (A)	1	1994	Yes	No
		SCA2	EP 869186 (A)	2	1996	No	No
			EP 878543 (A)	5	1997	Yes	—
			EP 1311667 (A)	7	2001	No	No
			EP 1392112 (A)	8	2002	No	—
		SCA3	EP 996746 (A)	9	1999	—	No
		SCA6	EP 834561 (A)	13	1996	Yes	Yes
			EP 932677 (A)	13	1997	Yes	Yes
PCT[d]	Granted *in US/EU*	SCA2	WO 0289567 (A)/US'239	8	2002	No	—
		SCA5	WO 0691579 (A)/US'931	11	2006	Yes	Yes
		SCA 6	WO 9844155 (A)/EP'628	12	1998	—	No
		SCA13	WO 06116407 (A)/US'629	18	2006	—	Yes
	Dead[b]	SCA1	WO 9501437 (A)/EP'647 (A)	1	1994	Yes	No
		SCA2	WO 9803679 (A)/EP'186 (A)	2	1996	No	No
			WO 9717445 (A)	3	1996	Yes	No
			WO 9742314 (A)	4	1997	Yes	Yes
			WO 9818920 (A)/EP'543 (A)	5	1997	Yes	—
			WO 0216417 (A)/EP'667 (A)	7	2001	No	No
		SCA3	WO 9943852 (A)/EP'746 (A)	9	1999	—	No
		SCA6	WO 9813490 (A)/EP'677(A)/US'332/US'658 (A)	13	1997	Yes	Yes
		SCA12	WO 0078943 (A)	17	2000	Yes	Yes

Green patents have no hampering effect; yellow patents pose a stumbling rock; orange patents pose a hurdle; red patents pose a roadblock; marroon cells point to the existence of a patent thicket related to the SCA gene panel (SCA1, SCA2, SCA3, SCA6, SCA7). (A): patent applications for which assessment of impact is based on the applicants' earlier licensing policies, or on personal communications with applicants.
[a]Claim set contains no claims in this category.
[b]Dead indicates deemed to be withdrawn, withdrawn, refused, expired or abandoned.
[c]EU stands for the Contracting States of the European Patent Organization. A European patent need not be acquired in all 38 contracting states, but only in the contracting states of interest to the patentee.
[d]PCT stands for international patent applications filed at the World Intellectual Property Organization (WIPO).

No opposition was filed. Meanwhile the patent has lapsed due to non-payment of maintenance fees in Austria, Denmark, Spain, Finland, Greece, Ireland, Italy, the Netherlands, Portugal and Sweden. It currently provides protection in six countries (Belgium, Switzerland, Germany, France, UK and Lichtenstein) until 2018 if maintenance fees continue to be paid.

With SCA6 being part of the common SCA gene panel (including SCA1, SCA2, SCA3, SCA6, SCA7), EP 1.015.628 forbids third parties to execute comprehensive genetic diagnostic testing of SCA in Europe. Whether European genetic diagnostic laboratories could legitimately offer SCA6 testing thus largely depends on the patentee's licensing policy (see 'Licensing policies' below).

EP 1.015.628 'Large scale genotyping of disease and a diagnostic test for spinocerebellar ataxia type 6'	
Applicant	Research Development Foundation (US)
Claim	1. A method of determining whether an individual has or is at risk for developing spinocerebellar ataxia type 6 (SCA-6), comprising assessing whether the number of CAG nucleotide repeat units in the alpha1A calcium channel subunit gene of said individual is greater than a control number, thereby indicating that said individual has or is at risk for developing SCA-6.

'Hidden' claims

The scope of a patent is not always clear to the untrained eye. Genes or diseases might not be named explicitly but may nevertheless be covered by the wordings of the claims. Identifying these patents by keyword searches is therefore challenging. A patent family entitled 'A gene related to migraine in man' and assigned to Rijksuniversiteit Leiden (NL), is, contrary to what the title suggests, drawn to three different diseases related to the *CACNA1A* gene, including SCA6. Gene sequences and detection methods are claimed, but whether the claims cover SCA6 diagnostic testing is unclear at first sight. Originally, mutations in *CACNA1A* were linked to familial hemiplegic migraine (FHM) and episodic ataxia type 2 (EA-2). In 1997, the link between a CAG repeat expansion in *CACNA1A* and *SCA6* was published.[21] The initial European patent application, EP 834.561 filed in 1996, fails to mention SCA6. A PCT application, WO 9.813.490, was subsequently filed in 1997 mentioning the three diseases related to this gene, including SCA6. The related European patent application, EP 932.677, has meanwhile been refused; the related US patent, US 6.825.332, is expired, and the related US patent application, US 2005-0090658, is abandoned (Table 2, Supplementary Table 2). Remarkable, however, is that while the title and most of the description of the applications EP 834.561 and EP 932.677 appear to relate to migraine and/or episodic ataxia type 2, their claims may also be relevant to SCA6 diagnosis. Recently, the SACGHS case studies have revealed similar situations concerning the patent on hearing impairment and Alzheimer's disease.[1,8]

