solar energy deposition into its atmosphere by a factor of 2.5 (*17*). The periodicity of albedo variations appears to provide an input to global planetary weather systems on a short time scale relative to Neptune's 164-year period of revolution around the sun. Neptune's orbit is almost perfectly circular, so its changing distance from the sun caused only an insignificant 0.5% decrease in total insolation since 1972. What appears remarkable is the extraordinary sensitivity of Neptune's atmosphere to the modulation of the solar output.

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$$F_{205} = 8.56 + 0.0185 W_{1083}\ \mathrm{W\ cm^{-3}}$$

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A Novel Human Gene Closely Related to the *abl* Proto-Oncogene

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A DNA sequence related to the *abl* proto-oncogene was identified in human placenta. Molecular cloning and nucleotide sequence analysis revealed two putative exons whose predicted amino acid sequence was most homologous to the corresponding sequences of c-*abl* and v-*abl* but was related to other tyrosine kinase genes as well. The new sequence was localized by in situ hybridization and somatic cell genetic analysis to human chromosome 1q24–25, which differs from the location of any previously identified tyrosine kinase gene. The detection of a novel 12-kb transcript by this gene in human normal and tumor cells establishes it as a new member of the tyrosine kinase family that is closely related to but distinct from c-*abl*.

PROTO-ONCOGENES ARE THE NORMAL counterparts of the oncogenes of acute transforming retroviruses (*1*). The normal functions of some of these genes are becoming increasingly better understood. Chain 2 of platelet-derived growth factor is encoded by the human *sis* proto-oncogene (*2*). A truncated version of the receptor for epidermal growth factor (EGF) is encoded by v-*erb*B (*3*), and the product of the *fms* proto-oncogene appears to be related to the receptor for macrophage colony-stimulating factor (CSF-1) (*4*). Both v-*erb*B and v-*fms*, as well as several growth factor and hormone receptors, are members of a family of tyrosine kinase–encoding genes (*5, 6*).

There are several examples of genetic alterations affecting members of the tyrosine kinase family in human tumors (*7–10*), including the specific translocation of the c-*abl* locus in chronic myelogenous leukemia (CML). Because of the significance of c-*abl* in neoplasia, we embarked on a search for other human tyrosine-kinase genes closely related to c-*abl*.

Additional members of some proto-oncogene families have been identified by finding their related sequences sufficiently amplified in particular tumors to allow detection (*9, 11, 12*). In order not to rely upon the fortuitous identification of tumor cells carrying amplified c-*abl*–related sequences, we attempted to detect such sequences in normal human DNA by molecular hybridization with a v-*abl* probe under conditions of low stringency. The tyrosine kinase–encoding domain of v-*abl* was selected as the probe, since this region is well conserved among members of the tyrosine kinase gene family.

Hybridization of the v-*abl* probe under stringent conditions with DNA prepared from human placenta revealed two Eco RI fragments (Fig. 1A, lane 2) that contained c-*abl* sequences, as expected (*13*). However, when hybridization was conducted under conditions of low stringency, an additional 12.5-kbp fragment was identified (Fig. 1A, lane 4). This 12.5-kbp fragment was not amplified in DNA from K562 (Fig. 1A, lane 3), a CML line that contains an amplified copy number of c-*abl*, further suggesting that the additional fragment did not represent c-*abl*.

To clone the 12.5-kbp fragment, an Eco

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RI digest of normal human placenta DNA was subjected to sucrose gradient centrifugation, and a fraction containing fragments of ~12 kbp was ligated into λEMBL. The resulting bacteriophage library was screened by plaque hybridization under conditions of low stringency with a radiolabeled v-*abl* probe. The physical map of a hybridizing phage (λarg 1) containing a 12.5-kbp insert, and two puc18 subclones containing a 0.75-kbp Eco RI–Sac I fragment and a 1.1-kbp Bgl II–Bgl II fragment (parg 1 and parg 2, respectively) are shown in Fig. 2. Regions of the 12.5-kbp fragment homologous to v-*abl* were identified by hybridization of radioactive v-*abl* probe to Southern blots containing the products of restriction enzyme digestions. The subclones shown in Fig. 2 each contained one hybridizing fragment.

