Purification of Human Double-stranded RNA-specific Editase 1 (hRED1) Involved in Editing of Brain Glutamate Receptor B Pre-mRNA*

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RNAs encoding subunits of glutamate-gated ion channel receptors are posttranscriptionally modified by RNA editing and alternative splicing. The change in amino acid sequence caused by RNA editing can affect both the kinetics and the permeability of the ion channel receptors to cations. Here, we report the purification of a 90-kDa double-stranded RNA-specific adenosine deaminase from HeLa cell nuclear extract that specifically edits the glutamine codon at position 586 in the pre-mRNA of the glutamate receptor B (GluR-B) subunit. Site-specific deamination of an adenosine to an inosine converts the glutamine codon to that of arginine. Recently, a gene encoding a double-stranded-specific editase (RED1) was cloned from a rat brain cDNA library. Antigens generated against the deaminase domain of its human homolog specifically recognized and inhibited the activity of the 90-kDa enzyme, indicating that we have purified hRED1 the human homolog of rat RED1. This enzyme is distinct from double-stranded RNA-specific adenosine deaminases which we and others have previously purified and cloned.

RNA editing, defined as an alteration in the coding capacity of mRNA other than splicing or 3' end processing, was first observed in the kinetoplast of trypanosomes (1). Originally thought to be a mechanism of generating genetic diversity only in the mitochondria or chloroplasts of lower organisms and plants, the discovery of editing of the apolipoprotein B (apoB)1 mRNA suggested that editing was also widespread in mammals (2, 3). To date there are several examples of mammalian RNA editing, the most dramatic perhaps being the editing of the apolipoprotein B (apoB)1 mRNA of the apoB-100 mRNA encoding subunit of the low-density lipoprotein receptors in hepatocytes. Editing of the apoB mRNA from different sources (24–26) suggests that editing of the apoB mRNA is required for the formation of chylomicrons (24–26). We investigated whether the dsRNA-specific adenosine deaminase (DRADA) is a ubiquitous enzyme that has been purified (20–23) and cloned from different sources (24–26). We investigated whether the DRADA we had isolated from calf thymus could edit the GluR-B pre-mRNA. We found that the purified enzyme was unable to edit the Q/R site in the GluR-B pre-mRNA to significant levels in vitro (27) but edited the R/G and hotspot 1 sites in addition to the Q/R site in the pre-mRNAs of the kainate receptor subunits GluR-5 and GluR-6 (27, 28). A comparison of the potential of these editing sites to form a double-stranded RNA structure suggested that DRADA could edit an adenosine if it was in a mismatched position, either a loop or a bulge, whereas the adenosine at the Q/R site is in a perfect duplex. These results suggested that the Q/R site in GluR-B pre-mRNA was very different from the sites edited by DRADA and was edited by a different activity (27).

Fractionation of HeLa cell nuclear extract separated an activity from DRADA that could specifically edit the GluR-B Q/R site (12, 27). One of the methods employed to separate these two activities was gel filtration, the molecular weight of the Q/R editing activity being lower than that of DRADA (27). It had been postulated that a complex between DRADA and a cofactor was responsible for Q/R editing (29–31), but we were unable to find such a complex. During fractionation of HeLa cell nuclear extract no fraction added to DRADA made it Q/R editing-competent nor could polyclonal antibodies raised

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1 The abbreviations used are: apoB, apolipoprotein B; GluR, glutamate-activated receptor channel subunits; RED1, double-stranded RNA-specific editase 1; ds, double-stranded; DRADA, dsRNA-specific adenosine deaminase; dsRBD, double-stranded RNA binding domain; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; PCR, polymerase chain reaction.

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against the dsRNA binding domain (dsRBD) of DRADA recognize the Q/R editing activity (27). Therefore, we concluded that another enzyme was responsible for editing the Q/R site in the GluR-B pre-mRNA.

