Human Erythrocyte Protein 4.2: Isoform Expression, Differential Splicing, and Chromosomal Assignment

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Human protein 4.2 (P4.2) is a major membrane skeletal protein in erythrocytes. Individuals with P4.2 deficiency exhibit spheroctosis and experience various degrees of hemolytic anemia, suggesting a role for this protein in maintaining stability and integrity of the membrane. Molecular cloning of P4.2 cDNAs showed that P4.2 is a transglutaminase-like molecule in erythrocytes but lacks the essential cysteine for cross-linking activity. Two cDNA isoforms have been identified from a human reticulocyte cDNA library, with the long isoform containing a 90-base pair (bp) in-frame insertion encoding an extra 30 amino acids near the N-terminus. Characterization of the P4.2 gene suggests differential splicing as the mechanism for generating these two cDNA isoforms. The donor site for the short isoform (P4.2S) agrees better with the consensus than the donor site for the long isoform (P4.2L) does. Expression of P4.2L was detected by a long-isoform-specific antibody raised against a peptide within the 30-amino acid insert. Western blot analyses showed P4.2L to be a minor membrane skeletal protein in human erythrocytes with an apparent molecular weight (mol wt) of approximately 3 Kd larger than the major protein 4.2, P4.2S. By in situ hybridization of a full-length 2.4-kilobase (kb) cDNA to human metaphase chromosomes, the gene for P4.2 was mapped to bands q15-q21 of chromosome 15, and it is not linked to the gene for coagulation factor XIIIa (plasminogen activator).

HUMAN ERYTHROCYTE protein 4.2 (P4.2) is a major protein in the membrane skeletal network that regulates the stability and flexibility of the erythrocytes.1,2 P4.2 represents about 5% of the total protein mass of the erythrocyte membrane. It associates with the cytoplasmic domain of the anion exchanger band 3 and interacts with ankyrin and possibly protein 4.1.3,5 Individuals with P4.2 deficiency in their erythrocyte membranes exhibit spherocytosis and experience various degrees of hemolytic anemia which may necessitate a splenectomy.5,6

Recently, we7 and other investigators8 cloned cDNAs of P4.2 and discovered that it is a member of the transglutaminase (TGase) (EC 2.3.2.13) family. TGases are enzymes that catalyze intermolecular γ-glutamyl-ε-lysine cross-links between protein substrates and play important roles in stabilizing cellular as well as extracellular structures.9,10 The members of the TGase family are widely distributed and specifically expressed in various types of cells and tissues. The homologies among P4.2, guinea pig liver TGase,11 and human coagulation factor XIIIa (plasma TGase)12,13 are especially pronounced around the catalytic site of the enzymes.7,8 P4.2, however, has an alanine instead of the indispensable cysteine residue14 in its potential active site, rendering P4.2 incapable of catalyzing the cross-linking of protein substrates.7,8 The coexistence of the membrane-bound P4.2 and the cytoplasmic TGase in erythrocytes poses important questions concerning their functions and regulation. Erythrocyte TGase is believed to be associated with cell aging/death by cross-linking of proteins on calcium activation.14 P4.2 may protect proteins from being cross-linked by the TGase or from being degraded by thio-proteases.7

We previously reported two P4.2 cDNA sequences that differ only by a 90-base pair (bp) in-frame insertion.7 The short isoform (P4.2S) cDNA encodes a protein of 691 amino acids with a calculated molecular weight (mol wt) of 77,022 and a pI of 8.95; the long isoform (P4.2L) cDNA predicts a protein of 721 amino acids with a calculated mol wt of 79,941 and a pI of 8.93.7 The presence of two cDNAs resembles the transcript heterogeneity found in other membrane skeletal proteins such as α-spectrin and β-spectrin,15,16 ankyrin,17 band 3,18 and protein 4.1,2,19 and suggests a specific regulation of P4.2 expression in human erythrocytes. The protein products of the two P4.2 cDNA isoforms in erythrocytes have not been defined, however.

