Identification of the Gene and the Mutation Responsible for the Mouse nob Phenotype

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PURPOSE. The available evidence indicates that the naturally occurring mouse mutant nob (no b-wave) provides an animal model for the complete form of human X-linked congenital stationary night blindness (CSNB1). The goals of the present study were to identify the nob gene defect, to characterize the expression pattern of the involved gene, and to assess visual sensitivity in nob mice.

METHODS. Positional cloning, screening of candidate genes, and sequencing were used to identify the nob gene. The expression pattern of the nyx gene was examined with Northern blot analysis and in situ hybridization. Visual sensitivity was measured with an active avoidance behavioral test.

RESULTS. The nob phenotype is caused by an 85-bp deletion in the mouse nyx gene, which encodes the nyctalopin protein. Expression of nyx was most abundant in the retina and, in particular, in the inner nuclear layer. The nyctalopin protein contains 11 leucine-rich repeats and is flanked by cysteine rich regions, which identifies it as a member of the small leucine rich proteoglycan family. Behavioral testing shows that nob mice have a significant decrease in visual sensitivity.

CONCLUSIONS. The nob mouse is a model for human CSNB1. This model will be useful in defining the role of nyctalopin in signal transmission between photoreceptors and retinal bipolar cells. (Invest Ophtalmol Vis Sci. 2003;44:378–384) DOI: 10.1167/iovs.02-04901

Vision is initiated in rod and cone photoreceptors when they hyperpolarize in response to a light stimulus. This electrical signal is then transmitted synaptically to bipolar cells, the principal second-order neurons in the retina. Presynaptically, the presence of light is communicated by the release of glutamate. Postsynaptically, this change is detected by two classes of bipolar cells that use distinct glutamate receptors. Sign-conserving, hyperpolarizing bipolar cells (HBCs) use an ionotropic glutamate receptor, whereas sign-inverting, depolarizing bipolar cells (DBCs) use a G-protein-coupled metabotropic glutamate receptor, mGlur6. The mGlur6 receptor activates an intracellular signal transduction cascade that involves cyclic guanosine monophosphate (cGMP) and culminates in the closure of a yet to be identified cation channel localized on the DBC dendrites.

Defects in the DBC signal transduction cascade are reflected as abnormalities in the electroretinogram (ERG) b-wave, which is generated by DBC activity. For example, in mice without either the mGlur6 receptor or the α-subunit of Gs, the ERG b-wave is absent, although photoreceptor function, reflected in the a-wave, is normal, as is overall retinal morphology. We have identified a spontaneous mouse mutant (nob; no b-wave) in which the ERG is similar to that recorded in mGlur6 and Goa-null mice. The ERG a-wave of nob mice is normal, indicating that rod phototransduction is unaffected by the mutation. The absence of a b-wave in nob mice indicates that the photoreceptors fail to activate DBCs. Similar to retinas of mGlur6- and Goa-null mice, those of nob mice appear morphologically normal at the light and electron microscopic levels.

From these findings, coupled with our observation that nob is an X-linked trait, we have suggested that the nob mouse may be a model for the complete form of human X-linked congenital stationary night blindness (CSNB1). Among other clinical features, patients with CSNB1 have an essentially complete loss of the ERG b-wave and a profound loss of rod-mediated visual sensitivity. These patients have a failure of synaptic transmission between photoreceptors and DBCs. CSNB1 is caused by mutations in the nyx gene, which encodes a novel leucine-rich repeat (LRR) protein of unknown function called nyctalopin.

In the present study, linkage mapping refines the location of the nob gene, and subsequent sequence analysis shows that the mutant phenotype is caused by an 85-bp deletion in the nyx gene. Expression of nyx is most abundant in cells within the inner nuclear layer (INL) of the retina, and behavioral studies demonstrate that nob mice have a marked loss of visual sensitivity. Taken together, these results confirm the initial suggestion that the nob mouse is a model for human CSNB1. As such, this mouse mutant has direct relevance to understanding CSNB1 and could be used to develop experimental treatments for this disorder. In addition, these results indicate that nyctalopin plays an important role in the photoreceptor to the DBC signal transduction process and the availability of this mouse model will help us to a better understanding of this process.