The editing activity that specifically edits the GluR-B Q/R site was purified from HeLa nuclear extracts by chromatography over seven columns. A second dsRNA adenosine deaminase, dsRNA-specific editase 1 (RED1), that can specifically edit the GluR-B Q/R and R/G sites has recently been cloned from a rat brain cDNA library (32). This enzyme is 31% identical to DRADA and is comprised of two dsRBD and a deaminase domain (32). Polyclonal antibodies were generated against its deaminase domain that recognized and inhibited the deaminase activity of the purified 90-kDa enzyme but not DRADA. We therefore conclude that we have purified human dsRNA-specific editase 1 (hRED1).

**EXPERIMENTAL PROCEDURES**

**GluR Constructs and Oligonucleotides—**GluR-B minigenes used in this study were B13 (encoding the Q/R- and hotspot 1-edited sites) (18) and pBgl (encoding the R/G site) (10); these constructs were linearized and used as templates described previously (10). The antisense oligonucleotides used in the primer extension assay was B-RT; 5'-GACACGGTGATCTTCTATGTC-3', which is another reverse transcriptase primer antisense on minigene B13; BFFK3, 5'-GACACGGTACCACACAACGG-3', which is a reverse transcriptase primer antisense on minigene B13; BFKK3, 5'-GACAGCCTTACCACAGGTGTTGATCTTCTATGCCG-3', which is another reverse transcriptase primer antisense on minigene pBgl; PCRK3, 5'-GACAGCCTTACCACAGGAGGGC-3', which is a PCR primer for cDNA primed with KMH3 or BFFK3; cis55, 5'-CTTCTGGGATCTAGAGTTCT-3', a vector specific 5'-primer; MH50, 5'-GACAGCCTTACCACAGGTGTTGATCTTCTATGCCG-3', antisense on minigene B13; MH36, 5'-TCACCAAGGGAAAACTATGCAAC-3', antisense on minigene pBgl; BFKK3, 5'-GACAGCCTTACCACAGGTGTTGATCTTCTATGCCG-3', and BFKK3, 5'-CTCTGCGAGCTCAGGTC-3', which is also antisense on minigene pBgl (27). The PCR primers used for cloning ESTs homologous to RED1 were R1, 5'-CTCCAGGTTCTCTCGGAGAGG-3', and R2, 5'-CCACCGTCAAGCTGTGACCACTGC-3'.

**Purification of hRED1**—The principal buffer used in this purification was buffer A (50 mM Tris-HCl, pH 7.9, 5 mM MgCl₂, 10% glycerol, 1 mM dithiothreitol, 0.5 mM phenylmethylsulfonyl fluoride, 0.4 µg/ml leupeptin). Most of the columns were developed with a KC1 gradient so therefore the KC1 concentration used is indicated below. All necessary reagents for editing, reverse transcriptase, and PCR amplification were purchased from Bio-Rad Laboratories and used as described (10). The column was washed with 2 column volumes and developed with an 8-column volume gradient from 5 to 500 mM KC1. The Q/R editing activity eluted between 190 and 330 mM KC1, and was dialyzed against buffer A containing 50 mM KC1 and 0.02% Nonidet P-40 (Nonidet P-40) which was added to all buffers from this stage on to increase protein stability. The active pool was loaded on an 8-ml Mono Q, washed with 2 column volumes, and developed with a 7-column volume gradient from 50 to 500 mM KC1. The Q/R editing activity eluted both in the flow-through and between 50 and 280 mM KC1. Due to the presence of DRADA in the Mono Q flow-through, the final two columns were run separately with either the Mono Q flow-through or bound fraction, and these active pools were not combined. The conductivity of the Mono Q flow-through and bound fraction was adjusted to 500 mM KC1, and they were loaded separately onto a 5 ml poly(I)poly(C) (Pharmacia Biotech Inc.) column. The column was washed with 2 column volumes and developed with an 8-column volume gradient from 500 to 2500 mM KC1. The Q/R editing activity eluted from both columns between 600 and 1800 mM KC1, the conductivity of the active pools was adjusted to 250 mM KC1 by dilution with buffer A minus KC1 and was loaded separately onto a 6-ml poly(I)poly(C) column which had been pre-equilibrated with buffer A. The column was washed with 2 column volumes and developed with a 7-column volume gradient between 250 and 1000 mM KC1. The Q/R editing activity eluted between 370 and 500 mM KC1. Protein concentration was determined by the Bradford method (34) with BSA as reference standard, except for the pure protein which was quantified on an SDS-polyacrylamide gel with different amounts of BSA as reference standard.