We demonstrated the existence of both isoforms of P4.2 in the erythrocyte membranes using antipeptide antibodies. We report the donor site sequences for P4.2S and P4.2L in a differential splicing mechanism that can account for formation of isoforms and also report the upstream sequences containing potential promoter elements for regulation of P4.2 expression. In addition, we report the assignment of the erythrocyte P4.2 gene to bands q15-q21 of human chromosome 15, a chromosome different from that assigned for the coagulation factor XIIIa gene.20

MATERIALS AND METHODS

Isolation and characterization of genomic clones for P4.2. An HaeIII/AIuI-partially digested human fetal liver DNA library in λ phage Charon 4A (CH4A) provided by Maniatis16 was screened with a 32P-labeled human P4.2 cDNA7 according to standard protocol.22 The two EcoRI fragments from a positive clone, X4-1, was subcloned into pBS (+) vector. For restriction mapping, the

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two EcoRI fragments were first end-labeled by the Klenow fragment of Escherichia coli DNA polymerase with [$^{32}$P]-dATP. The RI-A fragment was then digested with BanHI and the RI-B fragment was digested with SacI to generate one-ended labeled fragments (Fig 1A). These subfragments were then mapped by partial digestion with various restriction enzymes. For hybridization analyses, restriction fragments were electrophoresed on agarose gels, blotted, and hybridized with $^{32}$P-labeled probes containing various portions of the human P4.2 cDNAs.7

Nucleotide sequencing of P4.2 gene. Genomic DNA was sequenced by the dideoxynucleotide chain-termination method.23

Generation of long isoform-specific antibodies (anti-P4.2L antibody). Synthetic peptide AS33, a 16-mer, was synthesized (MultiPeptide Systems, San Diego, CA) to have an amino acid sequence of n-GEPSORSTGLAGLYAC-c, corresponding to the N-terminal 15 residues of the insert in P4.2L (Figs 2 and 3B), plus an extra cysteine for the purpose of peptide-carrier conjugation. The m-Maleimidobenzyl-N-hydroxysuccinimide ester (MBS) method of conjugation24 was used to couple the peptide onto keyhole limpet hemocyanin (KLH), the carrier protein. Two rabbits were immunized according to normal immunization procedure.

Generation of protein 4.2-specific antibodies (anti-P4.2 antibody). Synthetic peptide AS34, a 16-mer, was synthesized to have an amino acid sequence of n-KMEREDKNIIRPSC-c. This sequence corresponds to residues 485-499 of P4.2L (also present in the P4.2S)7 plus a cysteine at the C terminus (Fig 3A). The procedures for conjugation and immunization were the same as described above.

Western blot analyses of human erythrocyte membranes. Human erythrocyte ghost membranes were prepared according to established procedure.25 Ghost membrane proteins (30 μg) and molecular standards were electrophoresed26 in a 6.5% sodium dodecy sulfate (SDS)-polyacrylamide gel and electroblotted27 onto nitrocellulose paper. The blots were then stained with one of the antisera or preimmune sera (1:100) followed by goat anti-rabbit antibody conjugated with hors eradish peroxidase (1:3,000) (Bio-Rad, Richmond, CA).

RESULTS

Isolation and characterization of the genomic DNA for human P4.2. To understand the mechanism for generation of isoforms, we screened a human fetal liver genomic DNA library in CH4A vector for P4.2 gene using a previously cloned P4.2 cDNA7 (clone 7, 1.8 kb). Five

![Fig 1.](image-url)
HUMAN ERYTHROCYTE MEMBRANE PROTEIN 4.2

**A**

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**B**

Fig 3. Peptide sequences of P4.2 used in raising anti-P4.2 and anti-P4.2L antibodies and the partial sequence alignment of P4.2 with TGases and bcr protein. (A) Partial P4.2 amino acid sequence containing peptide antigen AS34 (overlined) was aligned by the method of Feng and Doolittle with TGases of liver, macrophage, endothelium, epithelial type I, keratinocyte, and coagulation factor Xlla. Sp. species from which sequence was derived; H, human; G, guinea pig; M, mouse; R, rabbit. Aligned residues identical to P4.2 are boxed. The AS34 peptide is a nonhomologous sequence located C-terminal to a highly conserved, potential calcium binding site. Amino acid numbers (aa#) in parentheses indicate the sequence from a partial cDNA clone. (B) Sequence of peptide antigen AS33 (overlined) in P4.2L with respect to the 30-amino acid insert (A) and the alignment between the insert-containing region of P4.2L and the bcr protein are shown. Homology was evident only in this 30-amino acid insert region plus the immediate downstream residues; there was no homology elsewhere on this plot.

positive clones were identified from 1 × 10^6 phages screened. All five clones contained an identical insert of 16.2 kb with an internal EcoRI site (Fig 1A). (The two EcoRI sites at both ends belong to the linkers added in constructing the genomic library.) The large EcoRI fragment RI-A is about 10.5 kb, and the small EcoRI fragment RI-B is about 5.6 kb. Hybridization analyses using four partial P4.2 cDNA clones showed that these genomic clones contain 5' cDNA sequences including the region that differentiates the two isoforms, but lack the 3'-end cDNA sequence (data not shown). The restriction map of human P4.2 genomic DNA with respect to five restriction enzymes is shown in Fig 2A.