A single-copy DNA probe containing sequences homologous to v-*abl* was generated by digestion of parg 1 with Apa I and Eco RI. The specificity of this probe was demonstrated by hybridization with human placenta DNA digested with Eco RI. As expected, the 12.5-kbp fragment was detected under conditions of high stringency (Fig. 1B, lane 3), whereas an additional fragment containing c-*abl* sequence hybridized only under conditions of low stringency (Fig. 1B, lane 4).

To more precisely characterize the *abl*-related regions, the two subclones were subjected to nucleotide sequence analysis. Two discrete open reading frames exhibiting nucleotide sequence homology to v-*abl* were observed (Fig. 2). Together they shared

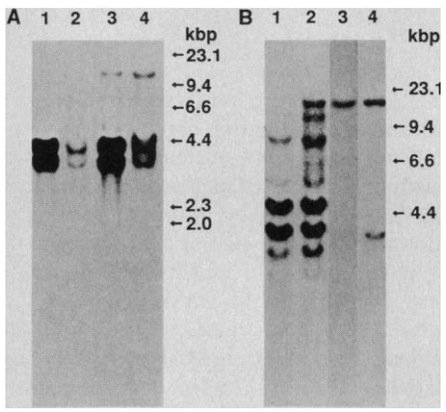

Fig. 1. Detection of *abl* and *abl*-related gene fragments in human placenta and K562 cells. DNA (20 μg) was cleaved with Eco RI, separated by electrophoresis in agarose gels, and transferred to nitrocellulose paper (*33*). Hybridization to ^{32}P-labeled probe (*34*) was conducted in a solution of 40% or 30% formamide, 0.75*M* NaCl, and 0.075*M* sodium citrate, at 42°C (*35*). After hybridization, the blots were washed first in 0.3*M* NaCl plus 0.03*M* sodium citrate at room temperature, and then in 0.015*M* NaCl, 0.0015*M* sodium citrate at 50°C. Hybridization was detected by autoradiography. (A) Hybridization of a v-*abl* probe to placenta (lanes 2 and 4) or K562 (lanes 1 and 3) DNA under stringent (40% formamide) (lanes 1 and 2) or relaxed (30% formamide) (lanes 3 and 4) conditions. The probe was a 0.75-kbp Sau I–Sau I fragment of v-*abl* encompassing nucleotides 2489 to 3238 of the provirus (*14*). (B) Hybridization to placenta DNA of v-*abl* (lanes 1 and 2) and *arg* probes (lanes 3 and 4) under stringent (lanes 1 and 3) or relaxed (lanes 2 and 4) conditions. The v-*abl* probe was a 1.7-kbp Hinc II–Hinc II fragment encompassing nucleotides 1867 to 3600 of the provirus. The *arg* probe was 0.52-kbp Eco RI–Apa I fragment of plasmid parg 1.

