Structure and Expression of Human Germline V<sub>H</sub> Transcripts
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Summary
The human V<sub>H</sub> family consists of two functional genes and one pseudogene. We have found a novel 1.2-kb V<sub>H</sub> gene transcript in normal fetal liver and cord blood and in transformed B lineage cells. V<sub>H</sub>-positive cDNA clones were isolated from precursor B acute lymphoblastic leukemia, B chronic lymphoblastic leukemia, Epstein-Barr Virus-transformed B cell lines, and cord blood, and were identified as transcripts of unrearranged V<sub>H</sub> genes (germline transcripts). The cDNA clones were derived from both functional and pseudo-V<sub>H</sub> genes. Most germline transcripts appear to initiate at the normal V<sub>H</sub> promoter and are cleaved and polyadenylated at sites several hundred bases downstream of the V<sub>H</sub> coding region. Correct splicing of the leader intron was observed in all clones. In functional and pseudo-V<sub>H</sub> cDNAs, an open translational reading frame extends from the leader to a termination codon in the nonamer. Only limited polymorphisms were observed in the coding as well as flanking regions of the V<sub>H</sub> transcripts. Functional and pseudo-V<sub>H</sub> cDNAs are also highly homologous throughout. The many similarities between human germline V<sub>H</sub> transcripts and previously identified murine germline V<sub>J</sub>558 transcripts are discussed.

The variable regions of immunoglobulin (Ig) heavy (H) chains are assembled from three groups of germline gene segments, V<sub>H</sub>, D, and J<sub>H</sub>. During precursor B cell differentiation in fetal liver and adult bone marrow, these segments are joined into a complete V<sub>n</sub>-D<sub>n</sub>-J<sub>H</sub> variable region by an ordered assembly process. First, D to J<sub>H</sub> segments are joined, followed by V<sub>n</sub> to D<sub>n</sub>-J<sub>H</sub> rearrangement (reviewed in reference 1). In humans, there are 100–200 V<sub>n</sub> gene segments, which have been classified into six families (V<sub>n</sub>1 to V<sub>n</sub>6) on the basis of nucleic acid sequence homology. V<sub>n</sub> families range in size from the single-member V<sub>n</sub>6 family to the large V<sub>n</sub>1 and V<sub>n</sub>3 families, each containing >25–30 members (reviewed in reference 2). The small V<sub>n</sub>5 family consists of two functional genes and one pseudogene (3–5). One of the functional V<sub>n</sub>5 genes is not present in all individuals (4).

In general, most V<sub>n</sub> segments are not expressed at detectable steady-state levels in unrearranged, germline configuration. V<sub>n</sub> to D-J<sub>H</sub> rearrangement brings the V<sub>n</sub> segment and its associated promoter elements into proximity of an enhancer located within the J<sub>n</sub>-C<sub>n</sub> intron, thus allowing for high-level transcription of the V<sub>n</sub>-D-J<sub>H</sub> rearrangement initiating at the V<sub>n</sub> promoter and continuing into the downstream constant region (reviewed in reference 6). In mice, at least some V<sub>n</sub> segments belonging to the large J<sub>n</sub>-distal J558 family are transcribed in unrearranged configuration outside the influence of the H chain enhancer (7). Germline V<sub>n</sub>J558 genes are specifically transcribed at the pre-B stage of B cell development. The function of germline V<sub>n</sub> transcription is unknown, although the specific expression of germline V<sub>n</sub>J558 transcripts in pre-B cells, the cells in which V<sub>n</sub> to D-J<sub>H</sub> rearrangement occurs, led to the proposal that germline V<sub>n</sub> transcription may be related to accessibility of the V<sub>n</sub> locus to recombinase enzymes (7).

The large size of the murine J558 family (up to 500–1,000 members; reference 8) has complicated more detailed analyses of germline V<sub>n</sub> transcription. Thus, although it is clear that germline V<sub>n</sub> transcripts are derived from multiple V<sub>n</sub>J558 genes (7), it is difficult to ascertain the exact number and nature of the V<sub>n</sub> segments that are expressed. Potential germline transcripts derived from the human V<sub>n</sub>5 family have been detected in B chronic lymphoblastic leukemia (B-CLL) tumors by Northern analysis (4). In contrast to the murine V<sub>n</sub>J558 family, the small size of the human V<sub>n</sub>5 family simplifies studies of germline V<sub>n</sub> expression. We have

1 Abbreviations used in this paper: ALL, acute lymphoblastic leukemia; BM, bone marrow; CLL, chronic lymphoblastic leukemia; ORF, open reading frame.
therefore further characterized human germline \( V_n \) transcripts in normal and transformed B lineage cells and compared them with murine germline \( V_nJ558 \) transcripts.

