Australian Government
National Health and Medical Research Council
NHMRC


Mr Elton Humphrey
Committee Secretary
Senate Standing Committee on Community Affairs
PO Box 6100
Parliament House
Canberra Act 2600

Dear Mr Humphrey

On 19 March 2009 I represented the National Health and Medical Research Council (NHMRC) at the public hearing for the Senate Community Affairs Committee Inquiry into Gene Patents (the Inquiry). During that hearing, Senator Catryna Bilyk raised some questions concerning a patented gene, namely SCN1A, and its association with Dravet syndrome, an epileptic encephalopathy occurring in infants.

In a conversation with Senator Bilyk, I offered to provide background information on the SCN1A gene. I would also like to take this opportunity to summarise the key issues associated with gene patenting as raised by NHMRC in its submission to the Australian Law Reform Commission's 2003 inquiry into the Patenting of Genetic Materials and Related Technologies.

Scientifically speaking, SCN1A is a sodium channel gene which is responsible for generating action potentials in nerve cells in the body. Mutations in the SCN1A gene impair this function, resulting in epilepsy syndromes such as Dravet syndrome (previously called Severe Myoclonic Epilepsy of Infancy or SMEI). The discovery of this gene has significant implications for improving analytical methods for the early diagnosis of Dravet syndrome such as direct sequencing of DNA or via quantitative methods. The journal article provided at Attachment A examines the SCN1A gene in patients diagnosed with Dravet syndrome.

The submission to the Senate Inquiry by Dr Luigi Palombi raised several concerns in relation to a pre-existing patent for the SCN1A gene. Dr Palombi's key concern is that the patent provides the patent holder, Bionomics, with a monopoly to the gene and its mutations, and has the potential to impede further research by other scientists in Australia.

In our submission to the 2003 Australian Law Reform Commission (ALRC) inquiry into the patenting of genetic materials and related technologies, NHMRC emphasised the importance of ensuring that gene patents do not pose a hindrance to acquiring further knowledge through research, but rather that they should balance protection and accessibility for research. While NHMRC is not aware of any specific examples where patenting practices have had a negative impact on research in Australia, NHMRC supports the proposal from the Australian


GPO Box 1421, Canberra ACT 2601
Level 5, 20 Allara Street, Canberra City ACT
T. 13 000 NHMRC (13 000 64672) or +61 2 6217 9000 F. +61 2 6217 9100 E. nhmrc@nhmrc.gov.au
ABN 88 601 010 284

Government's Advisory Council on Intellectual Property that research be exempt from provisions imposed by gene patents in Australia.

Gene patenting and research is a topical issue in medical research worldwide, and it is notable that the respected journal *Nature* recently published commentaries on the impact of gene patents on research and access to genetic tests in the US and Europe (Attachment B).

I also thought it might be useful to provide the Inquiry with a summary of the ethical considerations and other views raised in NHMRC's submission to the ALRC 2003 inquiry into the patenting of genetic materials (Attachment C).

I trust this information assists the Committee with its inquiry into gene patents.

Yours sincerely

Professor Warwick Anderson
Chief Executive Officer

23 April 2009

# Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients

C Depienne, O Trouillard, C Saint-Martin, I Gourfinkel-An, D Bouteiller, W Carpentier, B Keren, B Abert, A Gautier, S Baulac, A Arzimanoglou, C Cazeneuve, R Nabbout and E LeGuern

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# Spectrum of *SCN1A* gene mutations associated with Dravet syndrome: analysis of 333 patients

C Depienne,[1,2,3] O Trouillard,[1] C Saint-Martin,[2,3] I Gourfinkel-An,[2,4,5] D Bouteiller,[2] W Carpentier,[6] B Keren,[1] B Abert,[7] A Gautier,[8] S Baulac,[3] A Arzimanoglou,[9] C Cazeneuve,[1] R Nabbout,[5,10] E LeGuern[1,2,3]

► Supplementary tables are published online only at http://jmg.bmj.com/content/vol46/issue3

[1] AP-HP, Département de Génétique et Cytogénétique, Fédération de Génétique, Hôpital de la Salpêtrière, F-75013, Paris, France; [2] INSERM, UMR_S679 Neurologie & Thérapeutique Expérimentale, F-75013, Paris, France; [3] UPMC Univ Paris 06, UMR_S679, F-75005, Paris, France; [4] AP-HP, Pôle d'Epileptologie, Hôpital de la Salpêtrière, F-75013, Paris, France; [5] Centre de Référence Epilepsies Rares, France; [6] Plateforme Post-Génomique P3S, UPMC, Paris, France; [7] Service de Neuropédiatrie et CAMSP, Hôpital Gatien de Clocheville, CHU Tours, France; [8] Service de Neuropédiatrie, CHU Nantes, France; [9] Service d'Epileptologie Pédiatrique et CTRS-IDEE (Institute for Children and Adolescents with Epilepsy), University Hospitals of Lyon (HCL), France; [10] Département de Neuropédiatrie, AP-HP, Hôpital Necker-Enfants malades, Centre de Référence Epilepsies Rares, Paris, France and Inserm U663, Paris, F-75015 France; University Paris Descartes, Paris, F-75005 France

Correspondence to:
Dr C Depienne, INSERM U679, Groupe Hospitalier Pitié-Salpêtrière, 47 Boulevard de L'hôpital, 75013 Paris, France; christel.depienne@upmc.fr

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## ABSTRACT

**Introduction:** Mutations in the voltage-gated sodium channel *SCN1A* gene are the main genetic cause of Dravet syndrome (previously called severe myoclonic epilepsy of infancy or SMEI).

**Objective:** To characterise in more detail the mutation spectrum associated with Dravet syndrome.

**Methods:** A large series of 333 patients was screened using both direct sequencing and multiplex ligation-dependent probe amplification (MLPA). Non-coding regions of the gene that are usually not investigated were also screened.

**Results:** *SCN1A* point mutations were identified in 228 patients, 161 of which had not been previously reported. Missense mutations, either (1) altering a highly conserved amino acid of the protein, (2) transforming this conserved residue into a chemically dissimilar amino acid and/or (3) belonging to ion-transport sequences, were the most common mutation type. MLPA analysis of the 105 patients without point mutation detected a heterozygous microrearrangement of *SCN1A* in 14 additional patients; 8 were private, partial deletions and six corresponded to whole gene deletions, 0.15–2.9 Mb in size, deleting nearby genes. Finally, mutations in exon 5N and in untranslated regions of the *SCN1A* gene that were conserved during evolution were excluded in the remaining negative patients.

**Conclusion:** These findings widely expand the *SCN1A* mutation spectrum identified and highlight the importance of screening the coding regions with both direct sequencing and a quantitative method. This mutation spectrum, including whole gene deletions, argues in favour of haploinsufficiency as the main mechanism responsible for Dravet syndrome.

Severe myoclonic epilepsy of infancy (SMEI; OMIM 607208) or Dravet syndrome is an intractable epileptic encephalopathy occurring in the first year of life in a previously normal infant. Patients present with recurrent and prolonged seizures, usually febrile, hemiclonic or generalised tonic clonic, resulting commonly in status epilepticus.[1] Patients later develop other seizure types including atypical absence and partial seizures concomitant with developmental delay, ataxia and myoclonic jerks.[1 2] Cognitive outcome is poor, with a high risk of mental retardation. Dravet syndrome is usually sporadic but familial cases have been occasionally reported.[3]

Heterozygous mutations in *SCN1A*, the gene encoding the voltage-gated neuronal sodium channel alpha 1 subunit (Nav1.1), are a major cause of Dravet syndrome.[4] The Nav1.1 protein belongs to a protein family that includes 10 members in humans, which are involved in the genesis of action potentials and rapid membrane depolarisation. These channels contain four transmembrane domains (I–IV), each with six membrane-spanning segments (S1–S6). All types of mutations in *SCN1A* are observed in patients with SMEI, including missense mutations and all types of truncating mutations.[5] Recently, large intragenic deletions, undetected by standard techniques, have also been described.[6–10] This large mutation spectrum contrasts with that of generalised epilepsy with febrile seizures plus (GEFS+; OMIM 604233), an autosomal dominant condition also associating with febrile and afebrile seizures but with a usually benign outcome, in which only missense mutations in *SCN1A* are found.[11] Loss of function of the mutated allele is probably responsible for SMEI, as confirmed by the recent development of knock-out and knock-in mouse models,[12 13] whereas another mechanism could lead to GEFS+.

Several isoforms of *SCN1A* have been reported although the isoform(s) relevant for the physiopathology of Dravet syndrome remain(s) unknown: three different donor sites of intron 11 lead to alternative spliced isoforms containing short, intermediate or long versions of exon 11, effect of which is to modulate the length of the intracellular loop between segments IS6 and IIS1.[14] Furthermore, an exon 5N has been described, highly homologous to the exon 5 normally present in the adult isoform (exon 5A).[15] Replacement of exon 5A by exon 5N has been suggested to be developmentally regulated and to occur at a fetal stage, as previously described for SCN8A.[16] Recently, novel 5′ untranslated region (UTR) exons of *SCN1A* have been described; some of these 5′UTR exons and additional intronic regions have been shown to be highly conserved during evolution.[17]

The aim of this study was to screen a large series of patients with Dravet syndrome using combined approaches allowing both the detection of point mutations and exonic rearrangements. In addition, we analysed exon 5N and eight of the regions of the *SCN1A* gene conserved during evolution, to determine whether additional mutations could be found in these regions.

## METHODS

This study was approved by the ethics committee (CCPPRB of Pitié-Salpêtrière Hospital, Paris, no 69-03, 25/9/2003). Informed written consent was obtained from the patients' parents before blood sampling.

### Patients

In total, 333 probands diagnosed with Dravet syndrome were referred to our diagnostic laboratory for genetic testing of *SCN1A* in a 5-year period between April 2003 and April 2008. Most samples were received from specialised child neurology centres throughout France although a few samples were occasionally received from other countries (Slovenia, Germany, and Chile).