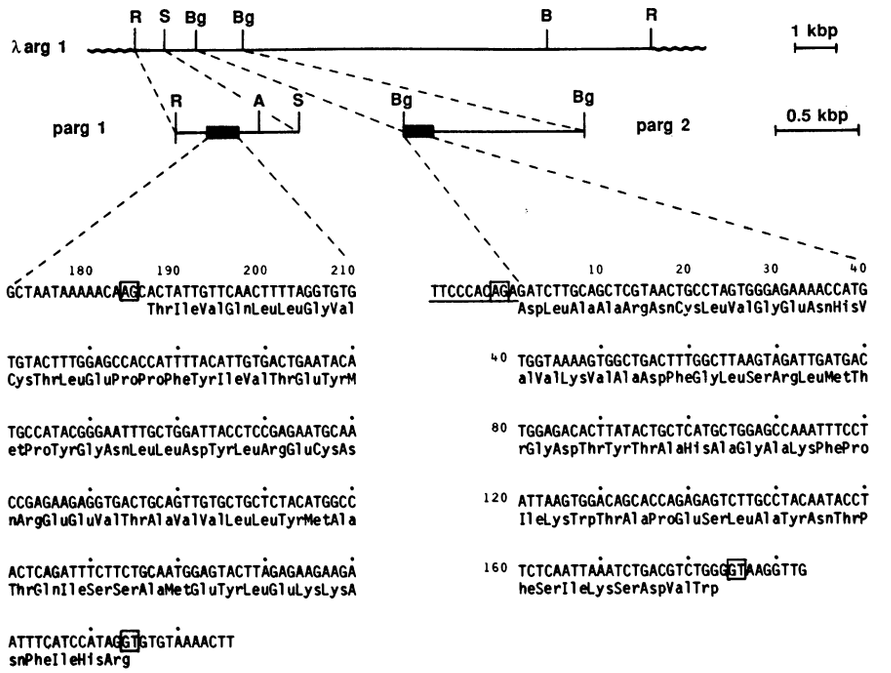

Fig. 2. Physical site map of λarg 1 and the inserts of plasmids parg 1 and parg 2. A, Apa I; B, Bam HI; Bg, Bgl II; R, Eco RI; S, Sac I. The sites were determined by electrophoretic analysis of the products of single and double digestions. Regions of λarg 1 homologous to the 1.7-kbp v-*abl* probe were identified by hybridization as described in Fig. 1. Two homologous regions (dark bars) were contained in the plasmid subclones. The nucleotide sequence and predicted amino acid sequence of the regions homologous to v-*abl* are shown. Possible processing sites at the borders of the putative exons are shown in boxes. The underlined nucleotides were obtained by analysis of the region 5′ to the first Bgl II site. Nucleotide sequence was performed by the dideoxy chain termination method (*36*).

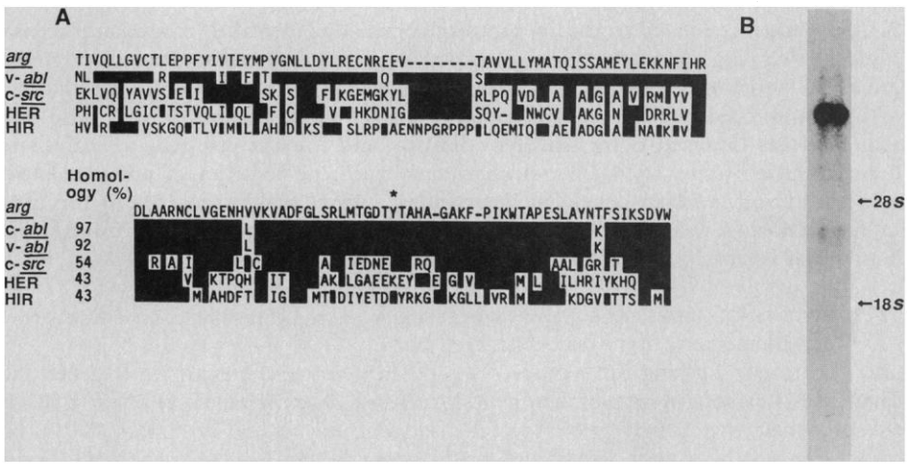

Fig. 3. (A) Comparison of the predicted amino acid sequences of the 5′ (upper) and 3′ (lower) exons of *arg* with v-*abl* (*16*), human c-*abl* (*14*), chick c-*src* (*37*), human epidermal growth factor receptor (HER) (*8*), and human insulin receptor (HIR) (*6*). Black regions represent identical amino acids. Sequence information was not available for the c-*abl* region homologous to the 5′ exon. The tyrosine residue autophosphorylated in v-*src* is indicated by an asterisk. Single-letter abbreviations for the amino acid residues are: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr. (B) Detection of messenger RNA derived from the *arg* gene. Polyadenylated RNA of a human glioblastoma cell line was separated by denaturing gel electrophoresis in formaldehyde (*38*) and transferred to nitrocellulose. Hybridization of the filter with the *arg* probe was performed as described in the legend to Fig. 1. Hybridization was detected by autoradiography.