EP 834.561 and EP 932.677 'A gene related to migraine in man'	
Applicant	Rijksuniversiteit Leiden (NL)
Claims (EP '561)	1. An isolated and/or recombinant nucleic acid encoding a Ca2+ channel α1 subunit related to (familial hemiplegic) migraine and/or episodic ataxia type-2, derived from, related to or associated with a gene which in humans is present on chromosome 19p13.1–19p13.2 or a specific fragment thereof.
(EP '677)	22. A method for localizing or identifying a gene using a nucleic acid molecule or a fragment of fragments thereof according to any of claims 1-21.
(EP '677)	25. A method according to claim 22, 23 or 24 wherein the gene is related to FHM and/or EA-2 and/or autosomal dominant cerebellar ataxia.

Licensing policies in the SCA patent landscape (step 4)

In cases where genetic testing makes use of a patented product or method, in principle a license has to be negotiated with the patent owner. An exception to such an obligation is the research or experimental use exemption. However, in Europe as well as in the United States, this exemption appears to be very narrow in scope of application. Despite differences in the national research exemption laws in Europe, it is doubtful that it would apply to diagnostic testing.[22]

Based on inquiries with the patent holders and/or licensees, it appears that most SCA patents are licensed under exclusive terms. In the United States, Canada and Japan, Athena Diagnostics has exclusively licensed-in the patents related to the genetic testing of SCA 1, 2, 3, 5, 6, 7, 8, 13 and 14. Athena pays royalties to the licensor institutions and actively enforces its rights by continuously monitoring and discouraging infringement (Athena Diagnostics, personal communication). Only US 6.855.497 related to SCA10 is currently licensed-out non-exclusively (Baylor College of Medicine, personal communication).

Despite numerous patent applications filed in Europe, only the SCA6 patent (EP 1.015.628) has currently been granted (see 'Blocking claims'). Clayton Biotechnologies Inc. (Houston, TX, USA) the for-profit company that seeks to commercialize the SCA6 patent on behalf of its patentee (RDF) sent a proposal for non-exclusive licensing to many diagnostic laboratories in Europe on 24 February 2009, even to labs in countries where no patent rights exist (anymore) or where the patents lapsed. The proposed license included an upfront fee of 10.000 USD and an earned royalty of 4% of net sales from all European sales under licensed assay with a minimum annual royalty of 10.000 USD creditable against earned royalties. As far as we know, most labs have not accepted this offer, most probably because valid patents did not (no longer) exist, or because patents did exist, but clinicians contemplated to send samples to labs in one of the countries where no rights exist (anymore). As Clayton Biotechnologies Inc. is after all willing to license-out non-exclusively in Europe, access to the blocking SCA6 patent is principally possible. We therefore categorize this patent not (yet) as a roadblock but as a hurdle that might be overcome in the event of non-exclusive licensing, provided it is affordable to the laboratories.

Assessing impact (step 5)

The data obtained in the previous steps – finding relevant patents (step 1), checking patent validity (step 2), determining scope of claims (step 3) and checking availability of a license (step 4) – have been ultimately combined to systematically rank the patents into five categories according to their actual impact on access to genetic diagnostic testing. Metaphorically speaking, we tend to believe that the impact of patents in the area of diagnostic testing increases from 'no hampering effect', to 'stumbling rock', 'hurdle', 'roadblock' or 'patent thicket' (Figure 1, Supplementary Information). The patent landscaping method was similarly applied to the patent applications identified in this study. In the absence of details on licensing, we assumed a licensing policy that corresponds to the applicants' earlier licensing policies or to what was disclosed in personal communications with applicants or licensees.

Stumbling rock

Patents or patent applications in this category claim non-essential elements of a genetic test or elements, which are not related to genetic testing. Access to the technology covered by these patents is rated as not so difficult. The claimed subject matter could for example be exchanged with a known or evident alternative (for example, claims to a very specific method, a specific DNA construct, a vector) or the claim could relate to a rare mutation, which does not represent an essential part of a basic diagnostic screen, such that the claims are not

insurmountable for diagnostic testing. Alternatively, licenses could be easily obtainable (for example, when offered at a reasonable royalty to every requester).