MATERIAL AND METHODS

Genetic Mapping

All procedures performed in animals were approved by the local institutional animal care and use committee and conformed to the
ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Intra- and interspecific breeding strategies were used to generate mouse pedigrees for linkage analyses. With the exception of nob mice, all other mouse strains were obtained from The Jackson Laboratory (Bar Harbor, ME). Affected BALB/cByJ nob males were crossed to normal C57Bl/6j females. The F1 female offspring, who must be carriers for the nob mutation (nob/+)/, were backcrossed to BALB/cByJ nob males. A total of 469 mice from these intraspecific backcrossed mice were used in the linkage analysis. To increase the number of polymorphic markers that were informative for linkage analyses, we also used an interspecific cross in which BALB/cByJ nob/nob (Mus musculus) females were mated to SPRET/Ei (Mus spretus) males. The F1 female carriers (nob/+/-) were backcrossed to affected BALB/cByJ males, yielding 303 interspecific backcrossed mice. All mice were phenotyped at 4 to 5 weeks of age, by using ERG, and were genotyped with various markers used for linkage analysis, as described previously.10

Isolation of New Markers Near the nob Critical Region
Several informative markers (DXMit103, DXMit187, DXMit52, DXMit605, DXMit139, and DXMit72) were present in the nob critical region, and each was used to isolate bacterial artificial chromosome (BAC) clones, by using a PCR-based strategy from commercial libraries (Research Genetics, Huntsville, AL, or Incyte Genomics, Palo Alto, CA). BAC contigs were extended by end-sequencing and rescreening the libraries until a BAC contig covering most of the nob critical region was assembled (Gregg R, unpublished results, 2002). Sequence fragments from the BAC clones were used to identify additional polymorphic markers in the nob critical region. One marker, UL107, was identified from BAC 402g19 (Research Genetics). Primer sequences to amplify this marker are UL107f (5’-cccgctctccaaacaaataa-3’) and UL107r (5’-gccgatagtgcaccgacaga-3’). PCR conditions were as described previously.10

Isolation of the Murine nyx Gene
To isolate the murine nyx gene, a cDNA clone (GenBank accession no. A1861796; http://www.ncbi.nlm.nih.gov/Genbank/) was isolated in the public domain by the National Center for Biotechnology Information, Bethesda, MD), containing a fragment of cDNA from the human NYX gene was obtained from the Image consortium (http://www.info@image.llnl.gov/; provided in the public domain and hosted by The Lawrence Livermore National Laboratory, Livermore, CA). The cDNA insert was isolated, radiolabeled by the random-primed oligo-labeling method (Amersham Pharmacia Biotech, Piscataway, NJ), and hybridized to BAC clones encompassing the nob critical region. For two positively hybridizing BACs, EcoRI and HindIII shotgun libraries were constructed and screened. A clone containing a 5.9-kb EcoRI fragment was identified from two different BACs and found through sequencing to contain exon 3 of the nyx gene. The remainder of the murine nyx gene was isolated by cloning and sequencing fragments that overlapped this clone. DNA fragments were sequenced using fluorescent cycle sequencing and analyzed on a DNA sequencer (model CEQ2000XL, Beckman-Coulter, Fullerton, CA). The sequence of the murine nyx gene was obtained by a combination of end sequencing of EcoRI and HindIII subclones of one BAC clone (402g19), primer walking, and import of sequences from the Ensembl trace database (http://www.ensembl.org/; provided in the public domain by the European Molecular Biology Lab [EMBL], Heidelberg, Germany, and the Sanger Centre, Hinxton, UK).14 The predicted coding region was determined from expressed sequence tag EST and genomic sequence. The several Internet-accessible resources that were used to analyze the nyx protein sequence will be indicated later.