69% nucleotide sequence identity with v-*abl*. While the sequence of c-*abl* homologous to the 5′ open reading frame was not available, that of the 3′ was 69% homologous to c-*abl* (*14*). In addition, the Bgl II site located at the 5′ end of this opening frame was also present in c-*abl*. The two putative coding regions were each flanked by the AG and GT dinucleotides that border the exons of eukaryotic genes (*15*). Furthermore, the putative amino acid sequence resulting from the joining of the two open reading frames at the indicated splicing junctions was homologous without gaps to the amino acid sequence of v-*abl* (*16*). These findings suggested that the sequences shown in Fig. 2 represented two consecutive exons, separated by an intron, of an *abl*-related human gene.

The homology of the predicted amino acid sequence of the two putative exons to corresponding sequences of other tyrosine kinase–encoding genes is shown in Fig. 3. The sequence encoded by the 3′ exon differs from both c-*abl* and v-*abl* at only 2 of 61 amino acids. Combined, the predicted sequences of both exons share 92% homology with v-*abl*. Of the partial nucleotide sequence available for the *met* oncogene (*17*), a putative exon encoding 23 amino acids shares 74% homology. The extent of homology observed with the predicted amino acid sequences of other tyrosine kinase–encoding genes was next best for c-*src* (54%). The tyrosine residue that is the site of autophosphorylation of the *src* protein (*18*) was conserved in the putative coding sequence of the *A*belson-*r*elated *g*ene, which we designated *arg*.

The *arg* gene is probably a single-copy sequence since single hybridizing fragments were detected by Southern analysis of DNA separately digested with 11 restriction enzymes. Two fragments were found in DNA digested with Pst I, a restriction enzyme that has a site within an *arg* exon. No polymorphism was detected in DNA from 10 individuals with these 12 restriction endonucleases.

To establish that *arg* was a functional gene, we investigated its expression in polyadenylated RNA's of a variety of cells. A 12-kb transcript was readily detected by an *arg* probe in human brain tissue, fibroblasts, and several established tumor cell lines. A representative *arg* transcript (Fig. 3B) in a cell line derived from a glioblastoma was distinct from the previously reported 6-kb and 7-kb c-*abl* transcripts (*19*). These findings demonstrate that *arg* is a new functional gene within the tyrosine kinase family.

The chromosomal location of the human *arg* gene was determined by in situ hybridization on 233 chromosome spreads. We