The DRADA extract used was from a previous purification prepared in a similar manner as described above except that the DRADA activity was in the flow-through of the Mono Q column, and all the Q/R editing activity bound to the column. The DRADA activity from the Mono Q flow-through was concentrated 3-fold from Centricron 30 (Amicon), and the units used in experiments corresponded approximately to 100 fmol of inosine/min as measured on dsRNA.

In *Vitro Editing*—dsRNA was transcribed and assayed for dsRNA adenosine deaminase activity as described previously (22). The assay was performed at 30 °C. An analysis of the GluR-B minigene B13 was performed by primer extension assay with B-RT primer specific for the Q/R site and the BHS-RT primer specific for hotspot 1. In the standard assay, 100 fmol of inosine/min was used as the concentration of inosine/min as measured on dsRNA. In the in *vitro* editing assay, dsRNA was transcribed (Superscript™ II RT, Life Technologies, Inc.), and the primers were KMH3 for the Q/R site and BFFK3 for the R/G site. The PCR products were then gel-purified, quantified and approximately 60 ng was used in a sequencing reaction on an Applied Biosystems 373A sequencer with dye terminators (Perkin-Elmer) according to the manufacturer’s instructions. MH36 was the sequencing primer for minigene B13 and BFFK3 for minigene pBgl.

**Overexpression of Histidin-tagged Protein Fusion and Antiserum Preparation**—The GluR-B ESTs, 1,25485 and 77035, were homologous to RED1. They were cloned into polylinker of the histidine tag expression vector pTREHisA (Invitrogen) and sequenced. *Escherichia coli* strain BL-21 was transformed with pTRE-ESt1/2 and subsequently induced at A₅₉₀ = 0.6 with 1 mM isopropyl-b-D-thiogalactopyranoside for
3 h at 37 °C. The overexpressed fusion protein was purified under denaturing conditions on a nitrioltriacetic acid-Ni²⁺ affinity column as specified by the manufacturer (Qiagen). Aliquots from fractions of the nitrioltriacetic acid-Ni²⁺ affinity column were analyzed by electrophoresis on an SDS-polyacrylamide gel and detected with Anti-Xpress™ antibody 1:10,000 (Invitrogen). Approximately 100 μg of protein was gel-purified and injected subcutaneously into a New Zealand White rabbit which had first been bled to obtain pre-immune serum. The antigen was emulsified with Specol adjuvant (Central Veterinary Institute, Lelystad, The Netherlands). The rabbit was boosted every 3 weeks with 50–100 μg of antigen, and blood was collected approximately 10 days after each boosting.

**Immunoblot Analysis**—Proteins were separated on a 8% SDS-polyacrylamide gel, blotted on nitrocellulose, and detected with chemiluminescence staining (ECL kit, Amersham) as described previously (25). The DRADA antiserum was diluted 1:4000, and the hRED1 antiserum was diluted either 1:1000 or 1:4000. The DRADA antiserum was chosen as the source for purification since it contained an editing activity analogous to that found in vivo in the brain that can specifically deaminate the adenosine at the GluR-B Q/R site. hRED1 was purified by chromatography over seven columns (Table I); ion exchange was the principal method used. Since the editing activity was capable of unspecifically deaminating adenosines in long dsRNA, the purification scheme chosen is very similar to the purification of DRADA from calf thymus (22).