In Situ Hybridization
After mice were killed with CO2, their eyes were enucleated and the eyecup isolated and immersion fixed for 20 minutes in 4% paraformaldehyde (Sigma Chemical Co., St. Louis, MO) in 0.1 M sodium phosphate buffer (pH 7.4). The retina was then removed from the eyecup, cryoprotected in a graded series of sucrose solutions in Na-PB, embedded, and frozen in solution containing a 2:1 ratio of 20% sucrose to OCT (Tissue-Tek; Ted Pella, Inc., Redding, CA). Transverse sections (12 µm) of the retina were cut on a cryostat and mounted on microscope slides. A 491-hp fragment of the mouse nyx cDNA and a 1.5-kb fragment of the murine rhodopsin cDNA were cloned into two respective vectors (pCRRII-TOPO; Invitrogen Inc., Carlsbad, CA, and pBluescript SK, Stratagene Inc., La Jolla, CA). Plasmid DNA was purified on a CsCl gradient, linearized using appropriate enzymes, and antisense and sense digoxigenin-labeled (Roche Diagnostics, Mannheim, Germany) cRNAs were synthesized with SP6 and T7 polymerases and an in vitro transcription kit (Maxiscrypt; Ambion, Inc., Austin, TX). The labeled cRNA probes were quantified by agarose gel electrophoresis and dot blot analysis. In situ hybridization reactions were performed as described.15

Behavioral Analyses
Light sensitivity was evaluated in a two-way active-avoidance paradigm, using a shuttle box as described previously.11 Each training and testing period consisted of 100 trials, which began with a 3-minute acclimation period. In each trial, a light stimulus on one side of the box preceded the presentation of a mild foot shock (0.8 mA) on the same side by 10 seconds. The duration (20–35 seconds) of the foot shock was randomized, which also resulted in randomization of the interflash interval. Animals could either avoid or escape the shock at any point during each trial by moving to the dark or “safe” side of the cage. Each animal was trained for eight consecutive days with an unattenuated light stimulus. After the task had been learned, neutral density filters (Oriel, Stratford, CT) were used to reduce the intensity of the light cue.

RESULTS
Genetic Localization
Our genetic mapping results and the localization of the nob (nyx) gene on the mouse X chromosome are summarized in Figure 1A. Previously, we located the nob gene between DXMit54 and 3.8 centimorgan (cM) and DXMit72 at 5.7 cM on the mouse X chromosome.10 This interval included several DXMit markers (DXMit103, -187, -52, -85, -139, and -72) that were informative in our interspecific backcross pedigree (Fig. 1A). The presence of recombinants in the interspecific pedigree with DXMit54 and DXMit139 restricted the nob critical region between these markers, which represents a 0.9-cM region. None of these markers were informative in the intraspecific pedigree. In addition, a newly identified marker, UL107, was generated within the critical region from a BAC 402g19 (Research Genetics) clone containing markers DXMit85 and was informative for most of the intraspecific and all the interspecific pedigrees. UL107 showed no recombination with the nob phenotype in a total of 772 informative meioses, indicating that the mutant gene was close to this marker. Subsequent work placed UL107 only 18.4-kb telomeric to the nyx gene.

Isolation of the Murine nyx Gene
When we were refining our linkage map and building a physical map of the nob-critical region, a novel human gene, NYX, was identified, mutations in which cause CNBH1.12–13 Because our previous results indicated that the nob phenotype matched that of human CNBH1 and the nob gene mapped to the mouse X chromosome in a region homologous to the human CNBH1 gene,10 we examined the NYX gene as a candidate for the nob mutation. Using a probe from a human NYX cDNA clone, we identified several BACs in our contig that contained the nyx
gene. Hybridizing subclones from these BACs were isolated and sequence analyses showed they contained exon 3 of the murine orthologue of the human NYX gene. Subsequent RT-PCR isolated cDNA fragments encompassing the entire coding region of the nyx gene and a recently deposited murine EST (GenBank accession no. BI732501) were used to determine the genomic locations of exons 1 and 2.

As does the human gene, nyx contains three exons, with exons 2 and 3 encoding the open reading frame (ORF). The encoded mouse protein, nyctalopin, is 476 amino acids with a predicted molecular weight of 52,429. Figure 1B shows a comparison between the amino acid sequences of the mouse (top line) and human (bottom line) proteins. Exact matches are shown in black, conservative substitutions in red, and nonconservative substitutions in purple. Inverted triangle: position at which the normal amino acid sequence is truncated in the nob mouse.