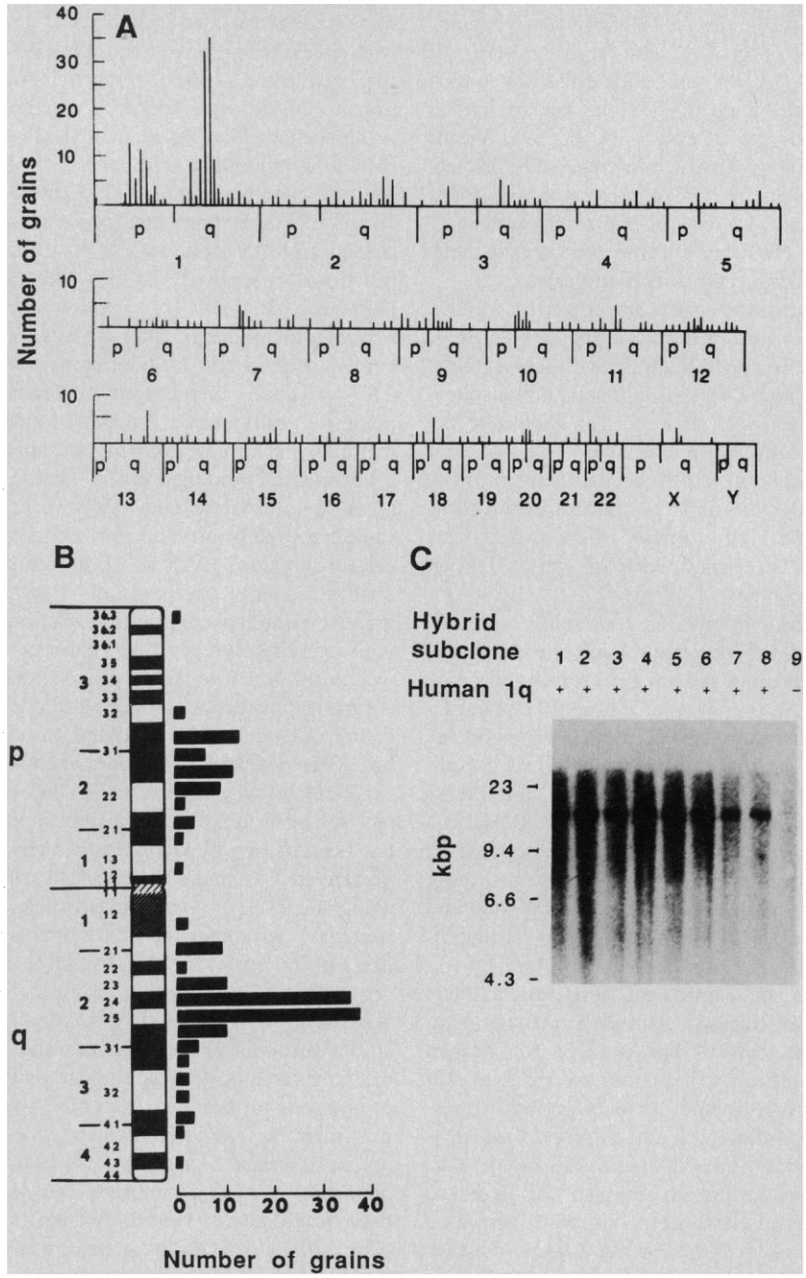

Fig. 4. (A) Distribution of autoradiographic silver grains on normal human chromosomes after in situ hybridization with *arg* probe. Human metaphases and prometaphases from methotrexate-synchronized normal peripheral lymphocyte cultures (*39*) were pretreated with ribonuclease and denatured in 70% formamide + 2× SSC (standard saline citrate) at 70°C. The *arg* probe was labeled with all four ^{3}H-nucleotides (Amersham, Arlington Heights, IL) to high specific activity (3.7×10^7 cpm/μg DNA). A hybridization solution containing 50% formamide, 5% dextran sulfate, 5 m*M* EDTA, 2× Denhardt's solution, 300 m*M* NaCl, 30 m*M* sodium citrate, single-stranded salmon sperm DNA (50 μg/ml), 200 m*M* phosphate buffer (*p*H 6.4) and 5×10^5 cpm of the labeled probe was layered onto each slide (*40*). The slides were covered with cover slips and incubated in a moist chamber at 42°C for 20 hours. After hybridizations, slides were washed successively in 50% formamide/2× SSC and 2× SSC at 42°C. For autoradiography, the hybridized slides were coated with nuclear track emulsion NTB-2 (Kodak, Rochester, NY), diluted 1:1 with H_2O and stored at 4°C for 14 days. For G-banding the slides were treated with a solution of 0.03% trypsin/0.012% EDTA (Gibco, Grand Island, NY) and stained with 0.25% Wright stain in 0.06*M* phosphate buffer (1:3, *p*H 6.8) (*41*). Previously photographed chromosome spreads were relocated and a second photomicrograph exhibiting G-bands was taken. Silver grains observed on 233 cells were plotted on a 400-band human ideogram (*42*). (B) Distribution of autoradiographic silver grains on chromosome 1. (C) Southern hybridization of DNA isolated from nine subclones of a single human-mouse somatic cell hybrid. DNA (10 μg) was digested with Eco RI, fractionated by 0.7% agarose gel electrophoresis, and transferred to a nylon membrane. Hybridization with a ^{32}P-labeled *arg* probe was performed as described (*43*) at 42°C in 50% formamide and 10% dextran sulfate. Hybridization was detected by autoradiography after washing the membrane at 55°C in 0.015*M* NaCl, 0.0015*M* sodium citrate, and 0.2% SDS. A 9-kbp mouse fragment homologous to *arg* was not detected under these stringent hybridization conditions.

found 169 grains (35% of total) on chromosome 1 (Fig. 4A). The largest number of grains (72) was on bands 1q24–25, which was equivalent to 43% of the grains on chromosome 1 and 15% of total grains scored (Fig. 4B). A minor site of hybridization on band 1p31 consisting of 31 grains accounted for 6% of the total number of grains. No other chromosome sites exhibited specific accumulation of grains.