**Materials and Methods**

**Cells and Tissues.** Acute lymphoblastic leukemia (ALL) samples were classified as immature B lineage malignancies (precursor ALL) by standard morphologic and cytochemical criteria (9); three were cell lines (NALL, NALM, and LAZZ) and the remainder were PBMC or bone marrow (BM) samples (>85% lymphoblasts) from ALL patients. B-CLL samples (>98% CDs1*) were obtained as described (3, 4). EBV-transformed lines were derived from adult PBMC or from fetal BM as described (10). EBV-21 and EBV-321 were transformants of normal CDs1* cells sorted from adult PBMC (11). Both lines were polyclonal as confirmed by sequencing functionally rearranged \( V_5-C_\mu \) transcripts (P.W. Tucker and C. Humphries, unpublished results).

Fetal livers were obtained with permission and Internal Review Board approval from patients undergoing spontaneous or medically indicated therapeutic abortions. Fetal age was estimated by last menstrual period and by fetal foot length. T cell–depleted PBMC were prepared from healthy donors as described (10). Adult spleens were obtained from patients undergoing splenectomy for abdominal trauma. Newborn cord blood was enriched for B cells as described (10).

**RNA Blotting and Preparation.** Preparation of total and poly(A)+ RNA, fractionation of RNA by formaldehyde/agarose gel electrophoresis, and blotting was done as described (7).

**Results**

**Transformed B Lineage Cells Express Novel-sized \( V_5 \) Gene Transcripts.** Pre-B ALLs have H chain rearrangements but lack sIg and thus appear to represent human pre-B cells (9). 10 pre-B ALLs were examined by Northern analysis for expression of the six human \( V_n \) gene families (\( V_1-V_6 \)). The ALLs expressed mature \( V_n-C_\mu \) H chain mRNA, with individual samples expressing \( V_n \) segments from a particular family. In addition, we detected a novel 1.2-kb transcript that hybridized to a \( V_\mu5 \) probe. Novel \( V_\mu5 \) transcripts were found in all precursor B ALLs examined, including three cell lines (Fig. 1 A, lanes 1–3) and seven PBMC or BM samples from ALL patients (Fig. 1 A, lanes 4–10). One ALL line (Fig. 1 A, lane 2) also expressed a novel \( V_\mu5 \) mRNA, slightly

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![Figure 1](image_url)

**Figure 1.** Northern analyses of \( V_\mu5 \) expression in transformed B lineage cells. (A) Expression of a 1.2-kb germ-line \( V_\mu5 \) transcript in pre-B ALL cell lines (lanes 1–3) and PBMC or BM from ALL patients (lanes 4–10). (B) Germ-line \( V_\mu5 \) transcript in B-CLLs. (C) Germline \( V_\mu5 \) expression in EBV-transformed B cell lines. B-CLL-12 and LAZZ pre-B ALL RNAs are included for comparison. Mature \( C_\mu \) H chain transcripts (\( V_\mu5-D_\mu4-C_\mu4 \)) derived from rearranged \( V_\mu5 \) genes were detected in some samples; e.g., EBV-21. EBV-21 and EBV-321 are transformants of sorted CDs1* cells. FB-EBV is a fetal BM line, and Sp-EBV and Br-EBV are PBMC lines (10). Amounts of RNA per lane were: A1–10, 10–20 μg total RNA; B1–4, 5 μg poly(A)+; C1–4, 5 μg poly(A)+; D1, 4 μg poly(A)+; D2–4, 5–10 μg total RNA.
greater than 1.2-kb, that is apparently derived from a partially assembled V\textsubscript{H}5-D rearrangement (J.E. Berman and FW. Alt, unpublished results). Occasionally, transcripts larger than mature H chain mRNA were detected with V\textsubscript{H} family probes other than V\textsubscript{H}5. However, they were not consistently observed in all ALLs and may represent precursor mRNAs (data not shown).