The referral physician completed a detailed clinical questionnaire for every patient. Clinical reports were also collected for most patients to assess the clinical history of the disease. All clinical files and questionnaires were examined by the same neuropaediatrician and neurologist (RN and IA) for consistent classification of the patients. Core features required for classification as classic Dravet syndrome were defined as: normal cognitive and motor development previous to seizure onset, onset of the seizures before 1 year of age, seizures mainly triggered by fever, long-lasting seizures (>15 min, that might evolve to status epilepticus), later occurrence of various seizures types (febrile and afebrile) and later cognitive regression. The presence of myoclonic jerks and/or ataxia was considered as a highly characteristic feature reinforcing the diagnosis but their absence did not exclude the clinical diagnosis of Dravet syndrome as both were previously shown to be inconsistent in patients.

In total, 271 patients had clinical features that conformed to this description. The remaining 62 patients were not considered as having typical Dravet syndrome: 6 patients had a clinical history highly suggestive of Dravet syndrome but were still too young (age<12, 13 and 15 months respectively) to fulfil all the clinical criteria, 6 patients had an onset after 1 year of age (12.5–15 months), 1 patient had a very early onset (10 days), 15 patients were reported as having only GTC although they fulfilled all other criteria, and 34 patients diagnosed with Dravet syndrome by their local neuropaediatrician were not classified due to absent or incomplete clinical information. Patients were first screened using direct sequencing of *SCN1A* coding sequence and patients without point mutation were subsequently analysed for exon deletion using MLPA.

### Analysis of the *SCN1A* coding sequence by direct sequencing

The 30 specific primer pairs amplifying the 26 exons of the *SCN1A* gene (transcript reference AB093548) have been described previously.[3 18] Primers specific to exon 5N and to eight regions of *SCN1A*, located in the 5'UTR or in introns 11 and 20 and highly conserved in orthologues and paralogues of *SCN1A*,[17] were designed to amplify the corresponding regions (supplementary table A online). Sequence products were run on an automated sequencer (ABI 3730; Applied Biosystems, Foster City, California, USA) and data were analysed with Seqscape V.2.5 software (Applied Biosystems). Mutations found in patients were investigated in available parents using direct sequencing of the corresponding exon. When the mutation was absent from both parents, parental testing was performed using microsatellite markers at the *SCN1A* locus to ensure that the mutation occurred de novo. In addition, 180 European controls (healthy spouses of patients with other neurological diseases) were included to test new variants of the *SCN1A* gene.

### Multiplex ligation-dependent probe amplification

Multiplex ligation-dependent probe amplification (MLPA) was used to search for rearrangements in *SCN1A*,[6] using a commercial kit (MLPA P137 Kit; MRC-Holland, Amsterdam, The Netherlands). MLPA reactions were carried out according to the manufacturer's instructions. Electrophoresis of PCR products was performed using an automated sequencer (ABI 3730; Applied Biosystems) and MLPA data were analysed using GeneMapper V.3.5 software (Applied Biosystems). Relative ratios were calculated using the formula r = mean (peak area$_{patient}$/control area$_{patient}$)/(peak area$_{control}$/control area$_{control}$).

### Characterisation of *SCN1A* deletions breakpoints using high-density single-nucleotide polymorphism arrays

Patients with large *SCN1A* deletions were further analysed using Illumina 370CNV-Duo genotyping BeadChip arrays (370 K). The genotyping reaction steps were performed according to the manufacturer's specifications (Infinium II; Illumina, San Diego, California, USA). Image analysis and automated genotype calling was performed using Beadstudio V.3.1 (Illumina). Breakpoints of the deletions were defined as the first and last single-nucleotide polymorphism (SNP) that were homozygous and presented a decreased log ratio (in the order of −0.5) in the region of the deletion.

### Bioinformatics analyses of *SCN1A* mutations

Mutation interpretation and amino acid conservation in orthologues was assessed using Alamut V.1.31 software (Interactive Biosoftware, Rouen, France; http://www.interactivebiosoftware.com/). For missense mutations, the Grantham chemical distance between amino acids[19] provided by the Alamut software was used to test whether the replacements between the residues are important with respect to a range of physiochemical properties (volume, charge and composition of the side chain).

## RESULTS

In total, 242 patients (73%) with *SCN1A* mutations (supplementary table B online) or deletions (table 1) were identified. A schematic representation of the localisation and nature of the mutations on the *SCN1A* gene is shown in fig 1.

### Point mutations detected by direct sequencing

Direct sequencing detected 200 different heterozygous mutations, 161 of which were novel, in 228 patients (supplementary table B online). Point mutations leading theoretically to missense amino acids substitutions were the most common mutation type, encountered in 42% of the patients (96/228). Other mutation types introducing premature termination codon (PTC) were also common: nonsense mutations (23%, 52/228), mutations altering splice sites (13%, 29/228), and small deletions or insertions leading to a frameshift (19%, 44/228). Finally, we identified five in-frame deletions (2%, 5/228), one mutation altering the adenine of the ATG initiation codon, and one intronic substitution located 10 bp upstream from exon 16, which was classified as a mutation on the basis that it occurred de novo in the patient although it has no predicted effect on *SCN1A* splicing (0.5% each, 1/228).

Interestingly, we found four patients harbouring two *SCN1A* variants with possibly deleterious effect: one carried the c.2816A→C/p.His939Pro and c.5364C→A/p.Asn1788Lys variants; the second had the c.3235G→A/p.Val1079Ile variant, inherited from his asymptomatic father, associated with the de novo c.2504_2508delTTGAC mutation; the third carried the c.4723C→T/p.Arg1575Cys variant, inherited from his asymptomatic mother, and the de novo c.1804G→T/p.Glu602X mutation; and the fourth had the c.3325C→A/p.Pro1109Thr,

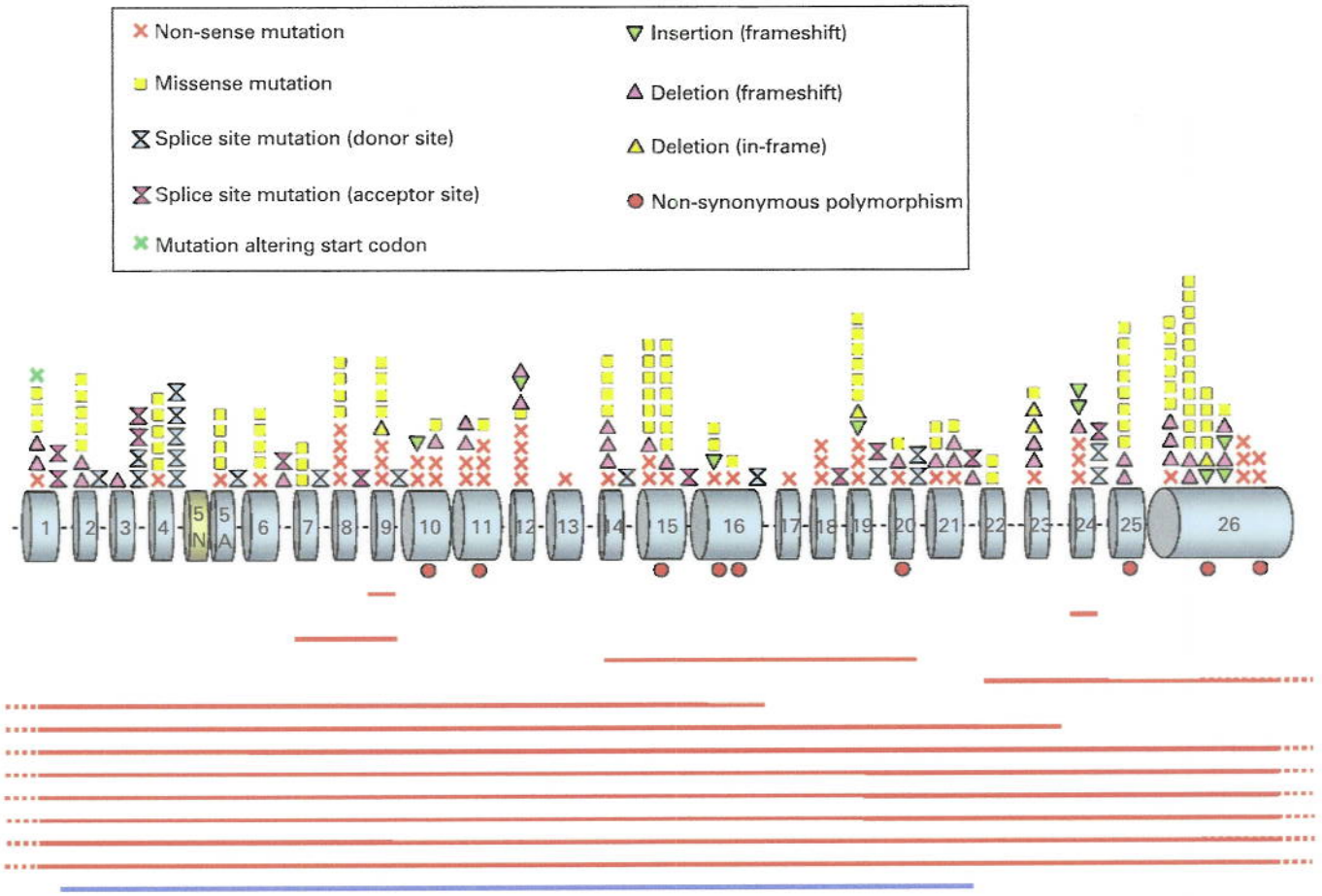


**Figure 1** Schematic representation of the mutations and rearrangements of the *SCN1A* gene identified in this study. (Top) Point mutations. (Bottom) Red circles, non-synonymous polymorphisms; red lines, deletions; blue line, duplication; dashed lines, deletion continues farther than the gene.

inherited from his father, and the de novo c.4133delA mutation. We hypothesised that p.Val1079Ile, p.Pro1109Thr and p.Arg1575Cys were novel rare non-synonymous polymorphisms, but we could not define which of the p.His939Pro and p.Asn1788Lys variants constituted the causative mutation, as the parents of this patient were unavailable for genetic analyses. Therefore, both were considered as potential missense mutations.