The purification of hRED1 was greater than 7000-fold from 14.7 g of protein of HeLa cell nuclear extract (Table I), the equivalent of approximately 2 kg of packed HeLa cells. The large amount of protein necessitated the running of the first two columns twice. The presence of RNases made the accurate measurement of Q/R editing activity in nuclear extract impossible, and the units of activity are estimated from the MacroPrep High Q pool. Aliquots of column fractions were dialyzed and assayed for both the presence of DRADA and hRED1 activity by primer extension (10) and for their ability to deaminate adenosine to inosine on extended dsRNA (22). The two editing activities eluted with overlapping peaks from the first four columns, but only hRED1 activity was pooled for further purification. The activities could be separated on a Mono Q column to which the HeLa DRADA activity does not bind. In general, hRED1 binds to Mono Q, but in this particular purification the activity split with half binding and the other half eluting in the flow-through. This was not the result of overloading the column since the protein did not bind when reappplied to a larger column. A similar problem had previously been encountered during the purification of DRADA from calf thymus (22). The hRED1 used in subsequent experiments was derived from the fraction that bound to Mono Q and contained no detectable DRADA activity.

A 30-fold purification of hRED1 was achieved by chromatography on a poly(I)-poly(C) column, and the enzyme was further purified and concentrated on a poly(G)-poly(C) column (Table I). The activity profile of this column shows a peak of activity in fractions 16–22 (Fig. 1A). This profile corresponds to Q/R editing analyzed by primer extension (Fig. 1B). The load fraction was too dilute, and only a faint band corresponding to editing activity is seen. No edited product was observed when the hotspot 1 site, which is edited by DRADA, was analyzed by the primer extension assay with these same column fractions (data not shown). A band of approximately 90 kDa co-migrated with Q/R editing activity when these fractions were electrophoresed on a 7.5% SDS-polyacrylamide gel (Fig. 1C). This band is the upper part of a doublet that could only be visualized by electrophoresis on a long SDS-polyacrylamide gel and allowing the 45-kDa marker to migrate out of the gel. The lower band of the doublet is present in the flow-through and in most fractions up to fraction number 24 and does not migrate with activity, neither does a smaller polypeptide of approximately 85 kDa which is also present in the flow-through. Moreover, antibodies generated to the deaminase domain of hRED1 specifically recognize only the upper band in the doublet (see below).

### TABLE I

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Protein (mg)</th>
<th>Activity (units)</th>
<th>Specific activity (units/mg)</th>
<th>Purification factor (%)</th>
<th>Recovery (%)</th>
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<td>87,349</td>
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<td></td>
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<tr>
<td>Macroprep Q pool</td>
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<td>210,800</td>
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<td>100</td>
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<tr>
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<td>100,800</td>
<td>153</td>
<td>4</td>
<td>48</td>
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<tr>
<td>Hydroxyapatite pool</td>
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<td>73,946</td>
<td>503</td>
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<td>1,036</td>
<td>28</td>
<td>25</td>
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<tr>
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<td>1,262</td>
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<td>19</td>
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<tr>
<td>Poly(I) · poly(C) pool</td>
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<td>38,868</td>
<td>38,868</td>
<td>1,034</td>
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<td>Poly(G) · poly(C) pool</td>
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<td>33,823</td>
<td>281,858</td>
<td>7,501</td>
<td>16</td>
</tr>
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* One unit = 1% editing per min of the Glur-B pre-mRNA at the Q/R site.
optimum is 100 mM, but no significant decrease in activity is observed between 25 and 150 mM KCl (data not shown). In competition experiments with 100 ng of poly(A), poly(U), poly(C), and poly(G), poly(U) inhibited the hRED1 activity by 97% (Fig. 3). The other polynucleotides either stimulated the enzyme [poly(A)] or inhibit only minimally by 5%. The affinity for poly(U) is very high, and when hRED1 is applied to a poly(U) column it is not possible to recover any activity from the column by high salt elution, which may be due to binding of the enzyme irreversibly. This is in contrast to DRADA which is only inhibited by poly(G) (22) and unaffected by the addition of poly(U). The activity of DRADA is strongly inhibited by o-phenanthroline which probably chelates a Zn$^{2+}$ ion that is required at its active site (25). At 5 mM o-phenanthroline DRADA is inhibited by 90% in comparison to the 30% inhibition of activity observed with hRED1 at the same o-phenanthroline concentration (Fig. 3). This result suggests that if there is an ion at the active site of hRED1, it is less accessible than in DRADA. Both enzymes are very sensitive to N-ethylmaleimide (NEM), at 5 mM the activity of hRED1 is inhibited on a 7.5% SDS-polyacrylamide gel, and proteins were visualized by silver staining. Molecular masses of the size markers are indicated in kilodaltons on the left. The arrow points to a protein of approximately 90 kDa.