Murine germline V\textsubscript{H} transcripts are expressed in pre-B lines and are not observed in more mature B lineage tumors such as B cell lymphomas and myelomas (7). In human slg\textsuperscript{+} CLLs, V\textsubscript{H}5 transcripts similar in size to the 1.2-kb species found in pre-B ALLs were detected by Northern blotting (4). Therefore, we examined transformed B lineage cells other than pre-B ALLs for V\textsubscript{H}5 expression. The novel 1.2-kb V\textsubscript{H}5 transcript was observed in some B-CLLs and EBV-transformed B lymphoblastoid cell lines, but in contrast to the pre-B ALLs, it was not found in all such lines (representative data are shown in Fig. 1, B, C, and D). As with the ALLs, germline transcripts of other V\textsubscript{H} families were not observed (data not shown).

The Novel-sized 1.2-kb V\textsubscript{H}5 Species Are Germline Transcripts. cDNA libraries were constructed from several ALL, CLL, and EBV-transformed B cell samples tested above, V\textsubscript{H}5-hybridizing clones were randomly isolated, and complete nucleotide sequences of two of the longest cDNAs (L3-4, L2-9) from a pre-B ALL library (LAZZ; Fig. 1 A) were determined. We also sequenced three V\textsubscript{H}5\textsuperscript{+} cDNAs randomly isolated from two B CLL samples (CL12, CL27) and from an EBV-transformed B cell line (EBV-21) that also expressed the 1.2-kb V\textsubscript{H}5 transcript (Fig. 1, B and C). Comparison of

![Figure 2](https://example.com/figure2.png)

Figure 2. Nucleotide sequences of germline cDNAs derived from the functional V\textsubscript{H}5 gene. Genomic sequences of unrearranged (V\textsubscript{H}251; 4) and rearranged (3-1R1; 5) functional V\textsubscript{H}5 genes are provided for comparison. Dashes indicate identity with the V\textsubscript{H}251 sequence; differences are indicated. cDNA sequences are condensed into a single line in regions of complete identity (1, L3-4; 2, CB-4; 3, EBV-21; 4, CLL-12). The leader is spliced in the cDNAs so the genomic intron sequences are not shown. Corrections have been made in the originally reported V\textsubscript{H}251 sequence (4) immediately 3' of the nonamer. The sequence of V\textsubscript{H}251 further downstream of the nonamer is previously unpublished. Heptamer and nonamer recombination sequences are boxed. The internal "V replacement" heptamer at the end of framework 3 is underlined. The asterisk and line above the nonamer indicate the end of the ORF. Polyadenylation signals are underlined in the untranslated region 3' of the nonamer.
these nucleotide sequences to genomic germline V\_5 sequences (4, 5) confirms that they represent germline transcripts of unarranged V\_5 genes (Figs. 2 and 3). The cDNAs extend from 5 to 39 bp upstream of the leader, through the coding regions, and, in contrast to rearranged V\_n gene transcripts, include the normally deleted recombination signals and 3' flanking regions.

**Germline Transcripts Are Expressed from both Functional and Pseudo-V\_n Genes.** As expected, some cDNAs were derived from the functional V\_5 gene (V\_n251, Fig. 2), but surprisingly, others were transcripts of the V\_5 pseudogene (V\_n15/ V\_n1-V, Fig. 3). To determine the relative steady-state levels of these two transcripts and to search for other germline V\_5 mRNA species, 10 V\_n5' clones from the LAZZ pre-B ALL (12; Fig. 1A, lane 3) cDNA library were randomly characterized. Half of the clones were derived from the functional V\_5 gene and the others were transcripts of the V\_5 pseudogene. 9 of the 10 cDNA clones were from similar regions of the V\_5 genes; however, one pseudogene-cDNA, L6-1, extended further upstream to ~420 bp 5' of the initiation codon and ended ~0.1 kb 3' of the nonamer (data not shown).

**Structure of Germline V\_n5 Transcripts.** Comparison of the V\_n5 cDNAs (including L6-1) and germline genomic V\_n5 sequences (V\_n251 coding region, reference 4; newly determined V\_n251 3' flank, Fig. 2; 1-V, reference 5) indicated that the leader intron was appropriately spliced but no additional splicing occurred in the 3' flanking regions. The germline V\_5 transcripts are polyadenylated, although there is apparently slight variation in the site of pre-RNA 3' end cleavage and polyadenylation since some cDNAs such as L3-4 and L2-9 extend beyond the beginning of the poly(A) tails present in CLI12 and CLI27 (Figs. 2 and 3). This variation is not surprising because there are multiple consensus polyadenylation/cleavage signals (reviewed in reference 13) at the 3' ends of both the functional and pseudo-V\_5 genes (underlined in Figs. 2 and 3).