Most missense mutations alter a highly conserved amino acid in the protein (96%, 92/96 different missense mutations; supplementary table C online). Furthermore, the amino acid substitutions involve residues that are chemically dissimilar as assessed by the Grantham distance formula;[19] 71% of the missense mutation show a distance >70, corresponding to dissimilar or very dissimilar changes (68/96); 77% alter a residue belonging to ion transport sequences (ie, sequences sharing significant homology to other ion channels and transporters; 74/96) or both (58%, 56/96). However, the missense mutations were located throughout the Nav1.1 channel, with no preferential location in transmembrane, extracellular or intracellular domains (fig 2). Interestingly, all the mutations found in exon 11 are located in the portion shared by all three alternatively spliced isoforms of this exon (ie, in the shortest isoform) and no variant or mutation specific to the long isoforms have been described to date.

For 149 patients with point mutation, both parents were available for genetic analyses. Direct sequencing failed to detect the mutation in either parent, in 133 cases out of 149 (89%), indicating that the mutation occurred de novo in these patients. For the 15 patients who inherited the mutation, it was inherited from the mother in 5 cases and from the father in 10. Two siblings (brother and sister) had the same mutation although it was undetectable in their parents. Interestingly, we found 9 patients with novel recurrent mutations (ie, an identical mutation in >1 patient) and 67 patients had mutations that have previously been reported by other authors (supplementary table B online). However, most mutations occurred de novo, indicating that they are repetitively generated through specific mechanisms. Further analysis of patients with inherited mutations is ongoing (Depienne *et al*, in preparation).

In total, 40 polymorphisms, 24 of which are novel, were identified in *SCN1A* (supplementary table D online), including polymorphisms detected in the relatives of asymptomatic patients and in controls. The eight non-synonymous variants (p.Arg542Gln, p.Arg604His, p.Ala924Thr, p.Val1079Ile, p.Pro1109Thr, p.Glu1308Asp, p.Arg1575Cys, and p.Arg1928Gly) were present in an asymptomatic parent, suggesting that they are benign variants; however, they were not found in 100 Caucasian controls, indicating that they are either rare or possibly specific to populations with a particular geographical origin. Surprisingly, all these variants, with the exception of p.Ala924Thr, also affect highly conserved amino acids of the proteins, but compared with the missense mutations found in patients, they mainly substitute chemically

**Table 1** Rearrangements identified by multiplex ligation-dependent probe amplification in patients with Dravet syndrome

| Proband code | Gender | Clinical classification | Age at onset, months | Exons | Mutation | Theoretical effect on the protein | Type | Transmission | Polymorphisms |
|---|---|---|---|---|---|---|---|---|---|
| N 07 0987 | F | Clinical data unavailable | 8 | 1–23 | c.1-?_4473+?del | Absence of protein synthesis | Partial gene deletion (exon 1 to 23) | Unknown (mother negative) | |
| N 06 1587 | M | Classic DR | 5 | 1–16 | c.1-?_3429+?del | Absence of protein synthesis | Partial gene deletion (exons 1 to 16) | De novo | |
| 18334_31416 | F | Classic DR | <6 | 1–26 | c.1-?_6030+?del | Absence of protein synthesis | Whole gene deletion | Unknown | |
| N 07 0770 | M | Clinical data unavailable | 2 | 1–26 | c.1-?_6030+?del | Absence of protein synthesis | Whole gene deletion | Unknown | c.4476+33G→A (homozygous) |
| JON_071_003 | M | Classic DR | <6 | 1–26 | c.1-?_6030+?del | Absence of protein synthesis | Whole gene deletion | Unknown | |
| N 08 0096 | M | Classic DR | 6 | 1–26 | c.1-?_6030+?del | Absence of protein synthesis | Whole gene deletion | Unknown | |
| N 07 1846 | F | Classic DR | 4.5 | 1–26 | c.1-?_6030+?del | Absence of protein synthesis | Whole gene deletion | Unknown | |
| N 08 0687 | M | Classic DR | 6 | 1–26 | c.1-?_6030+?del | Absence of protein synthesis | Whole gene deletion | Unknown (inherited in sibling pairs) | |
| N 05 0598 | F | Classic DR | 7 | 2–21 | c.265-?_4284+?dup | p.Ala1429_Lys2009delins46X | Partial gene duplication (exon 2 to 21) | Unknown | |
| N 07 0693 | F | Probable DR (age<13 months) | 9 | 7–9 | c.965-?_1377+?del | p.Arg322ThrfsX26 | Partial gene deletion (exons 7 to 9) | De novo | |
| N 08 0843 | F | Classic DR | NA | 9 | c.1171-?_1377+?del | p.Thr391_Gln459del | Partial gene deletion (exon 9) | Unknown | |
| N 06 1285 | F | Classic DR | 3 | 14–20 | c.2416-?_4002+?del | p.Phe807_Val1335del | Partial gene deletion (exons 14 to 20) | Unknown | |
| N 07 0755 | M | Classic DR | 3 | 22–26 | c.4285-?_6030+?del | p.Ala1429_Lys2009del | Partial gene deletion (exons 22 to 26) | De novo | |
| N 07 1278 | M | Classic DR | 4 | 24 | c.4477-?_4581+?del | p.Phe1493_Gly1527del | Partial gene deletion (exon 24) | Unknown | |

DR, Dravet syndrome; NA, not available.
Nucleotide numbering for all mutations and polymorphisms is designated according to the cDNA reference sequence (accession number AB093548), in which the "A" of the strat codon is nucleotide 1.

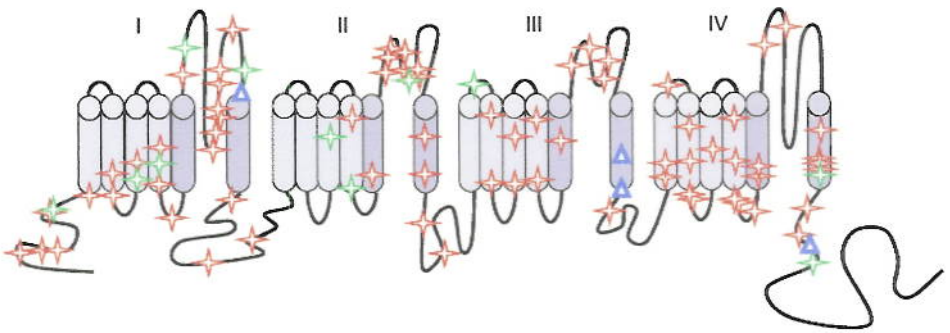


**Figure 2** Schematic representation of the missense mutations and in-frame deletions identified in this study on the Nav1.1 protein. Each star represents a missense mutation. Red stars, mutations identified in a single patients; green stars, recurrent mutations, blue triangles, inframe deletions.

similar amino acids (33% (3/9) have a distance >70 arbitrary units (AU), corresponding to dissimilar or very dissimilar changes, compared with 74% for missense mutation) and, with the exception of p.Arg1575Cys, none transforms a highly conserved residue belonging to ion-transport sequences in a chemically dissimilar residue.

### Microdeletions detected with MLPA and characterisation using microarrays

MLPA analysis of the 105 patients without point mutations found in 14 patients a heterozygous rearrangement in *SCN1A*, encompassing a variety of lengths from a single exon to the whole gene (13%, 14/105; table 1). Deletion of the whole gene was the most common abnormality, which was found in six patients (43%, 6/14), one of whom has an affected brother with the same deletion. The eight other partial rearrangements, including seven deletions (exon 9, exon 24, exons 1–16, exons 1–23, exons 14–20, exons 22–26, and exons 7–9 found in monozygous twins) and one duplication (exons 2–21) were all private and novel. Both parents of the three patients with deletions of exons 22–26, 1–16, and 7–9, respectively, were available for analysis, and this showed that all three deletions occurred de novo. Parents of the brothers with the whole gene deletion were unavailable although the presence of the same deletion in them indicates an inherited rearrangement.

To characterise the size and breakpoints of deletions encompassing the first and/or last exon of *SCN1A*, we analysed the nine corresponding patients using high-density SNP arrays (370 K; Illumina), and found that the eight detectable deletions have different breakpoints and size, (range 0.15 to 2.9 Mb), with the exception of two deletions (patients 3 and 4) with similar size and close breakpoints (figs 3,4). The nearby genes comprised in the deletion were therefore different between patients. The remaining deletion, covering exons 22–26, was the smallest and could not be detected with this method. The values obtained for the SNP in the region suggest that it is limited to the *SCN1A* gene. These results show that most genomic deletions encompassing *SCN1A* are generated through different molecular mechanisms.

### Screening of additional regions of *SCN1A* in negative patients

Tate *et al*[15] have described a highly conserved alternative exon (5N), located 95 bp upstream of the exon 5 present in the adult isoform (exon 5A), which introduces three differences in the 30 encoded amino acids (Tyr202Phe, Asp208Asn and Val212Phe) when incorporated instead of exon 5A.[15] The functional consequence of this substitution is to date unknown. However, the switch between these two isoforms is thought to be developmentally regulated, as has been shown for SCN8A, with transcripts containing exon 5N predominating in fetal and neonatal brain, and transcripts containing exon 5A being the preferential isoform expressed in adult brain. We identified several different types of mutation in exon 5A in our patients with Dravet syndrome, confirming previous studies.[5] To determine whether mutations or variants in exon 5N can be identified in patients with Dravet syndrome, we directly sequenced this exon in the remaining negative patients. No deleterious change was detected in exon 5N, indicating that this exon and the corresponding isoform are probably not involved in the physiopathology of the disease.