The US patent 6.515.197 forms an example of a stumbling rock patent (Table 2). It claims DNA constructs of an ataxin-2-encoding sequence, linked to either a Purkinje cell-specific promoter or a green fluorescent protein-encoding sequence, or both. One of the aims of this invention is the creation of a transgenic animal expressing human SCA2. The method claims in this patent family are all related to the identification of therapeutic agents for treatment of SCA2.

Hurdle

Getting access to patented technology categorized as a 'hurdle' is considered to be less obvious. Hurdle patents preferentially protect established methods or primers for which an alternative may not easily be found. Additionally or alternatively, obtaining a license to the hurdle is difficult, for example, because of the cost involved, because the technology is already licensed exclusively to another party and no sublicenses are available, because there is a lack of interest with the patentee for dealing with small-size players, or because of a lack of legal expertise to engage in licensing negotiations – a situation not unusual for a genetic testing laboratory. The US patent 6.623.927 is classified as a hurdle because it claims preferential primers located up and downstream of the CAG repeat expansion (Table 2).

Roadblock

Access to patented technology of this category is considered to be seriously blocked because one or several claims are drawn to an essential element of genetic testing and because circumstances are such that a license can not be obtained. When a patent protects subject matter for which an alternative does not exist or is not directly within reach (see 'Blocking patent', Supplementary Information), access to the protected technology would only be possible through licensing. However, in the case of a roadblock, the patent owner does not want to provide licenses or a license has already been granted on exclusive terms to a third party.

Patent thicket

A patent thicket is defined here as a dense web of multiple (blocking) patents held by multiple patent owners.[23,24] Access to the patented technology as a whole is almost completely blocked. Licenses are the only possible solution.

With 20 granted, valid United States patents covering genetic testing of 10 SCA subtypes (Figure 3, Table 2), the situation in the United States can be considered a 'patent thicket' as defined above. Exclusive licensing-out of the US patents has placed the rights to genetic testing of SCA in the United States in the hands of Athena Diagnostics. Several labs that infringed Athena's patent rights have reportedly stopped performing genetic testing of SCA, as a response to threats of patent enforcement.[5,25] Thus, Athena has cut through the thicket and is legitimately providing tests to the market, paying royalties to the licensor, but the exclusivity of these services has, in practical terms, given the company quite a monopolistic position, as the freedom to obtain a second medical opinion from an independent laboratory is likely to be restricted.

In Europe, the SCA patent landscape looks much less dense (Figure 3, Table 2). A considerable number of applications were filed but later withdrawn or refused. Reasons for this may have to be sought in the reputedly strict and long examination procedure at the European Patent Office. Yet, even in the absence of a patent thicket, the European situation is potentially problematic because of one blocking patent (see 'Licensing policies' above).

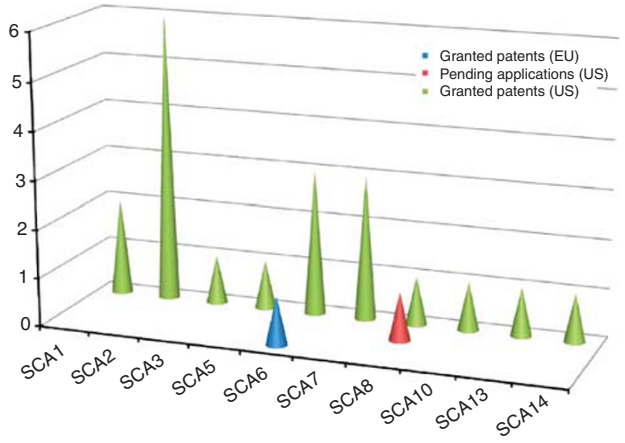

Figure 3 The SCA patent landscape considering granted and pending patents in Europe and in the United States (One Unites States patent is considered per patent family).

DISCUSSION

Stacking of patents may affect both genetic testing laboratories, by seriously reducing a clinical diagnostician's freedom to operate, and patients, by reducing the availability of genetic tests. However, not only patent thickets but also singular patents can throw up a roadblock in the field of molecular diagnostics. Only a few gene patents have direct impact on diagnostic testing, but their scope of protection and exclusive manner of out-licensing is a point of concern.