**Fig. 1.** Chromatography of a 90-kDa enzyme with GluR-B (Q/R) editing activity on a poly(G)-poly(C) column. A, the activity profile of the final poly(G)-poly(C) column measuring the conversion of adenosine to inosine by the primer extension assay. The units are expressed as the percent conversion of adenosine to inosine per hour. B, every other fraction of the poly(G)-poly(C) column was analyzed for Q/R editing by primer extension. The arrows indicate the position of P, the primer, U, the unedited product, and E, the edited product. The first lane shows the negative control without protein. Lanes 2 and 3 contain the load fraction, 0.5 and 1 µl, respectively. The flow-through was collected in 10 fractions, and 0.25 µl of it (f2–f10) as well as fractions 2–34 were assayed. C, SDS-polyacrylamide gel electrophoresis of poly(G)-poly(C) column fractions. Aliquots of 15 µl were electrophoresed on a 7.5% SDS-polyacrylamide gel, and proteins were visualized by silver staining. Molecular masses of the size markers are indicated in kilodaltons on the left. The arrow points to a protein of approximately 90 kDa.

**Fig. 2.** Sequence analysis of Glu-R-B at Q/R, hotspot 1, and R/G sites. Glu-R-B pre-mRNA B13 (encoding the Q/R and +60 hotspot 1 sites) and pBgl (encoding the R/G site) were incubated with either DRADA or hRED1. The RNA was analyzed by reverse transcriptase-PCR, and the products were sequenced, as described under “Experimental Procedures.” A, the trace data of the sequence surrounding Glu-R-B Q/R, +4, and hotspot (+60). Only the traces of adenosine and guanosine are shown. Glu-R-B was edited by both DRADA and hRED1; an arrow marks the Q/R and +60 sites. The edited nucleotides are in **bold** and *underlined*. B, the trace data of the sequence surrounding the Glu-R-B R/G site, which is edited by both DRADA and hRED1. An arrow indicates the edited nucleotides which are in **bold** and *underlined*.
by 85%, whereas DRADA is inhibited by 95% (Fig. 3).

The 90-kDa Protein Is the Human Homolog of RED1—Two ESTs, L25485 and T70335, listed in the data base have a high homology to the deaminase domains of RED1 and DRADA (32). A 575-base pair PCR fragment encoding both ESTs was fused to a histidine tag; the resulting protein was overexpressed in E. coli, and polyclonal antibodies were generated in a rabbit (see “Experimental Procedures” for details). This antiserum recognized the 90-kDa protein in fractions 16–20 of the poly(G) poly(C) column (Fig. 4A). Therefore, we conclude that we have purified the human homolog of RED1 because the same band that co-eluted with editing activity was detected in these fractions on the silver-stained SDS-polycrylamide gel (Fig. 1C).

The nucleotide sequence of hRED1 has a high homology to RED1 from rat and contains two dsRBD. Polyclonal antibodies directed against the first dsRBD of HeLa DRADA (25) recognized both the HeLa and the calf thymus enzyme but not hRED1 (Fig. 4B). The anti-hRED1 serum, raised against the deaminase domain of hRED1 recognized hRED1 but not DRADA (Fig. 4B). This result suggests that even though the two adenosine deaminases contain similar dsRBDs and deaminase domains, they are sufficiently different to prevent cross-reaction of the specific serum. The hRED1 antiserum inhibited approximately 50% of the deaminase activity of hRED1 but did not inhibit DRADA (data not shown). This is additional proof that the purified 90-kDa enzyme is indeed hRED1 and not a new member of the dsRNA adenosine deaminase family.