Recently, Martin *et al*[17] described seven novel non-coding exons of *SCN1A* (1a to 1g, corresponding to the 5′ UTRs). Furthermore, comparison with paralogous (*SCN1A* vs *SCN2A* and *SCN3A*) and orthologous (human vs mouse) sequences revealed 11 conserved non-coding sequences in *SCN1A* (in the 5′ UTR, intron 10 and intron 20), at least two of which could influence the transcription of the gene.[17] To determine whether variants or mutations in these regions can cause Dravet syndrome, we screened the eight most conserved regions in our negative patients. Eight different variants (two in the 5′UTRs, one in intron 11 and five in intron 20) were identified in seven patients (supplementary table E online). Analysis of the parents of three patients revealed that the c.1-52589T→C (5′UTR), c.2043+233C→T (intron 11), c.4003-661A→G, c.4002+2052T→C and c.4003-672_668delATTAT (intron 20) mutations were inherited from an asymptomatic parent. In addition, two variants (c.4002+2052T→C and c.4003-661A→G) were also identified in a Caucasian control population (supplementary table E online). These results suggest that none of the variants detected in the 5′UTR and intron 20 are involved in Dravet syndrome, and that mutations outside the coding region of *SCN1A* are not a common cause of Dravet syndrome for patients without mutations in the coding region.

In conclusion, this analysis found that 242 of 333 (73%) patients carried a mutation: 228 point mutations and 14 microrearrangements (8 partial *SCN1A* deletions, 3 of which were partial deletions extending outside *SCN1A* and 6 whole gene deletions).

## DISCUSSION

This study reports the wide mutation spectrum of *SCN1A* associated with Dravet syndrome, including both point mutations and rearrangements, in the largest series of patients reported to date. In addition, we screened the conserved non-coding regions of the gene and excluded causative mutations in these regions in patients negative for mutations in the coding sequence.

Our results confirm that all types of DNA alterations in the *SCN1A* gene are present in patients with Dravet syndrome:

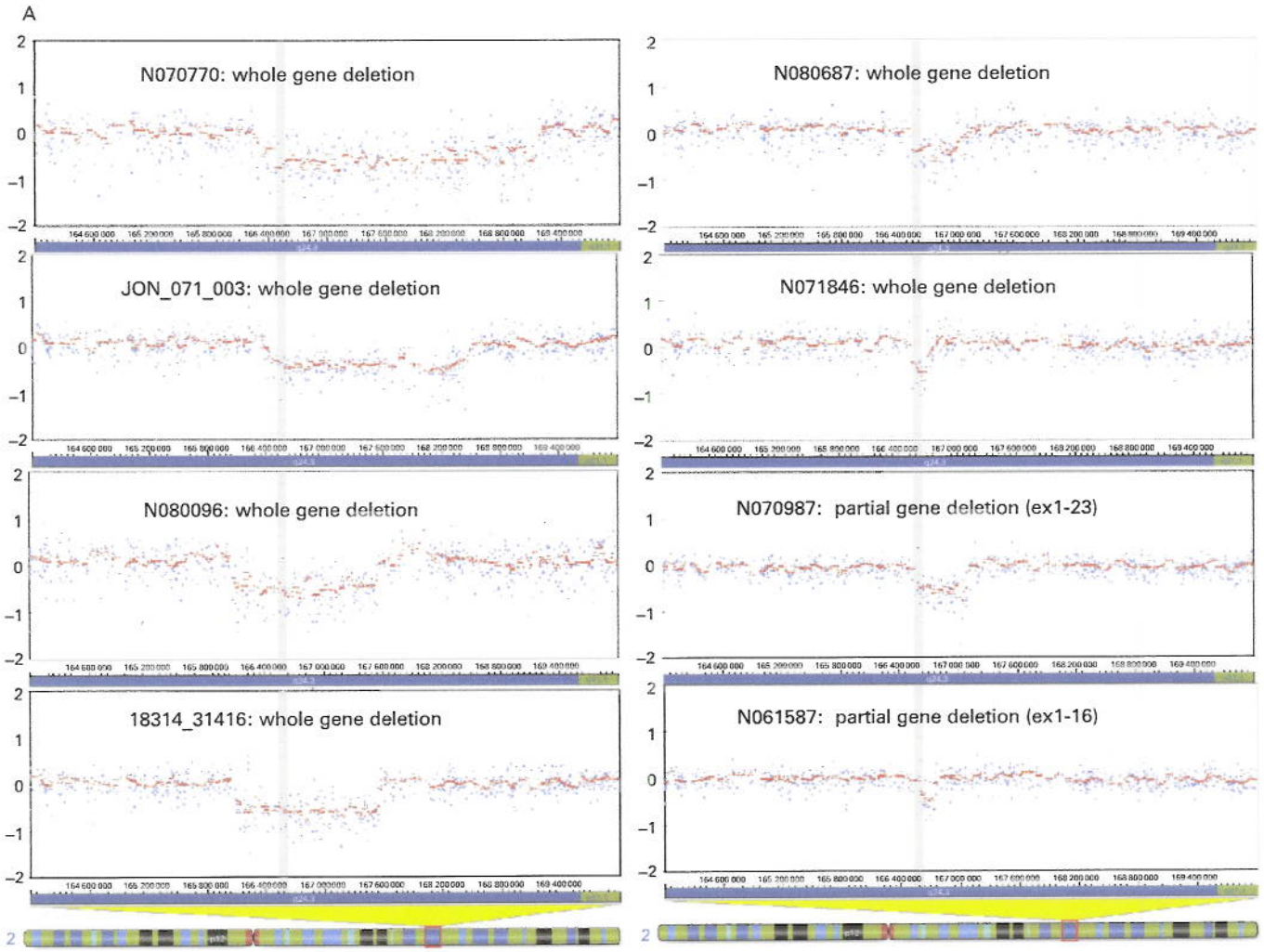


**Figure 3** Characterisation of the size and breakpoints of the rearrangements including the first and/or last exon of *SCN1A* using high-density SNP arrays (Illumina): log R profiles of the eight patients with detectable deletions, with position on the chromosome 2 (*x* axis) against log R (*y* axis). Grey stripes, location of *SCN1A*.

missense, nonsense, and splice-site mutations, small deletions and insertions, and rare large-scale deletions. Mutations in our patients were found all along the *SCN1A* gene. Missense mutations were the most common mutation type identified in our patient group (42%), in contrast to the initial report of Claes *et al*, which reported only truncating mutations.[4] The main remaining mutation types (nonsense, splice-site mutations, frameshift) introduce PTC into the mRNA, which are probably recognised and degraded via the nonsense-mediated mRNA decay surveillance system of the cell, with the exception of truncating mutations located in exon 26.[20] This hypothesis is compatible with the effects of the other mutation types detected including alteration of the initiation codon and the microdeletions that delete essential regions of the proteins, introduce PTC, or delete the whole gene in the heterozygous state. Consequently, the preferential mechanism suggested by this mutation spectrum would be haploinsufficiency ie, total loss of function of the mutated allele.

In spite of many functional studies, it remains unclear how missense mutations can cause a clinical phenotype indistinguishable from that of truncating mutations or whole-gene deletion. Kanai *et al* suggested a preferential location of the missense mutations in the S5 and S6 segments and the S5–S6 intracellular boucle, which together form the "pore" of the Nav1.1 channel.[21] The systematic classification of missense mutations using Alamut software revealed that most missense mutations found in our study affect highly conserved amino acids located in ion-transport sequences and result in chemically dissimilar changes in amino acid classes. However, these mutations were not preferentially located in S5–S6 segments, in contrast to the previous report.[21]

In addition to mutations detected by standard techniques, we identified 13 patients with partial (n = 7) or complete (n = 6) gene deletions and one patient with a partial gene duplication. This is the largest series of patients with rearrangements in *SCN1A*, and the first duplication reported to date. It raises the number of partial rearrangements in *SCN1A* to 14, including the 6 intragenic deletions previously reported.[6 9 10] Whole-gene deletion was the main event detected, but analysis of the patients with this abnormality using high-density SNP arrays revealed that, with the exception of two patients who shared a deletion similar in size, all other deletions were private rearrangements that also delete nearby genes in the 2q24 region, including in particular other genes encoding voltage-gated sodium channels (*SCN7A* and *SCN9A*). In the three patients with partial deletion for whom the parents were