Our study highlights the striking differences between patenting for SCA in Europe and the United States. The abundance of blocking patents, particularly in the United States, claiming either the gene sequence or the basic method of genetic testing is remarkable. In combination with a restrictive licensing regime, these patents appear to exclude all laboratories from offering the genetic SCA test in the US, Canada and Japan until at least 2015, except the exclusive licensee. On the other hand, even in the absence of a patent thicket, the enforcement of one blocking patent can have far-reaching consequences in some European countries.

The present study is intended to serve as an eye-opener to the genetics community. Geneticists are either not aware of patents related to their tests or choose to ignore them.[2] This does not provide a sustainable solution in the long run. Especially in the era of establishing standards for genetic testing,[11,12] it appears necessary to raise awareness on patent matters. Moreover, worldwide efforts to harmonize and standardize genetic testing require a way to practice genetic diagnostics legitimately, without violating IP rights, in line with recommendations made by the OECD[26] and the ESHG.[27]

Recent evolutions in the field of molecular diagnostics at the nanoscale (eg, biochips) not only provide for increased sensitivity and earlier disease detection, but also facilitate multiplexed diagnostics both in preventive and predictive medicine.[28] In this way, individuals can be screened rapidly, accurately and simultaneously for the presence or the risk of developing different genetic diseases. For example, inherited mutations in neurological disease genes that could lead to overlapping phenotypes could become part of one single test panel based on several disease genes. It has already been suggested to incorporate genetic testing of SCA2 in the genetic screening of autosomal dominant Parkinsonisms, and more recently, it has been proposed that intermediate-length CAG-repeats in the *SCA2* (*ATXN2*) gene might confer genetic risk for amyotrophic lateral sclerosis.[29,30] As cerebellar ataxia has been reported along with Parkinsonism in SCA1,

SCA2, SCA3, SCA7 and SCA17[16] and phenotypic overlap has also been documented with FXTAS[31] and Huntington's disease,[32] multiplexing could become more a general or standard practice in future.

The presented data underscore the need for swift and efficient licensing and/or cross-licensing mechanisms for patents on diagnostic technologies. Non-exclusive and collaborative licensing models in diagnostics, such as patent pools or clearinghouses, have been suggested to render gene patents more easily accessible[25,33] as well as compulsory licenses[34] to attenuate the potentially hampering effect of patents on health care services.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This research was supported by grant number G.O120.04 of the Fund for Scientific Research (FWO, Belgium) and EuroGentest, an EU-FP6 supported NoE contract number 512148. Special thanks go to Isabelle Huys, Liesbet Paemen, Esther van Zimmeren and Birgit Verbeure for interesting discussions and helpful comments on the manuscript.

DISCLAIMER

This paper is informational only and is not to be taken as legal advice.