Together, the functional germline V\_5 cDNAs encompass 967 bp of sequence and the pseudo-V\_n5 cDNAs span a 1,001-bp region. Assuming an ~250-base poly(A) tail (13), the cDNA clones correspond to the full-length 1.2-kb transcript. This suggests that transcriptional initiation of the majority of V\_n5 germline mRNA sequences occurs within 100 bp upstream of the leader, probably from the normal V\_n promoter; although the L6-1 cDNA indicates that there is also some transcriptional initiation upstream of the V\_n promoter, at least for the pseudo-V\_n5 gene.

Although from different individuals, the coding region sequences of the four functional germline V\_n5 cDNAs and the corresponding genome (V\_n251) are highly conserved.
Unexpectedly, a high degree of conservation is also found (>98% similarity; Fig. 2). This is consistent with previous L3-4 TGTTTGGTGATTGTTTTCCTTTUATAATATGTACTGAATAATTUTCTTTGTGCCAATTUTAAGTATTC stream of the nonamer. part of the spacer region, thus bringing the internal heptamer 12 by up-
tamer, nonamer). In L2-9, a 24-bp deletion removes the heptamer and sequences are boxed (from 5' to 3' they are: V replacement heptamer, hep-
terminal amino acid sequences of the putative truncated H chain proteins is shown), and the 3' flanking regions are 86% similar. Predicted 000H-
Figure 4. Germline transcripts of functional and pseudo-V.5 genes are highly related. The coding regions of functional (L3-4) and pseudo-V.5 (L2-9) cDNAs (isolated from LAZZ, see text) are 91% similar (only FR3 is shown), and the 3' flanking regions are 86% similar. Predicted COOH-terminal amino acid sequences of the putative truncated H chain proteins encoded by the germline V.5 transcripts are shown. Recombination signal sequences are boxed (from 5' to 3' they are: V replacement heptamer, heptamer, nonamer). In L2-9, a 24-bp deletion removes the heptamer and part of the spacer region, thus bringing the internal heptamer 12 bp up-stream of the nonamer. (>98% similarity; Fig. 2). This is consistent with previous findings of limited V.251 coding region polymorphism (14). Unexpectedly, a high degree of conservation is also found in the 3' flanking regions of the functional V.5 sequences, all of which are >98% similar. Even the pseudo-V.5 sequences are >98% similar throughout both the coding and flanking regions (Fig. 3).

Open Reading Frames (ORF) Are Found in the Germline V.5 cDNAs. In the germline cDNAs derived from the functional V.5 gene, an ORF extends throughout the V.5 coding region and ends in a termination codon within the nonamer recombination sequence (see asterisk in Fig. 2). Beyond the nonamer there are multiple stop codons in all reading frames. A search of GenBank did not reveal significant homologies between this 3' untranslated region and other human or murine genes. The germline cDNAs potentially encode a V.5 region the same as that of a rearranged gene, except for 11 COOH-terminal residues (His-Thr-Val-Arg-Pro-Glu-Pro-Val) identically encoded within the heptamer/23-bp spacer/nonamer region of all the functional V.5 cDNAs (Fig. 2). A similar ORF was also found in the pseudo-V.5 cDNAs, again terminating within the nonamer, but only three additional amino acids (Gly-Thr-Ile) are encoded beyond FR3 due to a deletion within the recombination sequences (Figs. 3 and 4; see Discussion).

Identical Germline V.5 Transcripts Are Expressed in Normal Tissues. Characteristic 1.2-kb germline V.5 transcripts were observed on Northern analyses of fetal liver (15 and 17 wk) and cord blood, but were not seen in adult T cell-depleted PBMC or in adult spleen (Fig. 5, A and B; confirmed by S1 analysis, data not shown). The sequence of a germline V.5 clone (CB-4) isolated from a cDNA library of normal cord blood (Fig. 5 B, lane 2) was essentially identical to functional V.5 cDNAs isolated from transformed B lineage cells (Fig. 2). As with the transformed lines, we did not detect germline-length transcripts with V.5 family probes other than V.5 (data not shown).