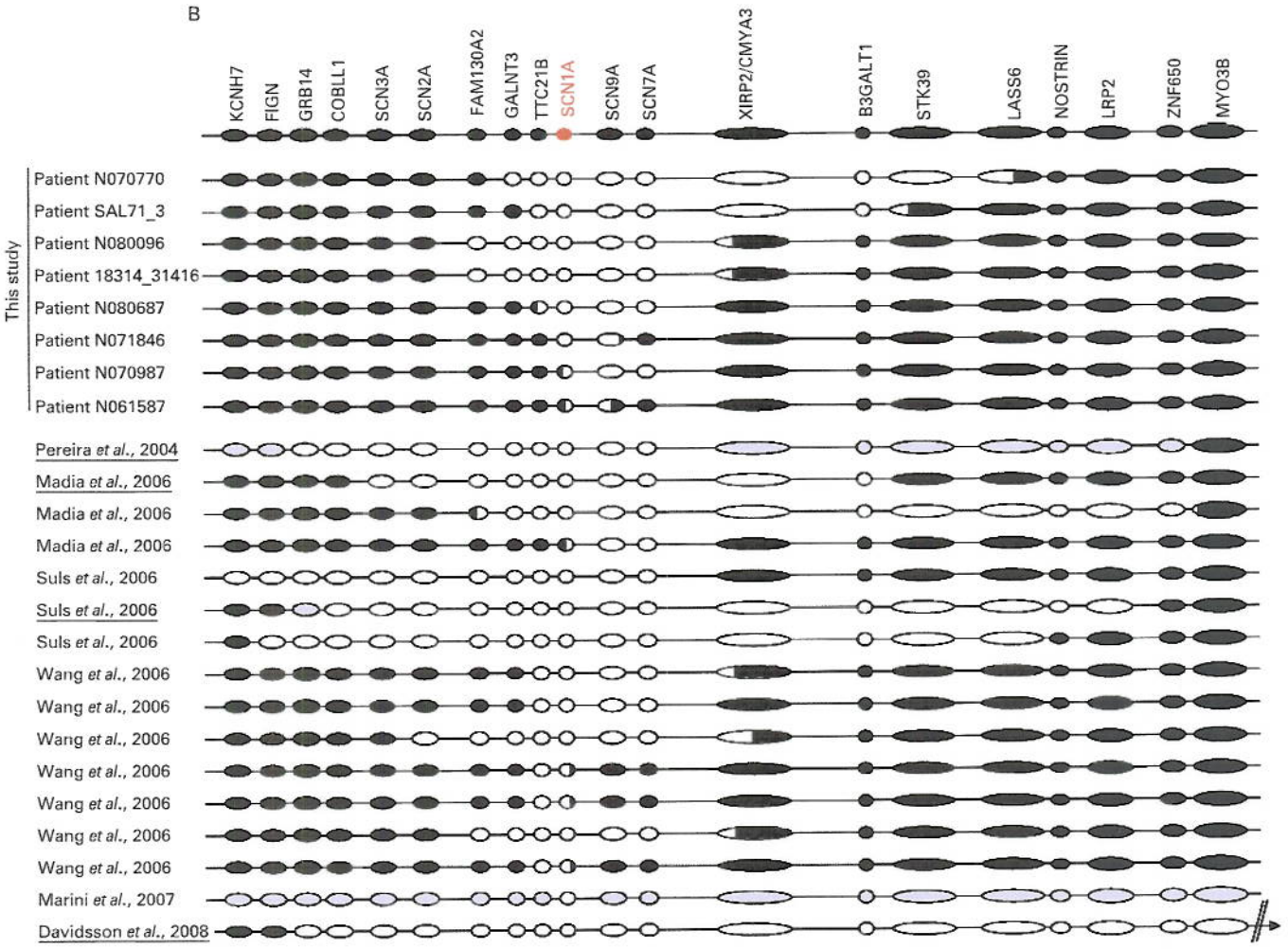


**Figure 4** Schematic representation of genomic microdeletions extending the *SCN1A* gene (red) detected in this study and reviewed from the literature. Filled black figures, two copies of the corresponding genes (normal); blank ellipses, genes that are deleted in an allele; underlined references, reported complex phenotype.

available, the deletion was confirmed to have arisen de novo. The presence of two brothers with the same complete gene deletion showed that occasionally, rearrangements can also be inherited from an asymptomatic parent, as already described for point mutations. The mechanisms involved in these inherited mutations will be investigated in detail elsewhere (Depienne *et al*, in preparation).

Strikingly, the patients with these large deletions had similar clinical features compared with those with point mutations, and none presented with additional features. These results suggest that the haploinsufficiency of these voltage-gated sodium channels genes, in which missense mutations have been occasionally reported in patients with various epileptic phenotypes, including benign familial neonatal–infantile seizures,[22 23] does not worsen the clinical features of patients with SMEI. On the other hand, four patients in previous studies were reported to have features additional to SMEI: one patient had autism, precocious puberty and palatoschisis;[7] the second had features of a neurodegenerative disorder including acquired microcephaly, psychomotor and visual regression, very severe photosensitive epilepsy, athetosis of the four limbs, and hepatomegaly;[8] the third had dysmorphic features, growth failure, hypotonia, cardiac defects and limb abnormalities;[24] and the fourth presented with muscular hypotonia, dysmorphy, cleft palate, high anal atresia, atrial septal defect and syndactyly.[25] However, most of these clinical features, which differ between patients, are unlikely to be due only to haploinsufficiency of genes located in these regions, as at least one patient with "pure" Dravet syndrome had a deletion encompassing these genes (fig 3), with the exception of the last patient who had the largest distal deletion.[25] Nevertheless, in the remaining cases, the deletion could reveal mutations or variants located in one of these genes on the undeleted allele, which could contribute to the clinical picture. The additional features could also be due to other alterations unrelated to the 2q24 (*SCN1A*) deletion in the genome of the patients. However, several very large deletions encompassing more than the 2q24.3 chromosomal band have been reported (for review see Davidsson *et al*[25]). In contrast to patients identified and reviewed in this study, patients with these very large deletions could have consistent dysmorphic features including ear abnormalities, microcephaly, micrognathia and brachysyndactyly.[25]

The proportion of patients with *SCN1A* mutations in our series is 73% (242/333). This proportion has been highly variable in previous studies, ranging from 33%[18 26] to 80–100%.[4 5 27 28] These discrepancies may be due to the sizes of the series and the

use of different clinical criteria to define Dravet syndrome. Supporting this hypothesis, the proportion of positive patients is higher in SMEI using strict criteria than in epileptic syndromes closely related to SMEI including ICEGTC (intractable childhood epilepsy with generalised tonic–clonic seizures) or SMEB (borderline SMEI).[27–29] In our series, we also had to take the various clinical presentations of the patients into account (see Methods). Considering only the patients with typical Dravet syndrome (n = 271), the proportion of patients with *SCN1A* mutation reaches 78% (212/271). These results confirm that approximately 20% of patients presenting with classic features of Dravet syndrome do not have mutations in *SCN1A*, even when microrearrangements have been excluded. These results validate the mutation frequencies recently reported in the literature.[10 29] In addition, recent studies have established that rare pathogenic mutations in *SCN1A*, some of which are de novo, can also be identified in other infantile epileptic encephalopathies such as cryptogenic generalised epilepsies, cryptogenic focal epilepsies or infantile spasms.[26 29 30] This extension of the clinical spectrum related to *SCN1A* has questioned the initial concept of SMEI, because neither clinical nor genetic criteria are sufficient to delimit accurately the various syndromes. Interestingly, we report two mutations, p.Arg393Cys and p.Arg1596Cys (previously identified in patients with cryptogenic focal epilepsy[29]) in patients with typical SMEI. This suggests that the variation in clinical presentation is not intrinsic to the mutations themselves but rather to their interaction with other yet unidentified genetic or environmental factors. We also report the p.Arg1575Cys variant, recently identified in a patient with Rasmussen encephalitis,[31] in a patient who had another de novo p.Glu602X mutation and in his asymptomatic mother. This variant has been shown to increase persistent sodium current compared with the normal channel in *in vitro* studies.[31] Our results confirm that this rare variant is not associated with Dravet syndrome. Neither this variant nor another *SCN1A* variant was found in three patients with Rasmussen syndrome (C Depienne & R Nabbout, personal communication). The study of additional patients with this variant is needed to confirm whether it is a risk factor for Rasmussen syndrome.

As *SCN1A* is the main gene involved in Dravet syndrome, we hypothesised that other mutation types located in this gene but missed using both direct sequencing and MLPA, could be identified in negative patients. We therefore screened exon 5N, which is suspected of involvement in early fetal stages of the development, and highly conserved non-coding regions of the gene, which could be important for normal gene expression and regulation. However, this screening did not reveal any additional mutation, indicating that mutations outside the coding region of *SCN1A* are uncommon and suggesting that Dravet syndrome is genetically heterogeneous. Further genetic studies are needed to determine the causative mutations and genes involved in the remaining *SCN1A*-negative patients.

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further pressurizing an over-burdened system. At the same time, the plummeting success rates lead referees and applicants alike to focus on safe, incremental research rather than larger, more ambitious work.

But a ban on researchers — even those whose consistent lack of success disproportionately overburdens the system — is a clumsy way to try to break this cycle. When success rates are so low, the peer-review system cannot reliably identify the worst performers: rankings can vary so much from one reviewer to the next that many solid proposals end up being rejected along with the weak ones, just by the luck of the draw. And even if the system were reliable, the scientists involved have no time to adjust: the policy is being applied retrospectively. Worse still, this temporary ban could easily leave a permanent stain — particularly on the careers of young researchers.

Any benefit an applicant ban might have provided is being outweighed by the bad feeling its abrupt introduction has engendered. Some potential reviewers are talking of boycotts because they don't want to contribute to a system in which their decisions can shut out colleagues. Researchers also feel that they were not sufficiently consulted on the specifics of such a controversial decision.

Other options were available. Using an expert-committee triage to sift through outline applications before the full peer review, for example, would give instant feedback to researchers on where they are going wrong, speeding up the recovery process. Introducing regular deadlines for submission might help regulate the flow of applications from particularly voluminous applicants.

**"Any benefit an applicant ban might have provided is being outweighed by bad feeling."**

On its own, the ban is likely to achieve little and provoke much. It might have been more happily accommodated if accompanied by an overarching set of reforms, discussed with the wider community. Maintaining the peer-review system for grant applications depends on the trust and cooperation of its reviewers — the researchers themselves, who do the bulk of the work. The EPSRC seems to be alienating the very scientists its system depends on. ■

# Property rights

## The granting of patents on human genes has so far not been the disaster it was predicted to be.

In 1980, the Bayh–Dole Act gave US universities the right to patent discoveries made with government funding. Not long after, universities and companies began the much-criticized practice of patenting genes, laying claim to human DNA sequences for research and diagnostic purposes. Europe and Japan followed suit, legalizing gene patenting in the 1990s.

Researchers and health professionals alike attacked the strategy. They worried that patents would make it harder to develop new genetic diagnostic tests; that corporate monopolies would hamper patients' access to the tests; and that thickets of interlinked intellectual property would scare off those interested in researching and improving the tests. To solve these ills, suggestions have included patent pools in which developers would share buy-in rights for a collection of patents — and even the total abolition of gene patents. But for all the fuss, few, if any, of the initial concerns have been borne out.