**Figure 1.** Map of nob critical region and the nyctalopin sequence. (A) The nob critical region was defined previously. Numbers indicate distance in centimorgans. The refined critical region based on recombinant chromosomes in two pedigrees is shown expanded on the second line. The number of recombinants with each marker in each of the two pedigrees is indicated below the map. (B) Comparison of the mouse (M) and human (H, GenBank accession no. AF254868) proteins. The signal sequence and the LRRs are shown by horizontal lines above the sequence. The predicted cleavage site (GGA) for attaching the putative GPI anchor site in human is underscored. Identical amino acids are shown in black, conservative substitutions in red, and nonconservative substitutions in purple. Inverted triangle: position at which the normal amino acid sequence is truncated in the nob mouse.
Figure 2. Expression of mouse nyx. (A) Northern blot analyses of expression of nyx in retina, brain, and kidney from control mice and retina from nob mice. (B) Blot shown in (A), stripped and reprobed with a β-actin probe to demonstrate that approximately the same amount of RNA was loaded for each sample. (C) In situ hybridization. Left: staining after hybridization with an antisense probe to rhodopsin (color reacted for 1 hour). Middle and left: staining after hybridization to antisense and sense nyx probes, respectively (reacted for 12 hours). These data show that nyx is expressed most abundantly in the INL.

respectively; Pfam database, http://pfam.wustl.edu/; provided in the public domain by Washington University, St. Louis, MO. There are several serine and threonine residues in the carboxy terminus (Fig. 1B, underlined) that show potential for O-glycosylation (http://www.cbs.dtu.dk/services/NetOGlyc/; provided in the public domain by the Center for Biological Sequence Analysis, The Technical University of Denmark, Lyngby, Denmark). The overall amino acid sequences of the mouse and human nyctalopin are 83% identical and 86% similar in terms of their protein structure. Considering just the core LRR portion of the mouse protein (mouse amino acids 23–366), it is 91% identical with human. The most disparate regions between the two species are the amino- and carboxy-terminal ends. In humans, there are two possible initiation codons near the amino terminus and the codon that maximized the length of the ORF was chosen.12,13 In mouse, the first of these two initiation codons is absent, indicating that the mouse protein is either five amino acids shorter at the amino-terminal end than in humans, or that the second initiation codon is used in humans, which is the most likely explanation given the otherwise high degree of similarity between the human and mouse genes. However, it should be noted that the translation start prediction program NetStart (http://www.cbs.dtu.dk/services/NetStart/; provided by The Technical University of Denmark) gives significant prediction scores for both the ATG that maximizes the human ORF (starting at base pair 99 in GenBank accession no. AF254868), as well as the ATG that encodes methionine-6. Confirmation of the correct start site in human necessitates end sequencing of nyctalopin.

Murine nyctalopin, as well as the human orthologue, is predicted to have 9 typical LRRs that are flanked by LRRs rich in cysteines (LRRNT and LRRCT). The flanking cysteine-rich repeats make the mouse protein a member of the small-leucine-rich proteoglycans (SLRPs).13 Mouse nyctalopin includes an amino terminal signal sequence and a carboxy-terminal region that may be cleaved. There is little support for a predicted GPI anchor sequence in the mouse (EXPASY, DPGr program, http://us.expasy.org/; provided in the public domain by the Swiss Institute of Bioinformatics, Geneva, Switzerland), which was predicted for the human protein.12,15 This difference is not caused by sequence errors in the mouse, because these regions generated by sequencing two independent mouse BAC clones from 129sv libraries match exactly those generated by the mouse genome sequencing project. The localization of two transmembrane domains to the carboxy-terminal region also have some support from the results using several analysis programs (TMHMM, TopPred2 via the ProteinPredict server, http://www.embl-heidelberg.de/predictprotein.html/; provided in the public domain by EMBL).20 These data indicate that most of the murine nyctalopin protein is extracellularly anchored to the cell surface by either one or two transmembrane domains. However, resolution of these differences between murine and human proteins necessitates direct experimental confirmation.

Expression of nyx

To examine the expression pattern of nyx, we used Northern blot analysis and in situ hybridization. Figure 2A shows a Northern blot that indicates that the nyx gene is expressed abundantly in normal retina and at a lower level in retina of nob mice. The nyctalopin transcript is undetectable in normal brain and kidney. From these data, we estimate that the nyx mRNA is 7 kb in length. Shown for comparison, is the same blot stripped and rehybridized with a probe for β-actin, demonstrating equivalent RNA loading across lanes (Fig. 2B). The size of mouse nyx mRNA is considerably larger than the cDNA sequence reported for human NYX,12,15 although neither group predicted transcript size on the basis of Northern blot analysis. This larger size may result from 5′ and/or 3′ untranslated regions, which were not represented in the human cDNA sequences. Analyses of mouse genomic DNA sequence downstream of the termination codon indicate that there are three possible polyadenylation sites (polyadq form, http://argonaug.csulab.org/polyadq_form.html; provided in the public domain by Cold Spring Harbor Laboratory, Cold Spring Harbor, NY), which also are associated with ESTs. Use of one or more of these sites would produce transcripts of a length more consistent with our Northern blot data. These data also indicate that nyx is expressed at lower levels in nob mouse retina (Fig. 2A, compare lanes 1 and 2). This presumably results from