Discussion

Limited Polymorphism among Germline V.5 cDNAs. We have demonstrated that unrearranged functional and pseudo-V.5 gene segments are transcribed in normal and transformed B lineage cells. Although germline transcripts of the poly-

Figure 5. Germline V.5 expression in normal tissues. (A) Germline V.5 expression in T cell-depleted PBMC (lanes 1-3) and fetal liver (15 wk, lane 4; 17 wk, lane 5). RNA from the LAZZ pre-B ALL line is shown for comparison. (B) Germline V.5 expression in normal cord blood (lane 2). RNA from B CLL/12 is shown for comparison. Complete V.5-C5 chain mRNA was detected in fetal liver and in cord blood, and both V.5-C5 and V.5-C2 mRNA were seen in adult PBMC. Amounts of RNA per lane were: A1-3, 10 μg total RNA; A4-5, 6 μg poly(A)*; A6, 4 μg poly(A)*; B1-2, 5 μg poly(A)*.
morphic V5 gene (V\(_{\mu}32/V_{\nu5}2R1; 4,5\)) were not isolated, a detailed analysis of multiple clones was only done with the LAZZ cell line, which lacks this gene (J.E. Berman and F.W. Alt, unpublished results). The relative proportion of transcripts derived from the functional and pseudo-V\(_{\nu5}\) genes may vary among cell lines; e.g., several germline cDNAs isolated from the polyclonal EBV-321 line (Fig. 1C) were all derived from a functional V\(_{\nu5}\) gene (V\(_{\nu251}\)) (P.W. Tucker and C. Humphries, unpublished observation).

The sequences of the functional and pseudo-V\(_{\nu5}\) transcripts are highly conserved in the 3′ flank as well as in the coding regions. It has been suggested that the limited polymorphism seen in coding regions of the smaller V\(_{\mu}\) gene families (V\(_{\mu4}, -5, -6\)) may be related to critical antigen specificities encoded by these genes (14, 15). This explanation does not account for the high degree of conservation among the pseudo-V\(_{\nu5}\) coding region sequences or among the 3′ flanking regions of both the functional and pseudo-V\(_{\nu5}\) genes. Such conservation could be due to recent emergence and duplication of the V\(_{\nu5}\) family, but may also be explained by the fact that these regions are expressed in germline transcripts. Conservation of the 3′ untranslated regions could be due to a functional role such as regulating mRNA stability. The V\(_{\nu5}\) pseudogene is likely to be nonfunctional with regard to VDJ rearrangement due to its abnormal recombination sequences; however, conservation of the ORF in the pseudo-V\(_{\nu5}\) gene might reflect a function of an encoded germline V\(_{\nu5}\) protein.

3′ Flanking Regions of Functional and Pseudo-V\(_{\nu}\) Germline cDNAs. The functional and pseudo-V\(_{\nu5}\) cDNA sequences are highly homologous throughout the coding (91% similar) and 3′ flanking regions (86% similar). A comparison of the 3′ flanking regions of functional (L3-4) and pseudo-V\(_{\nu5}\) (L2-9) cDNAs reveals two major regions of divergence: ~0.16 kb 3′ of the nonamer and immediately 3′ of the coding regions (Fig. 4). A 24-bp deletion in the immediate 3′ flank of the pseudogene results in loss of the heptamer and part of the spacer region, thus placing the nonamer 12 bp 3′ of the internal ‘V replacement’ heptamer (16, 17). Therefore, on the basis of the 12/23 joining rule (reviewed in reference 1) there could be direct rearrangement between the V\(_{\nu5}\) pseudogene (12-bp spacer) and J\(_{\nu}\) segments (23-bp spacer). As yet there is no evidence for direct pseudo-V\(_{\nu5}\) to J\(_{\nu}\) joining perhaps due to the orientation of the internal heptamer relative to the nonamer. Although it may be a coincidence, it is notable that the 24-bp deletion in the pseudogene does not shift the reading frame; thus, the translational site in the nonamer is conserved.