In the United States, the longer history with gene patents and the privatized nature of health care have indeed enabled a few companies to secure a monopoly on some tests. But as described in the Commentary on page 405, genetic tests from companies with exclusive licensing rights are no more expensive or harder to access than those offered by various providers under non-exclusive licence.

Nor is there any empirical evidence to suggest that companies are quashing innovation. A survey last year revealed that for more than 40,000 gene patents, only six instances of litigation came up in relation to diagnostic testing (C. M. Holman *Science* **322,** 198–199; 2008). All six were settled or dismissed within a year and a half, suggesting that the scale of litigation is not as high as some suspected. Reports of researchers being blocked from access to patented DNA sequences or being sued for infringement are extremely rare, and workarounds are not difficult from a legal perspective. Moreover, a study by Loet Leydesdorff at the University of Amsterdam and Martin Meyer of the Catholic University of Leuven in Belgium set to be published in *Scientometrics* later this year, suggests that the trend for patenting genes is waning among universities as they increasingly recognize that the return on investment is not as high as had been predicted.

In Europe, the number of gene-patent applications is rising faster than in the United States — although Europe's later start means that the licensing of intellectual property is still extremely low. Moreover, as noted in a second Commentary on page 407, in publicly run academic and medical genetic testing facilities in Europe, users of diagnostic tests are largely unaware of the patent status of the technologies involved — nor do they seem particularly concerned about the legal implications. In part, this attitude may arise because even if they are infringing a patent — which can be difficult to prove — the facilities are so small and dispersed that it would be hard for patent holders to pursue and secure damages.

But such safety from litigation cannot be relied on — witness the long battle by the University of Utah in Salt Lake City to have its patent on the *BRCA1* breast-cancer gene recognized in Europe. European testing labs, some of whom have stated in the past that they intend to continue *BRCA1* testing in defiance of the patent, will need to tread carefully.

Dire predictions that patents will cripple genetics research should be viewed with scepticism on both sides of the Atlantic. This is not an argument for complacency. Nor is it a defence of the patent system as a whole, which needs major reform to address the scope and purpose of patents. If academics are going to continue to patent intellectual property, they need to recognize that it must be respected and licensed properly. Moreover, patent holders need to accept that patent rights come with a responsibility to honour the spirit in which they are awarded. Patents are meant to encourage and reward innovation, and, although this shouldn't happen at the cost of further innovative development, it is a premise that shouldn't be discarded purely because there is a vague hint that harm might one day occur. ■

COMMENTARY

# The dangers of diagnostic monopolies

**In the first of two commentaries on intellectual property, Robert Cook-Deegan, Subhashini Chandrasekharan and Misha Angrist show how the United States can address glitches with exclusive licences.**

Gene patents are meant to encourage innovation, but in DNA diagnostics, they have stirred controversy. Amid worries and worst-case scenarios, there are few empirical studies to help form an accurate picture of how patents affect clinical genetic testing in the United States. We assembled eight case studies addressing the effects of patents and licensing on access to genetic tests for ten conditions (see 'Gene-test licensing in the United States', overleaf). The studies were prepared for a task force of the Secretary's Advisory Committee on Genetics, Health and Society and are available as inputs to a draft report[1] for the US Secretary of Health and Human Services. They paint a complex picture of the patent landscape.

Despite the fears, patents have not caused irreparable harm in genetic diagnostics, but neither have they proven greatly advantageous. Although our findings detect no pervasive effects that consistently help or hinder clinical access to genetic testing, there are some problems that could be addressed to the benefit of patients, researchers, health professionals and companies alike.

## Pricing and availability

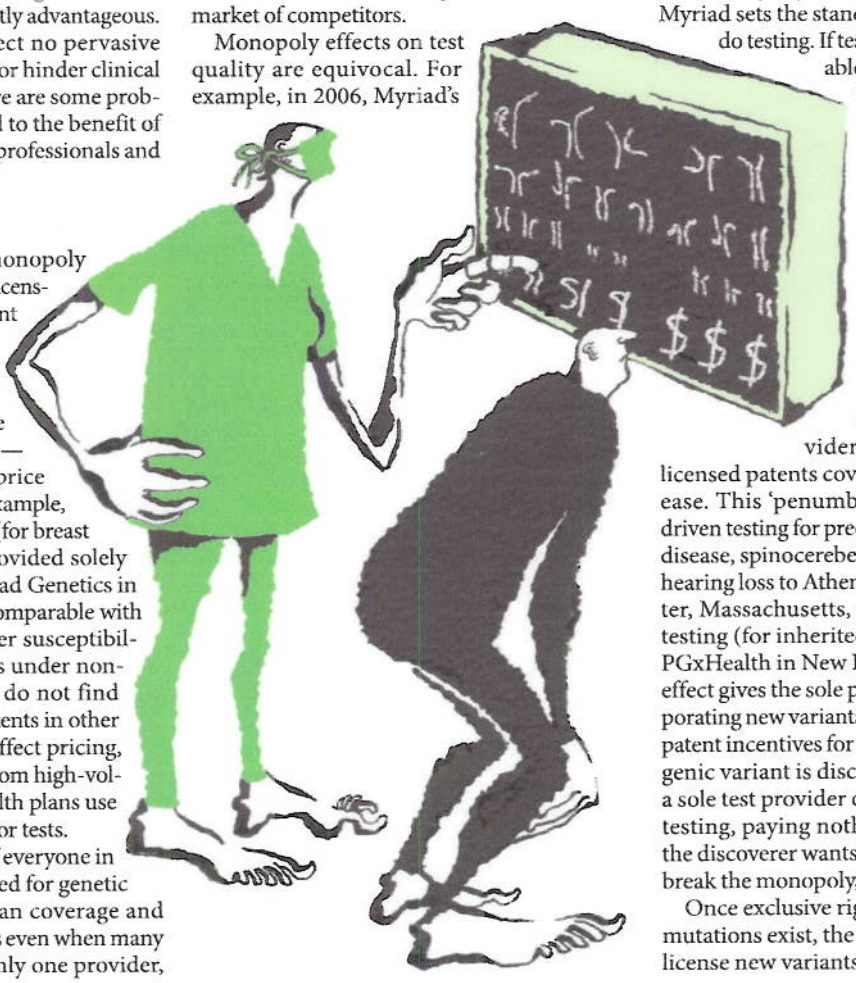
Most concerns centre on monopoly situations, in which exclusive licensing results in a single dominant provider. But prices of patented and exclusively licensed tests are not dramatically or consistently higher than those of tests without a monopoly — a contrast with the strong price effects of drug patents. For example, unit prices for BRCA testing (for breast cancer susceptibility) — provided solely in the United States by Myriad Genetics in Salt Lake City, Utah — are comparable with similar tests for colon cancer susceptibility available from many labs under non-exclusive licences. We also do not find consistent price effects of patents in other case studies. Other factors affect pricing, such as efficiencies of scale from high-volume testing and the way health plans use administrative codes to pay for tests.

Prices would matter less if everyone in the United States were insured for genetic diagnostic tests. Health-plan coverage and reimbursement are problems even when many labs offer a test. But with only one provider, the absence of alternatives can exacerbate the problem. Some health plans do not have a contract with the sole provider, for example. Nevertheless, after ten years of testing, Myriad now reports payment arrangements that substantially cover costs for more than 90% of tests, so problems in coverage and payment cannot solely be attributable to monopolies.

One justification for gene patents is that they speed up the development of tests. But the patent incentive is usually not necessary. Barriers to test development are fairly low compared with in the 1990s, when the genetic bases for most of the conditions we studied were elucidated. Academic labs typically offer testing soon after publication of an association, when demand exists. After exclusive licences are issued, however, the licensee enforces patents to 'clear' the market of competitors.

Monopoly effects on test quality are equivocal. For example, in 2006, Myriad's methods of BRCA testing were shown to miss some DNA deletions and rearrangements[2]. Yet such problems cannot be ascribed only to the monopoly. Problems are apparent in genetic testing for other conditions offered by labs with non-exclusive rights. Test quality is a general problem but monopolies can exacerbate it.

Sole providers can also, for better or worse, establish standards of care. Licences for patents related to risk prediction for Huntington's disease and Alzheimer's disease enforced clinical standards set by the professional community[3]. If compliance with standards is desirable, patents can achieve it. But is a standard of care set by a single provider desirable? In other countries, testing labs take various approaches before ordering full-sequence BRCA testing as licensed by Myriad. Yet in the United States, Myriad sets the standard because it alone can do testing. If testing alternatives are valuable, exclusive licences limit their availability.



B. MELLOR

Exclusive licences are difficult for other companies to develop around. Most genetic disorders are heterogeneous — different genes and mutations lead to clinically similar syndromes. An exclusive licence to one or a few common genes or mutations can drive testing to one provider, regardless of whether licensed patents cover all varieties of the disease. This 'penumbra effect' seems to have driven testing for predisposition to Alzheimer's disease, spinocerebellar ataxia and hereditary hearing loss to Athena Diagnostics in Worcester, Massachusetts, and long-QT syndrome testing (for inherited cardiac arrhythmia) to PGxHealth in New Haven, Connecticut. The effect gives the sole provider a leg-up in incorporating new variants into its assay. It also alters patent incentives for others. If a gene or pathogenic variant is discovered but not patented, a sole test provider can incorporate it into its testing, paying nothing to the discoverer. If the discoverer wants a piece of the action or to break the monopoly, he or she must patent it.