DISCUSSION

Ca²⁺ permeability of the AMPA receptors is controlled by the presence in their GluR-B subunit of an arginine residue at the Q/R site that is generated by RNA editing of pre-mRNA (15, 16). There have been contradictory reports in the literature concerning the enzyme(s) that mediate this editing event (12, 27, 29–32). It was reported that DRADA edited the hotspot 1 site in intron 11 but required additional cofactors to edit the Q/R site (30, 31). Other investigators found that DRADA could be partially separated from the Q/R editing activity (12, 27).


Melcher et al. (32) reported that a novel enzyme RED1 was responsible for the editing of the Q/R site. Here, we confirm the latter results by demonstrating that the Q/R site is edited in vitro by a 90-kDa enzyme from HeLa cells that represent the human homolog of RED1. The R/G site is edited to almost the same extent by hRED1 and DRADA, whereas the hotspot 1 in intron 11 is edited by DRADA only.

The 90-kDa homolog of RED1 was purified more than 7000-fold from HeLa cell nuclear extract by ion exchange chromatography. To ensure that the purified enzyme had the same fidelity of editing in vitro as was observed in vivo (11, 18), PCR products of the edited GluR-B RNA were sequenced directly so that populations instead of individual clones could be analyzed. A subset of the sequencing data is shown in Fig. 2. No nonspecific editing was observed with either hRED1 or DRADA. It is interesting to speculate why two similar enzymes are required to edit adenosines at two different sites in GluR-B pre-mRNA.

The answer may lie in the different structural environment of the adenosines that are edited (27). Double-stranded RNA forms an A-type helix, and the amino group of the adenosine that is deaminated lies in the poorly accessible major groove (35). DRADA can deaminate the amino group of an adenosine...
which is mismatched or in a bulge, such as at the R/G and hotspot 1 sites (27) since a bulged adenosine widens the narrow major groove to twice its normal width (36). In contrast, hRED1 is able to recognize and deaminate the adenosine at the Q/R site which is present in a perfect duplex and is less accessible (18). This appears to be the preferred substrate, since under the same editing conditions hRED1 can edit the Q/R site to 100% but edits the R/G site to only 80% (Fig. 2), suggesting that the adenosine at the R/G site is not in as favorable an environment.

There are many similarities between DRADA and hRED1. The purification scheme used for the purification of hRED1 is comparable with that of DRADA (22), which reflects their similarity in amino acid composition and the capacity of both enzymes to bind dsRNA. Both proteins perform the same enzymatic reaction in the absence of additional cofactors and are capable of deaminating up to 50% of the adenosines present in extended dsRNA, and in particular, they both edit the adenosine at the R/G site in GluR-B pre-mRNA. Even though editing of GluR-B pre-mRNA occurs in the brain, the enzymes responsible for this site-specific editing are present and active in HeLa cells suggesting the existence of additional RNA substrates for these enzymes in other cell types.

There is evidence that the two enzymes have differences in their active site which may underly their ability to deaminate adenosines in different editing sites. Both enzymes have opposite behaviors in competition experiments with poly(U) and poly(G); poly(U) completely inhibits the activity of hRED1, whereas poly(G) inhibits DRADA (Fig. 3). Differences were also observed when o-phenanthroline was added to the editing reaction; hRED1 was less sensitive to the inhibitor than DRADA (Fig. 3). This suggests that if there is a Zn^{2+} ion at the active site of hRED1, its environment is different to that in DRADA.

Antibodies directed against the deaminase domain of hRED1, its environment.

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Note Added in Proof—At a higher antibody titer, the hRED1 serum displays some cross-reactivity with DRADA.

REFERENCES


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