Comparison of Murine and Human Germline V\(_{\nu}\) Transcription. Several aspects of human and murine germline V\(_{\nu}\) transcription are similar. Although mouse and human germline V\(_{\nu}\) transcripts vary in length, murine germline V\(_{\nu}\) cDNAs have an ORF similar in size to that of the human germline V\(_{\nu5}\) transcripts, also ending in a termination codon within the recombination signals (but in the 23-bp spacer region rather than in the nonamer; reference 7). Thus, murine and human germline V\(_{\nu}\) transcripts potentially encode truncated V\(_{\nu}\) proteins of a similar size. Transcription of only one V\(_{\mu}\) family has been readily found in humans (V\(_{\mu5}\)) as well as in mice (J558). Although the V\(_{\nu5}\) family has no obvious murine counterpart (i.e., >70% nucleic acid similarity), V\(_{\nu}\)J558 members are the most closely related. Of course germline transcripts from other murine and human V\(_{\nu}\) gene families may exist at undetected, lower steady-state levels. In mice and humans, most germline V\(_{\nu}\) transcription initiates at the normal V\(_{\nu}\) promoter, although more 5′ initiation has been seen with V\(_{\nu}\) pseudogenes that still retain ORFs (see above and reference 7).

Specificity of Germline V\(_{\nu5}\) Expression. The consistent expression of germline V\(_{\nu5}\) in pre-B ALLs may provide an additional diagnostic marker for disease in tissues such as PBMC, which normally lack detectable germline V\(_{\nu}\) mRNA. In contrast to the pre-B specificity of murine germline V\(_{\nu}\) expression, we also detected human germline V\(_{\nu5}\) transcripts in more mature B lineage cells. Germline V\(_{\nu5}\) expression in some B-CLLs and in some EBV-transformed B cell lines might argue against the proposal that germline V\(_{\nu}\) transcription reflects processes that regulate V\(_{\nu}\) to D-J\(_{\nu}\) rearrangement in pre-B cells. On the other hand, germline V\(_{\nu}\) expression beyond the pre-B cell stage may be unique to transformed cells and may reflect the difficulty of staging human B lineage tumor cells. Germline V\(_{\nu}\) expression may also be restricted to certain B cell subpopulations. Germline V\(_{\nu5}\) mRNA was observed in fetal liver, but was not detected in PBMC or in adult spleen cells, suggesting that normal mature B cells do not express germline V\(_{\nu5}\). Nevertheless, germline V\(_{\nu5}\) transcripts may be expressed in some normal CD5⁺ B cells based on their presence in some CD5⁺ B-CLLs and in cord blood and fetal liver, tissues that are rich in CD5⁺ cells (18, 19). We saw no evidence for germline V\(_{\nu5}\) transcripts analogous to the unusual species found in human T cells, consisting of a novel 5′ exon spliced to an unrearranged V\(_{\nu4}\) gene (20).

Function of Germline V\(_{\nu5}\) Transcription. Germline V\(_{\nu}\) expression may regulate accessibility of the V\(_{\nu}\) locus during H chain rearrangement; alternatively, truncated V\(_{\nu}\) proteins encoded by germline transcripts may play a role in B cell development (7). Germline V\(_{\nu}\) cDNAs presumably possess the same 5′ signals required by mature H chain transcripts for translation since the transcription start sites seem similar. Furthermore, in vitro transcription and translation of the germline V\(_{\nu5}\) cDNAs demonstrated that the transcripts are translatable into a protein consistent with the size (13.9 kD) of the predicted ORF (J. E. Berman and F.W. Alt, unpublished results). These putative truncated V\(_{\nu5}\) H chain proteins are reminiscent of other members of the Ig gene superfamily, such as Vpre-B (21), and would consist of a single Ig domain possessing the two cysteine residues necessary for formation of the characteristic intra-chain disulfide-bonded loop.

Conservation of germline V\(_{\nu}\) gene transcription in humans as well as in mice suggests an important functional significance. The complexity of the J558 family has made it difficult to ascertain the heterogeneity of murine germline transcripts and to identify the corresponding genomic germline genes that are transcribed. Detectable germline J558 expression in mice could be the result of low level transcription
of multiple genes and/or high level expression of a limited subset of the large J558 family. The relative simplicity of the human V\textsubscript{6} family allows us to conclude that human germline transcripts derived from just two unrearranged V\textsubscript{6} genes are readily detectable and their genomic counterparts have already been isolated and are available for further analysis. This should facilitate future study of factors such as associated regulatory regions, which may control germline V\textsubscript{H} gene transcription.

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