Once exclusive rights to common genes or mutations exist, the only realistic option is to license new variants exclusively, either to the

GENE-TEST LICENSING IN THE UNITED STATES

| Condition | Test provider(s) | Patent(s) owner | Licensing |
|---|---|---|---|
| Tay-Sachs disease | Various | National Institutes of Health (NIH) | Not licensed |
| Inherited risk of colorectal cancer | Myriad and others | University | Non-exclusive |
| Inherited risk of breast/ovarian cancer | Myriad Genetics | University, Myriad, NIH | Myriad (exclusive) |
| Canavan disease | Various | Miami Children's Hospital | Private settlement |
| Cystic fibrosis | Various | University and hospital | Non-exclusive |
| Alzheimer's disease | Athena Diagnostics | University | Athena (exclusive) |
| Spinocerebellar ataxia | Athena | University and Athena | Athena (exclusive) |
| Haemochromatosis | Various | BioRad | Non-exclusive |
| Hearing loss | Athena and others | University and hospital | Athena (exclusive) |
| Long-QT syndrome | PGxHealth | University | Possible mutual block |

existing sole provider (augmenting the monopoly) or to a rival company. Indeed, the potential for mutually blocking patent rights seems to be developing: PGxHealth has been the sole long-QT test laboratory for several years, based on exclusive rights to several patents. But the University of Utah in Salt Lake City recently awarded exclusive rights for other long-QT-related patents to Bio-Reference Laboratories in Elmwood Park, New Jersey. It remains to be seen how this situation will affect patient access.

## An instrumental right

Some companies that have used patents to build their businesses claim that their services are of equal or better quality than university and reference laboratory services. But, in our case studies, clinicians, patient groups and even other companies argue that patents should be non-exclusively licensed for diagnostic purposes. Who should provide proof as to whether patents and exclusive licences are promoting or interfering with progress?

We propose that patient rights should trump patent rights if a company engages in practices that undermine the purpose of patents in the first place (see 'Recommendations in cases of monopoly'). The burden of proof should lie with the companies enforcing patent rights.

Patenting is a right, but an instrumental one. The US Constitution states that patents are granted to promote public good through advancing science and technology. The stakes are high when human health is involved. Governments should take action when harm is apparent or foreseeable, especially when technologies spring from public funding. The government has powers that have not been used: to decide coverage and reimbursement for tests, to regulate and to ensure that patent rights promote health and safety under the 1980 Bayh–Dole Act.

Academic institutions play an important part in clinical genetic testing. They own most of the patents relevant to Mendelian disease testing[4], and 60% of clinical genetic testing laboratories are within universities[5]. Academic institutions thus both own most genetic-diagnostic patents and operate many of the laboratories against which such patents are enforced. This paradox derives from technology licensing and clinical laboratory services that are run by different parts of universities and have different missions. These need to be aligned. A non-binding statement endorsed by the Association of University Technology Managers in 2007 says "licenses should not hinder clinical research, professional education and training, use by public health authorities, independent validation of test results or quality verification and/or control".[6]

As we attempted to reconstruct custody chains for the relevant intellectual property, university technology licensing offices were often among the missing links, failing to provide information despite repeated inquiries. If we are to demand transparency from private genetic testing laboratories, academic institutions that license technologies arising from federal grants should be at least as willing to provide information. Research institutions that use public dollars to create licensed inventions are publicly accountable for the disposition of the resulting intellectual property.

Looking to the future, robust genomic technologies promise to transform genetic testing. The price of full-genome sequencing will drop, and speed and accuracy will improve. Soon, sequencing a person's entire genome will cost less than current tests for one or a few genes. Yet thousands of patents claim human DNA sequences[7] and so some patent claims will be infringed by full-genome sequencing. This legacy of patented sequences could cause considerable mischief, depending on how intellectual property is managed. As genetic testing is transformed by new technologies, patenting and licensing practices and government oversight should focus on the net social benefit for patients as well as on freedom to innovate. ■

**Robert Cook-Deegan, Subhashini Chandrasekharan** and **Misha Angrist**, are at the Institute for Genome Sciences and Policy, Duke University, Durham, North Carolina 27708, USA.
e-mail: gelp@duke.edu

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This article represents the authors' opinions and not those of the Secretary's Advisory Committee for Genetics, Health and Society or its task force.

**See Editorial, page 386, and online at http://tinyurl.com/dlnksh.**

**Recommendations in cases of monopoly**

We find six obstructive practices and policies that we think should negate gene patent enforcement for diagnostic-testing companies with exclusive rights. Patient rights should trump patent rights if a company's policies do not permit:

- Basic and clinical research, including genetic testing in clinical trials or health-services research.
- Performing a test in a form that it does not offer (such as prenatal or preimplantation diagnosis).
- Testing in a territory where the company does not offer a test but has exclusive rights.
- Getting second opinions or verification testing.
- Testing those not covered by its payment agreements with insurers and health plans.
- Research and development to make testing more comprehensive, more accurate or less expensive.

As unique guardians of key information, sole-provider laboratories have a responsibility to:

- Share data about allele frequency, number of tests, aggregate results and other facts relevant to public health.
- Contribute to public databases that catalogue variants and contribute to their interpretation.
- Perform proficiency testing and otherwise ensure quality of testing.
- Disclose intellectual-property ownership and licensing provisions related to genetic diagnostics.

COMMENTARY

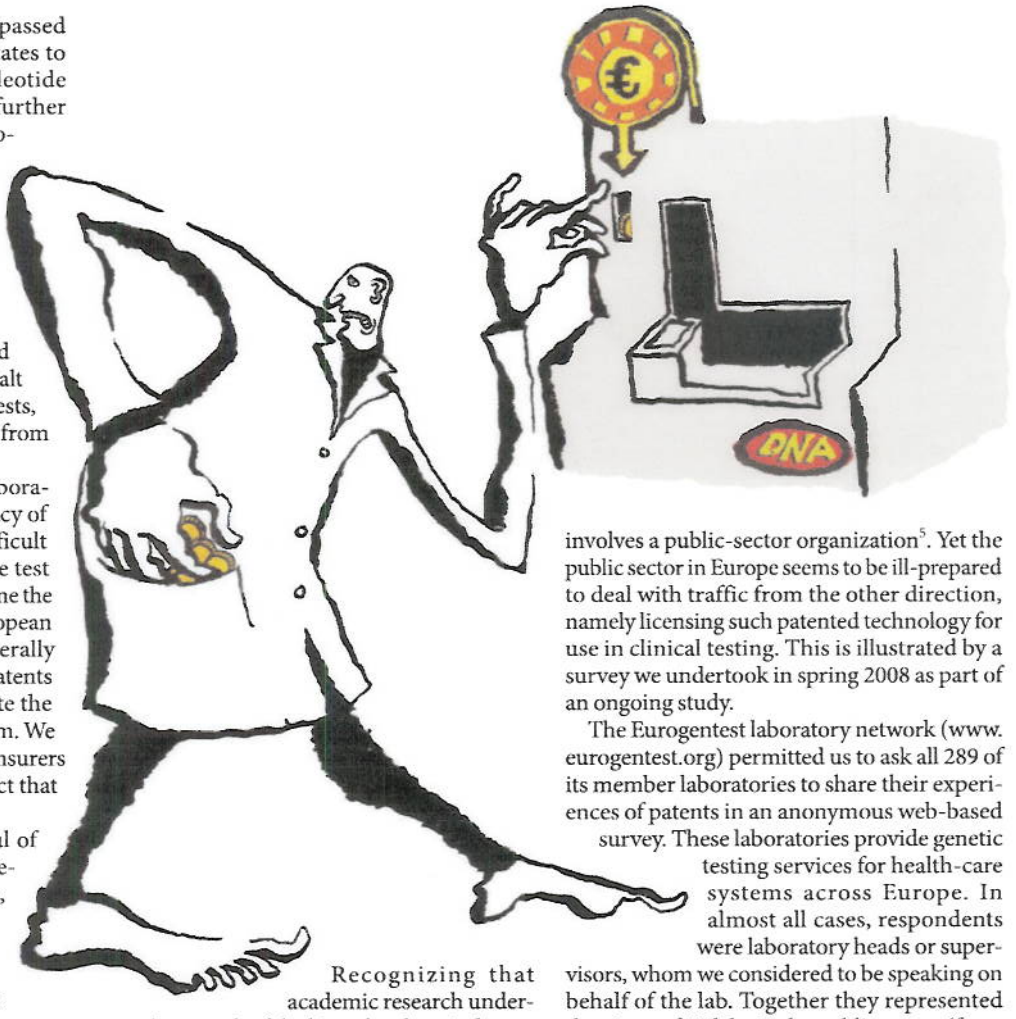
# The phantom menace of gene patents

**In this, the second of two Commentaries, Sibylle Gaisser, Michael M. Hopkins and colleagues discuss a survey demonstrating that European health-care systems are ill prepared for the commercial reality of gene patents.**

In 1998, the European Parliament passed a law that requires EU Member States to recognize isolated genes and nucleotide sequences as patentable inventions, further reiterating obligations under the European Patent Convention. Patents can also be granted for methods of genetic testing without claiming genes themselves, as illustrated by recent rulings of the European Patent Office Board of Appeal. These rulings upheld patents granted to the biotechnology firm Myriad Genetics and the University of Utah, both based in Salt Lake City, for *BRCA1*-related cancer tests, in the face of considerable opposition from European scientists.

Some European clinical-genetics laboratories refuse to recognize the legitimacy of such patents, arguing that they are difficult to invent around, excessively increase test prices and hinder innovation[1]. To examine the extent of such effects we surveyed European labs and found that, in fact, they generally had little experience of dealing with patents and require more support to negotiate the changing patent landscape around them. We suggest that public and private health insurers will have to come to terms with the fact that costs could rise.

Although we found only a handful of cases in which there was patent enforcement against testing labs in Europe, the financial stakes are rising. More companies are investing in genetic diagnostics, and private market analyses have projected high annual growth in the next 5 years[2].




B. MELLOR

## Fair and reasonable

As the market matures, so too must the views of those offering or buying genetic tests. For example, there are different perceptions of what constitutes 'fair' or 'reasonable' licensing fees between non-commercial clinical scientists and biotechnology investors[1]. Such problems are compounded by the licensing strategies of some patent holders, who could deny laboratories the choice to offer a test[3].