[Image 190x496 to 550x734]
instability of the mRNA containing the 85-bp deletion in exon 3 (see below).

To determine which cells within the mouse retina express the nyx gene, we used in situ hybridization. Figure 2C (left) shows the retinal expression pattern of our rhodopsin mRNA control. Rhodopsin expression is restricted to the photoreceptor cell bodies in the outer nuclear layer (ONL) and to their outer segments as expected. Figure 2C (middle) shows that the retinal expression pattern of the nyx gene is more abundant in cells located in the INL. This is most easily seen by comparing the staining patterns in the ONL and INL, using the antisense (middle) and sense (right) probes, respectively. Although not quantitative, the development times needed to obtain similar levels of staining for nyx and rhodopsin (18 hours for nyx and 1-3 hours for rhodopsin) indicate that the level of expression of nyx is lower than that of rhodopsin. The sections reacted with the sense (control) probe for nyx (Fig. 2C, right panel) show very low background in all retinal layers, although there is a low level of nonspecific staining in the ganglion cell layer (GCL).

**Mutation Responsible for the nob Phenotype**

To determine whether a mutation in the nyx gene was present in the nob mice, we designed mouse-specific primers and used PCR to amplify fragments encompassing each exon of the nyx gene from both nob and control retinal cDNAs. One PCR product, which encompassed most of exon 3, was significantly shorter when DNAs from nob mice were used as template. The short fragment cosegregated with the nob phenotype, whereas the long fragment segregated with the normal phenotype, and obligate carrier females had both fragments (Figs. 3A, B). When both PCR products were cloned and sequenced, an 85-bp deletion in exon 3 was found in the fragment amplified from the nob mice (Fig. 3C). The deletion results in a frame-shift mutation that fuses 170 amino acids that do not match nyctalopin, to 188 amino acids from the amino terminus of the normal nyctalopin protein. This results in a loss of 288 amino acids from the carboxyl terminus of the protein, which includes seven LRRs. These data, combined with the decrease in mRNA expression observed in nob retina (Fig. 2A), indicate that this mutation is most likely a loss-of-function mutation.

**Visual Sensitivity of nob Mice**

Patients with CSNB1 exhibit a profound loss of visual sensitivity. Based on our current finding that nob and CSNB1 both result from mutations in orthologous genes, and our previous finding that the ERG b-wave in nob mice was greatly reduced in amplitude, we examined the visual sensitivity of nob mice, by using a classic-conditioning active-avoidance paradigm. Figure 4 shows that both normal and nob mice learned to move to the opposite side of a chamber to avoid a mild foot shock (unconditioned stimulus) that was paired with a bright light (conditioned stimulus). Mice in which the eyes had been enucleated failed to learn this task. To compare light sensitivity, mice that had learned the task were tested with light stimuli of varying intensity and the light intensity at which the mice performed at the same level as their control partners was determined. Figure 4 shows that both normal and nob mice had similar visual sensitivity to light.

**DISCUSSION**

The mutation responsible for the nob phenotype is an 85-bp deletion in the mouse orthologue of the human NYX gene. This gene encodes a novel protein, nyctalopin, of unknown function. Database searches and analysis of the predicted protein’s secondary structure using several prediction programs
indicate that nyctalopin is a member of the SLRP family of proteins, which can be extracellular, intracellular or membrane bound. The human NYX gene has been hypothesized to be a GPI-anchored glycosylated extracellular protein.\(^1\) In contrast, the mouse gene has no GPI anchor sequence, although it has a putative transmembrane domain at its carboxyl terminus. Given that both the mouse and human arise from mutations in the same gene and are very similar phenotypically,\(^7\) this difference in method of cellular anchoring most likely reflects inaccuracies that are inherent in the prediction programs. A definitive determination for the location of the nyctalopin protein must await experimental verification. Regardless of these differences, nyctalopin is likely to have the majority of the amino terminus, including the LRRs, on the extracellular surface of the membrane. Given that this motif is thought to be involved in protein–protein interactions it will be of great interest to determine the proteins with which nyctalopin interacts. Comparison of nyctalopin with database sequences revealed significant matches with many proteins that contain LRRs, consistent with nyctalopin’s being a new member of the SLRP family.\(^1\)\(^,\)\(^2\)\(^,\)\(^5\)