Differential splicing of P4.2 mRNAs. We previously reported two P4.2 cDNAs, 2.382 and 2.472 bp, that differ only by a 90-bp in-frame insertion located three codons downstream from the putative initiation site. To determine how these two cDNAs arise, genomic sequences flanking the 90-bp insert were obtained with oligonucleotide primers corresponding to the cDNA sequences 5' and 3' to the 90-bp insert (Fig 2). The genomic sequence showed that the first exon contains all the 5'-untranslated cDNA sequence and 10 nucleotides in the coding region (encoding the first three amino acids of P4.2). The 90-bp insert in P4.2L cDNA (Fig 2) is contiguous with the first exon, and the end of this 90-bp insert sequence is connected to the rest of the intron sequence.

These results show that the two P4.2 cDNAs can arise from a single gene with its primary RNA differentially spliced using two different donor sites and one common acceptor site (Figs 1B and 2). This intron is approximately 5 kb, with its donor sites in the RI-B fragment and its acceptor site in the RI-A fragment. These two donor sites and the acceptor site were listed with consensus sequences of eukaryotic RNA splice sites.

5' Upstream DNA sequence of the human P4.2 gene. The genomic sequence upstream from the P4.2 cDNA startsite is also shown in Fig 2. The size of the predominant hybridizing band (~2.4 kb) in our Northern blot analysis of reticulocyte RNA2 (Fig 3 in ref 7) suggested that our reported cDNAs of 2.472 bp and 2.382 bp are full-length sequences. The nucleotides upstream from the cDNA startsite (nt 1) are CAGT (nt -4 to -1), agreeing well with the CA cap signal. Nucleotides -26 to -21 upstream from the cDNA startsite have a sequence of ATAAAA, which agrees well in sequence and position with the TATA box for eukaryotic genes. Within the reported -385 nt upstream sequence, where upstream promoter elements are located, a CCAT sequence was also noticed (G/C to A/T ratio 3:1). Within this region exists a sequence of CCCACCCCCC containing a CACC element (nt -83 to -80) that is a potential binding site for Sp1 nuclear factor. Two AGATAA sequences for potential binding of erythroid-specific transcription factor GATA-1 are located at nt -175 to -170 and at nt -28 to -23. The significance of these potential elements is now being investigated.

P4.2 isoform expression on human erythrocyte membranes. To detect P4.2 isoforms on erythrocyte membranes, we generated two peptide-specific antibodies, anti-P4.2L and anti-P4.2. The partial amino acid sequences of P4.2 where
the two peptide antigens were derived are shown in Fig 3. The anti-P4.2L antibody recognizes P4.2L only; the anti-P4.2 antibody recognizes both P4.2S and P4.2L.

The typical major erythrocyte membrane protein P4.2 was observed on the gel after electrophoresis of human ghost membrane proteins and staining by Coomassie blue (Fig 4, lane 1), as well as on the nitrocellulose transblot stained with the anti-P4.2 antibody (Fig 4, lane 2). The anti-P4.2 antibody was raised against a synthetic peptide AS34 which had the 15-amino acid sequence at residues 485-499 numbered according to P4.2L (Fig 3A). This peptide sequence is located next to the C-terminus of a region that are identical between P4.2 and the other members are boxed in Fig 3A. The α-helical, highly charged sequence of AS34 peptide is a unique sequence of P4.2 not found in other members of the TGase family, however, eg, factor XIIIa, keratinocyte TGase K, endothelial TGase, macrophage TGase, and liver TGase. The anti-P4.2 antibody raised against the peptide AS34 therefore is not expected to cross-react with other TGases. Western blot analysis of human erythrocyte membranes showed that this anti-P4.2 antibody specifically reacted with the typical band of P4.2 (P4.2S, a major protein in ghost membranes) (Fig 4, lane 2). In addition, it also reacted with a minor protein, presumably P4.2L, which migrated slightly above P4.2S.