1 Cook-Deegan R, Chandrasekharan S, Angrist M: The dangers of diagnostic monopolies. *Nature* 2009; **458**: 405–406. Also see the case studies carried out by Cook-Deegan and his team: Patently Complicated: Case studies on the impact of patenting and licensing on clinical access to genetic testing in the United States. *Genet Med* 2010; 12(4 suppl): S1–S211.
2 Gaisser S, Hopkins MM, Liddell K, Zika E, Ibarreta D: The phantom menace of gene patents. *Nature* 2009; **458**: 407–408.
3 Kaye J, Hawkins N, Taylor J: Patents and translational research in genomics. *Nat Biotechnol* 2007; **25**: 739–741.
4 Klein RD: Gene patents and genetic testing in the United States. *Nat Biotechnol* 2007; **25**: 989–990.
5 Cho MK, Illangasekare S, Weaver MA, Leonard DG, Merz JF: Effects of patents and licenses on the provision of clinical genetic testing services. *J Mol Diagn* 2003; **5**: 3–8.
6 Matthijs G: The European opposition against the BRCA gene patents. *Fam Cancer* 2006; **5**: 95–102.
7 Matthijs G, Halley D: European-wide opposition against the breast cancer gene patents. *Eur J Hum Genet* 2002; **10**: 783–785.
8 SACGHS: *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*. SACGHS, NIH: Bethesda, MD, April 2010. Available at http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf.
9 Ibarreta D, Elles R, Cassiman JJ, Rodriguez-Cerezo E, Dequeker E: Towards quality assurance and harmonization of genetic testing services in the European Union. *Nat Biotechnol* 2004; **22**: 1230–1235.
10 Barton JH: Emerging patent issues in genomic diagnostics. *Nat Biotechnol* 2006; **24**: 939–941.
11 Cassiman JJ: Research network: EuroGentest - a European Network of Excellence aimed at harmonizing genetic testing services. *Eur J Hum Genet* 2005; **13**: 1103–1105.
12 ACMG (American College of Medical Genetics): Standards and guidelines for clinical genetics laboratories 2007 edition. Available at http://www.acmg.net.
13 Hopkins MM, Mahdi S, Patel P, Thomas SM: DNA patenting: The end of an era? *Nat Biotechnol* 2007; **25**: 185–187.
14 Jensen K, Murray F: Intellectual property landscape of the human genome. *Science* 2005; **310**: 239–240.
15 *Article 28 (1) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs Agreement)*, 1994 (http://www.wto.org/english/docs_e/legal_e/27-trips.pdf).
16 Schöls L, Bauer P, Schmidt T, Schulte T, Riess O: Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. *Lancet Neurol* 2004; **3**: 291–304.
17 Edlefsen KL, Tait JF, Wener MH, Astion M: Utilization and diagnostic yield of neurogenetic testing at a tertiary care facility. *Clin Chem* 2007; **53**: 1016–1022.
18 Verbeure B, Matthijs G, Van Overwalle G: Analysing DNA patents in relation with diagnostic genetic testing. *Eur J Hum Genet* 2006; **14**: 26–33.
19 Huys I, Berthels N, Matthijs G, Van Overwalle G: Legal uncertainty in the area of genetic diagnostic testing. *Nat Biotechnol* 2009; **27**: 903–909.
20 Bird WE: Using the EPO opposition procedure as a strategy against patents on diagnostic methods; In: Van Overwalle (ed): *Gene patents and Public Health*. Brussels: Belgium, Bruylant, 2007; pp 75–78.
21 Riess O, Schöls L, Bottger H *et al*: SCA6 is caused by moderate CAG expansion in the alpha1A-voltage-dependent calcium channel gene. *Hum Mol Genet* 1997; **6**: 1289–1293.
22 Van Overwalle G, van Zimmeren E, Verbeure B, Matthijs G: Models for facilitating access to patents on genetic inventions. *Nat Rev Genet* 2006; **7**: 143–148.
23 Merges R: Contracting into liability rules: Intellectual property rights and collective rights organizations. *Calif Law Rev* 1996; **84**: 1293–1293.
24 Shapiro C: Navigating the patent thicket: Cross licenses, patent pools and standard setting; In Jaffe E, Lerner J, Stern S (eds): *Innovation Policy and the Economy*, (vol. 1.), Cambridge, MA: MIT Press, 2001, pp 119–150. Available at http://faculty.haas.berkeley.edu/shapiro/thicket.pdf.
25 Ebersole T, Guthrie M, Goldstein JA: Patent pools as a solution to the licensing problems of diagnostic genetics. *IP Techn Law J* 2005; **17**: 1–8.
26 OECD: Guidelines for the licensing of genetic inventions. Available at www.oecd.org/sti/biotechnology/licensing.
27 European Society of Human Genetics: Recommendations on patenting and licensing in genetic testing. *Eur J Hum Genet* 2008; **16**: 405–411.
28 Azzazy H, Mansour M, Kazmierczak S: Nanodiagnostics: A new frontier for clinical laboratory medicine. *Clin Chem* 2006; **52**: 1238–1246.
29 Modoni A, Contarino MF, Bentivoglio AR *et al*: Prevalence of spinocerebellar ataxia type 2 mutation among Italian Parkinsonian patients. *Mov Disord* 2007; **22**: 324–327.
30 Elden AC, Kim H-J, Hart MP *et al*: Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. *Nature* 2010; **466**: 1069–1075.
31 Macpherson J, Waghorn A, Hammans S, Jacobs P: Observation of an excess of fragile-X premutations in a population of males referred with spinocerebellar ataxia. *Hum Genet* 2003; **112**: 619–620.
32 Schneider SA, Walker RH, Bhatia KP: The Huntington's disease-like syndromes: What to consider in patients with a negative Huntington's disease gene test. *Nat Clin Pract* 2007; **3**: 517–525.
33 Van Overwalle G (ed): *Gene Patents and Collaborative Licensing Models. Patent Pools, Clearinghouses, Open Source Models and Liability Regimes*. Cambridge: Cambridge University Press, 2009.
34 Van Zimmeren E, Van Overwalle G: A Paper Tiger? Compulsory License Regimes for Public Health in Europe. *International Review of Intellectual Property and Competition Law (IIC)* 2011, 4–40.

Supplementary Information accompanies the paper on European Journal of Human Genetics website (http://www.nature.com/ejhg)