Health-care systems must respond to the possibility that the tests they rely on may be patented by organizations seeking a return on their investments high enough to compensate for the risk of commercial failure. Recognizing that academic research underpins the growth of the biotechnology industry, European countries have strongly promoted patenting in the public sector[4]. This had been spurred on by the lucrative profits of some universities and by the 1980 Bayh–Dole Act in the United States, which permitted patenting of research supported by federal funding. Similarly, the European Parliament's 1998 law (Directive 98/44/EC) that encouraged gene patents is itself a policy response to the perceived economic value of biotechnology patents.

As a result of such stimuli, one in three patent applications on human genetic material involves a public-sector organization[5]. Yet the public sector in Europe seems to be ill-prepared to deal with traffic from the other direction, namely licensing such patented technology for use in clinical testing. This is illustrated by a survey we undertook in spring 2008 as part of an ongoing study.

**"Often labs fail to check for patents, may be able to work around a patent or challenge its validity."**

The Eurogentest laboratory network (www.eurogentest.org) permitted us to ask all 289 of its member laboratories to share their experiences of patents in an anonymous web-based survey. These laboratories provide genetic testing services for health-care systems across Europe. In almost all cases, respondents were laboratory heads or supervisors, whom we considered to be speaking on behalf of the lab. Together they represented the views of 77 labs in the public sector (from hospitals, universities and government labs).

The response rate is lower than that of a similar survey in the United States[6], perhaps indicating that the issue of patenting is seen as less important in European labs. Indeed, in telephone calls to non-responders, lack of time was the only reason given for not participating. We detected no response bias in nationality or laboratory size. Because of low response numbers per country, we report on the experiences of European labs overall rather than drawing national-level inferences.

Our findings highlight poor aware-

ness of patent licensing conditions in the European Union. Only 22% of responding labs (17) thought they performed tests on patented genes, while 55% (42) said they did not and 23% (18) did not know. Notably, of the 17 labs testing patented genes, just one lab paid royalties directly, another lab had negotiated with a licenser, but did not pay. Two further labs were aware that royalty fees were included in test-kit prices. There is little evidence of labs being put off patented tests by licensing costs. Only four labs reported costs to be prohibitive, whereas 60% (46) said they did not know enough about licensing costs to comment.

This lack of awareness may be because labs sometimes buy kits for which a patent licence is bundled in the purchase price. In other cases, labs simply develop in-house tests with little concern for patent infringement[3]. These 'home brews' vary in quality but are often less expensive than buying commercial kits[7]. Nevertheless, their use could prompt legal action by patent holders. We did not explicitly ask lab supervisors to state if they infringed patents as this may have discouraged some from responding to the survey. Furthermore, such a question would assume the act of infringement is clear cut. Often labs fail to check for patents, and in other circumstances may be able to work around a patent or challenge its validity.

When it comes to support in dealing with patents, 37% (28 of 75; some did not respond) of public labs reported that they did not have sufficient information or support to deal with patent-related issues. Only 32% (24/75) said they were confident that they did. Furthermore, when asked if the legal advice they needed was available, 26% (19/73) said yes, but for 33% (24/73) legal advice was not available.

**"This is the logical consequence of current policy, and the price we pay for the commercialization of science."**

## No menace in Europe — yet

For all the concern from geneticists about the effect of patents on genetic diagnostics (see 'The fear of patenting'), there is still relatively little evidence of friction in Europe between patent owners and labs. We found that just 4% (3/77) of responding public-sector labs have ever been prevented from offering a testing service because of a patent-related issue. Three out of six private companies that also responded to our survey said they have been similarly prevented. These figures are still low compared with previous surveys in the United States where 25% (30/122) of labs reported not being able to offer a service as a result of patents held by other organizations[6]. This may be due to a delayed effect, either because patents take much longer to grant in the European Union than in the United States, or because patent owners are yet to take action. But, at this time, our data suggest the concerns about patented genetic inventions have been overstated in Europe.

One possible reason for the trans-Atlantic difference is that fewer genetic inventions are patented in Europe. A 2007 study of human nucleotide sequence patents followed more than 15,000 patent applications filed before December 2003 and found that only 750 had been granted in Europe compared with more than 5,000 in the United States by 2005 (ref. 8). In part, this reflects the higher costs of patenting and the historically higher patentability bar in Europe in this field. Thus, many US inventors have not patented in Europe to the same extent that they have domestically, even though they have had the opportunity to do so. Other reasons for differences in observed enforcement may be due to differences in patent law, market size and patterns of service delivery that make litigation by patent owners (anywhere in the world) less attractive in the European Union. In addition, the European Commission monitors closely the implementation of the EU biotechnology directive and its effects[9].

Although gene patents might not be as menacing as some geneticists have suggested[1,10], government and health-care systems can no longer afford to ignore patents on genetic inventions. Their current approach might be perceived as hypocritical. Governments continue to promote patenting as a means to improve the return on investment in scientific research, and hospital labs operate increasingly like businesses by charging for their services.

Furthermore, labs generally offer many types of genetic tests, and a growing number use multiple nucleotide sequences, for example, in DNA 'chips' (microarrays). Thus it is increasingly likely that a test that laboratories wish to offer will be affected by a patent at some point. Accordingly, labs are more likely to be called on to respect valid patents, negotiate licences for expensive technologies and pass costs on to their clients. Equally they must be able to spot invalid patents or workarounds. Governments and health-care systems must ensure patients can access useful tests, provide support to labs facing commercial challenges and pick up the bill. This is the logical consequence of current policy, and the price we pay for the commercialization of science. ■

**The fear of patenting**

Comments made on our survey reflect the fears, both real and perceived, surrounding gene patents in the European Union:

**"Enforcement of intellectual-property right would ruin most of the private laboratories. It's a threat."**

**"The costs for paying royalties are not covered by the fees paid by health-insurance companies, nobody is aware of these costs."**

**"The system will collapse, because the patent owners will never get their money, except in the very big labs, or via kits."**

**Sibylle Gaisser** is at the Fraunhofer Institute for Systems and Innovation Research, 48 Breslauer Street, 76139 Karlsruhe, Germany; **Michael M. Hopkins** is at SPRU: Science and Technology Policy Research, at the University of Sussex, Brighton BN1 9QE, UK; **Kathleen Liddell** is at the Centre for Intellectual Property and Information Law, University of Cambridge, Cambridge CB3 9DZ, UK; and **Eleni Zika** and **Dolores Ibarreta** are at the European Commission Joint Research Center, Institute for Prospective Technological Studies, Edificio Expo, Inca Garcilaso, E-41092 Seville, Spain.
e-mail: m.m.hopkins@sussex.ac.uk

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This article represents the authors' opinions and not those of the European Commission.

**See Editorial, page 386, and online at http://tinyurl.com/dlnksh.**

# Summary of key issues identified in NHMRC's 2003 submission to the ALRC's inquiry on the patenting of genetic material and related technologies

## ISSUE

In October 2003 NHMRC provided a submission to the Australian Law Reform Commission's (ALRC) inquiry into the patenting of genetic materials and related technologies. In attachment to NHMRC's submission, the NHMRC's Australian Health Ethics Committee (AHEC) provided an additional view on the ethical considerations raised by the ALRC inquiry.

## KEY CONSIDERATIONS PRESENTED IN THE SUBMISSION

NHMRC view

The submission noted that the complex nature of the ALRC inquiry and the broad range of views held by NHMRC Council members, made it difficult for the NHMRC to provide a consensus position on all of the issues raised by the inquiry.

Nevertheless, the concluding comments of the submission conveyed that the requirements for patentability should now be interpreted such that:

- isolated genetic sequences *per se* would not be patentable;
- inferred possible functions for a genetic sequence without the development of a new use for the sequence, such as a new genetic test, should not be patentable; and
- patent applications for genetic materials need to disclose an invention that provides a practical use and that examinations of such applications cover all aspects of use being specific, substantial and credible.

Ethical issues raised by the NHMRC's AHEC

AHEC raised the following ethical considerations that could be argued to be relevant to patenting genetic material:

- gene patents may restrict or prevent research in ways that could offend the ethical principle of beneficence.
- denial of beneficence – priority being given in both the subject matter of research and of potential patent targets to genes with functions for conditions of high prevalence in developed countries or populations of socio-economic advantage.

- injustice – the grant of some gene patents may differentially affect some communities because of their characteristic genome, not their socio-economic status.

- respect for persons – consent of participants in research that leads to the grant of a patent needs to be informed on all issues.

- justice – the enforcement of patents may increase the cost of providing health care.

- commutative justice – should there be sharing of commercial benefits of patent use with participants in the research that was used to gain the patent?

- beneficence and justice – a patented genetic invention should be available for prevention or treatment of emergency situations threatening public health.

AHEC's ethical considerations can be summarised as follows: integrity of researchers, respect for persons and its precedence over benefits to knowledge, the requirement for consent, beneficence, justice among populations and for participations and research merit and safety.

The NHMRC submission identified three main issues that are central to consideration of whether any changes are necessary to the existing system of patents in order to properly address the ethical and social dimensions:

1. whether there are fundamental ethical concerns associated with the patenting of human genetic material that suggest that the patenting of human genetic material should be dealt with differently to the patenting of other technologies.

   Response: Council members consider that it is not necessary, based on ethical considerations, to introduce express exemptions for genetic material into the Patents Act.

2. whether the patenting system raises issues of access and equality in relation to genetic based therapies and genetic tests.

   Response: Council considers that it would be very difficult to consider issues of the "public good" in patent assessments and therefore other mechanisms to ensure equitable access to healthcare services need to be considered.

3. whether the rights of the donors of the original tissue, or research participants are sufficiently taken into account.

   Response: Council does not feel that these issues should necessarily be dealt with within the patents system, as there are other mechanisms designed that the rights of the donor are paramount.