To verify that the minor band above P4.2S recognized by the anti-P4.2 antibody is truly the predicted long isoform of P4.2 that has the 30-amino acid insert (P4.2L), we made a long-isoform-specific antibody. The anti-P4.2L antibody was made against peptide AS33 located within the 30-amino acid insert of P4.2 (residues 4-19) (Fig 3B). This antipeptide antibody specifically reacted with only one ghost membrane protein in Western blot analysis (Fig 4, lane 3). The position of this band corresponded to the minor band recognized by the anti-P4.2 antibody (Fig 4, lanes 2 and 3). The presence of P4.2L in the erythrocyte membrane therefore is demonstrated by two independent peptide antibodies recognizing two separate regions of the expected protein. To confirm further the position of P4.2L relative to P4.2S, these two antibodies were mixed in one immunostaining experiment (Fig 4, lane 4); the results showed two distinct bands corresponding exactly to P4.2S and P4.2L.

The relative mol wt of P4.2S on an SDS-polyacrylamide gel is typically 72,000, and the relative mol wt for P4.2L (Fig 4, lanes 2 through 4) is approximately 75,000. The relative mol wt for P4.2S and P4.2L on an SDS-polyacrylamide gel differed by approximately 3,000, which agrees very well with the calculated mol wt for the 30-amino acid insert (2,936 dalton). There was little or no protein on the gel at the position corresponding to P4.2L after Coomassie blue staining, and the presence of P4.2L can be detected only by the more sensitive Western blot analysis. These results demonstrate that P4.2L is indeed expressed in human erythrocytes and that it is a minor protein that remains associated with the ghost membranes. No protein in the erythrocyte cytoplasm can be detected by these two antibodies (data not shown), suggesting that both isoforms become incorporated into the membrane skeleton after synthesis. With the anti-P4.2 antibody, the immunostaining intensity ratio of P4.2S to P4.2L was approximately 15:1 (Fig 4, lane 2). Erythrocyte P4.2 has been estimated to exist in approximately 250,000 molecules per cell. Thus, P4.2L may be estimated to exist in about 17,000 molecules per cell, assuming that the anti-P4.2 antibody has a similar affinity toward these two isoforms. These two isoforms share identical 691 amino acids except for the extra 30 amino acids near the N-terminus. Such an assumption is reasonable, although the possibility that the extra 30 amino acids may actually affect the affinity by virtue of its hydrophobicity or by altering the tertiary structure of the molecule cannot be ruled out.

**Mapping of the human P4.2 gene to chromosome 15 at bands q15-21.** A cDNA clone containing the constructed full-length 2.4-kb cDNA of P4.2 was labeled with biotin-
lated 11-dUTP and used as a probe for in situ hybridization to locate the gene for P4.2 on human chromosomes. Immunofluorescent signals were detected and their chromosomal locations were identified by parallel Q-banding and R-banding analysis. A total of 32 fluorescein isothiocyanate fluorescent dots were counted in 30 metaphase spreads. Twenty of these dots were located on a specific region, q15-q21 of chromosome 15 (Fig 5). From these data, the gene for human erythrocyte P4.2 is assigned to chromosome 15 at bands q15-21. This work was reported previously in abstract form and agrees well with the mapping of P4.2 gene to 15q14-15 reported by Najfeld (also in abstract form).39

**DISCUSSION**

Molecular cloning of P4.2 has led to identification of two P4.2 cDNA isoforms.4 They were obtained by PCR amplification of a reticulocyte cDNA library and differ by the presence of a 90-bp insert in only the long isoform. Using an antibody raised against the predicted amino acid sequence of the insert and another antibody that recognizes a common region of these two isoforms, we demonstrated for the first time the presence of P4.2L as a minor protein in human erythrocyte membranes.

Our genomic sequence showed that these two P4.2 cDNAs may be generated by differential splicing. This conclusion is in agreement with that reported by Korsgren and Cohen.41 The donor site for P4.2L matches less closely with the consensus sequence as compared with P4.2S (Fig 1B). Our previous report that one of four cDNA clones obtained by polymerase chain reaction (PCR) amplification of a reticulocyte cDNA library contained the 90-bp insert suggested that P4.2L is the less abundant species in reticulocyte mRNA. That smaller transcript was present in "much greater" abundance than the larger one was recently demonstrated by PCR amplification of the reticulocyte RNA. At least two reports describe some P4.2-deficient patients with a P4.2 doublet with a mol wt of 72,000 and 74,000 in their erythrocyte ghost membranes. Appearance of the P4.2 doublet in patients may represent an underexpression of P4.2S (relative mol wt 72,000) and an overexpression of P4.2L (relative mol wt 75,000) resulting from a mutation(s) near the splice sites of its gene. One additional isoform of P4.2 lacking 234 bp and the tissue distribution of the mRNA splicing isoforms have been described in an abstract.44