The physiological phenotype of the nob mutant is characterized by a reduction in the ERG b-wave and a marked decrease in light sensitivity, although the gross morphology of the retina is normal. Taken together, these features indicate that there is a failure in synaptic transmission between photoreceptors and DBCs in these mice. Our in situ hybridization data suggest that there is a failure in synaptic transmission between photoreceptors and DBCs in these mice. It is likely that the defect in nob mice and patients with CSNB1 is localized postsynaptically. However, when the human NYX gene was used to probe paraffin-embedded human retina, all retinal cell bodies were labeled.\(^1\)\(^,\)\(^2\)\(^,\)\(^5\) This difference in expression patterns could reflect either a species difference or the unusually long incubation times (3–5 days) needed to obtain labeling with the paraffin-embedded human retinal sections. Lending further support to a postsynaptic location for the defect is evidence that the kinetics and amplitude of the a-wave of the ERG is normal in both nob mice and patients with CSNB1, reflecting a normal response of their photoreceptors to a light stimulus. That said, it is possible that there is a defect in neurotransmitter release. However, our observations of defects in outer plexiform layer (OPL) synaptic structure in mice without the L-type calcium channel in photoreceptors argues otherwise.\(^1\)\(^,\)\(^6\) These mice without the \(\beta_2\) subunit of voltage-dependent calcium channels in the central nervous system and are called CNS-\(\beta_2\)-null mice. Because this subunit is necessary for channel assembly, the \(\alpha_\mathrm{subunit is absent from the OPL, and presumably there is no neurotransmitter release, which is consistent with the absence of a b-wave in the ERG from these mice. The CNS-\(\beta_2\) null mice also have a greatly thinned OPL and have abnormal ribbon synapses. We have interpreted these data to indicate that release of neurotransmitter is essential for synaptic formation and/or development. Therefore if neurotransmitter were not released from the terminals of the rod photoreceptors in the nob mice, we might expect a similar abnormality in the OPL, which is clearly not the case.

Our previous ERG data, combined with our new behavioral assays of light sensitivity firmly establish that the nob phenotype is identical with the CSNB1 phenotype in humans. It is notable that nob mice and patients with CSNB1 do not completely lose visual function. The nob mice can learn a visual task if the light stimulus is bright, and evoked potentials recorded over their visual cortex are present at stimulus offset.\(^7\) Patients with CSNB1 retain reasonably good visual acuity, light sensitivity and color vision under daylight conditions.\(^1\)\(^1\) Moreover, analysis of the cone ERG of patients with CSNB1 indicates that response components generated to flash offset are normal.\(^2\)\(^,\)\(^3\) These observations suggest that the function of DBCs may be selectively compromised in both the rod and cone pathways in nob retinas and that the residual visual function present in nob mice and patients with CSNB1 is mediated through the HBC pathway.

Signaling through rod DBCs requires that glutamate is released by photoreceptors and binds to the mGluR6 receptor that is located on the rod bipolar cell dendrite.\(^2\)\(^,\)\(^3\) The mGluR6 receptor is G-protein–coupled, and its activation initiates an intracellular cascade that terminates in closure of a cation channel.\(^2\)\(^,\)\(^4\) Both the specific steps in this cascade and the identity of the cation channel are presently unknown, although recently one important component, Go\(\alpha\), has been identified.\(^5\) Given our data, it is likely that nyctalopin is either directly involved in the DBC signal-transduction pathway or in the organization of the protein complexes of this pathway. Future characterization of nyctalopin and the nob mouse will be instrumental in elucidating the role of this protein in the signaling processes of retinal DBCs and in examining potential treatments for patients with CSNB1.

References


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