It would be interesting to know whether the 30-amino acid insert has any functions in erythrocytes. Two patients with P4.2 deficiency have β-spectrin/ankyrin, band 3, and protein 4.1 phosphorylated to a higher degree (approximately twofold) than normal.6 Whether the increased

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**Fig 5. Chromosomal localization of the P4.2 gene by fluorescence in situ hybridization.** The chromosome preparations were stained simultaneously with propidium iodide and DAPI. Hybridization signal was detected by use of a fluorescence microscope equipped with filter combinations for excitation wave lengths of 450 to 490 nm (for fluorescein and propidium iodide fluorescence) and 330 to 380 nm (for DAPI fluorescence). Three partial metaphase spreads (left, a, c, and e) show hybridization signals on R-banded chromosomes (arrows). Partial metaphase spreads with Q-banding (right, b, d, and f) are the same as a, c, and e, respectively. Chromosome 15 and the Y chromosome are indicated. P4.2 gene was mapped to chromosome 15 at bands q15-21.
phosphorylation is related to an increase of P4.2L and/or the decrease of P4.2S is of interest. The insert has a homology (33.3% identity) with an area of human breakpoint cluster region (BCR) protein (Fig 3B). The bcr sequences, when fused with the abl tyrosine protein kinase (in CML and ALL), activate the tyrosine kinase and actin-binding activities of the bcr/abl fusion proteins. This finding has led to a speculative suggestion that the insert sequence may be involved in regulating erythrocyte kinase activities and hence phosphorylation of membrane skeletal proteins. The homology search also disclosed a group of tyrosine kinase-related transforming proteins, eg, c-src. The homologies are located in the catalytic domain (subdomains IV and V) of the kinase, although the homologies are moderate and may or may not be significant. In addition, this 30-amino acid insert resembles signal peptides because it contains a stretch of hydrophobic residues, but this insert does not appear to be required for the association of P4.2 to membranes since both isoforms are able to reach their destination on the normal erythrocyte membrane and be retained in the ghost.

P4.2 belongs to the TGase family. Many of the gene families have their homologous genes clustered in one region of a chromosome. The β-like globin genes are all linked on chromosome 11, whereas the two α genes and the two embryonic ε genes are linked on chromosome 16. The present finding that the genes for P4.2 and factor XIIla are located on different chromosomes indicates that the two genes evolved long ago from a common gene progenitor, although these two genes share remarkable similarities in the sizes of the paired exons and splice junction class of each corresponding intron.

The restriction map we report for the P4.2 gene is different from that reported by Korsgren and Cohen. Among all the restriction enzymes shown, only EcoRI was used in both studies. The EcoRI site between exon 1 and exon 2 in our genomic sequence is not present in the sequence described by Korsgren and Cohen (Fig 1A). Whether the difference is due to polymorphism or other reasons is not clear. Additional differences were also apparent between our 385-nucleotide upstream sequence and the corresponding 265-nucleotide sequence reported by Korsgren and Cohen (Fig 6). Three Gs are not present in our sequence at positions of −206, −169, and −88. These differences are in the region where promoter elements were observed by us and by Korsgren and Cohen. Indeed, one of the differences led to identification of a CCAT promoter element in our upstream sequence (nt −89 to −86). Sequence discrepancy also exists at the donor site for P4.2L. Individuals of different ethnic groups are currently being screened to establish whether polymorphism is involved.

ACKNOWLEDGMENT

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NOTE ADDED IN PROOF

The human transglutaminase K gene has been mapped to 14q2-3n. Therefore, the gene mapping results so far have shown that each of the genes for the three members of the TGase family is located in a different human chromosome.

Fig 6. Upstream genomic DNA sequences for P4.2 sequenced using the dideoxynucleotide method. G, A, T, and C refer to nucleotides. Brackets in A, B, and C indicate nt −210 to −201, −170 to −161, and −90 to −81, respectively. Strands labeled 5' and 3' are the sense strands. Within each bracket, one nucleotide discrepancy was observed as compared with that reported by Korsgren and Cohen. Arrows point to the positions where additional nucleotides of Gs were reported by Korsgren and Cohen. (C) Bracket contained a CCAT promoter element in our sequence.
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Human erythrocyte protein 4.2: isoform expression, differential splicing, and chromosomal assignment

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