As an independent approach to confirm the location of *arg* on the long arm of chromosome 1, 82 human-rodent somatic cell hybrids (*20*) that segregate human chromosomes were analyzed. An *arg* probe detected a 12.5-kbp human Eco RI fragment specifically in DNA prepared from those hybrid cell lines that contained human chromosome 1. In contrast, there was at least 18% discordancy with all other human chromosomes.

Analysis of hybrids containing segments of human chromosome 1 permitted regional localization of the *arg* gene on this chromosome. Among a series of nine subclones of a human-mouse hybrid cell line, eight retained an intact chromosome 1 and the *arg* sequence. One subclone, which contained a deletion of part of the long arm, lacked the *arg* gene (Fig. 4C). This subclone (lane 9) contained short arm markers including phosphoglucomutase-1, L-*myc*, N-*ras*, and the 6.2-kbp metallothionein sequence; whereas the 2.8-kbp metallothionein sequence and peptidase C long arm markers were not retained. An independent human-hamster hybrid was positive for human chromosome 1p isoenzyme markers (6-phosphogluconate dehydrogenase, phosphoglucomutase-1, and enolase-1) as well as the L-*myc* proto-oncogene (*21*) and the 6.2-kbp metallothionein sequence (*22*). It lacked the human N-*ras* proto-oncogene located on proximal 1p as well as the 2.8-kbp metallothionein sequence and peptidase C on chromosome 1q. This hybrid, which lacked the long arm of chromosome 1 but retained most of the short arm, did not contain the *arg* gene. All of these results confirmed the assignment of *arg* to chromosome 1q by in situ hybridization and excluded a locus for this gene on the short arm of chromosome 1.

Five proto-oncogenes have previously been assigned to chromosome 1: c-*fgr* (1p36.1–36.2) (*23*), B-*lym* (*24*), and L-*myc* (*21*) at the same band (1p32), N-*ras* (1p11–13) (*25*), and *ski* (1q22–ter.) (*26*). The in situ localization of *arg* to 1q24–25 coincides with the location of a constitutional fragile site (*27*). Nonrandom numerical changes involving the long arm of chromosome 1 have been observed in several human cancers (*28*). Trisomy for the segment 1q25–32 was initially demonstrated in a series of patients with myeloproliferative disorders (*29*) and, subsequently, complete or partial duplications 1q21–32 were found in a variety of malignancies (*28*). The segment 1q22–24 is commonly modified in Burkitt lymphoma cell lines not associated with Epstein-Barr virus (EBV). It has been postulated that amplification at this region may have a functional equivalence to the presence of EBV (*30*).

Some members of the tyrosine kinase family, such as the EGF receptor and the CSF-1 receptor, are membrane proteins that possess a cytoplasmic catalytic domain, a membrane spanning domain, and an extracellular ligand binding domain. Others, such as those encoded by c-*abl* and c-*src*, appear to be cytoplasmic proteins that lack an extracellular domain. Analysis of the complete coding sequence of *arg* should provide an understanding of its structural relationships with other known tyrosine kinase genes as well as insights into its possible functions.

Oncogenes that are closely related to, but distinct from, known retroviral oncogenes have been detected by a variety of approaches. N-*ras* (a close relative of H- and K-*ras*) has not been identified in a retrovirus, but has been shown by transfection analysis to be activated as an oncogene in a variety of malignancies (*12*). Genes closely related to retroviral oncogenes have also been identified on the basis of their amplification in certain human tumors. For example, N-*myc* and L-*myc* were detected by virtue of their amplification in neuroblastomas and small cell lung carcinomas, respectively, by means of *myc* gene probes (*11*). Recently, c-*erb*B-2 was identified as an amplified gene in a human mammary carcinoma (*9*) and independently in normal cellular DNA (*10*) by hybridization with v-*erb*B. A transforming gene initially detected by transfection analysis of chemically induced rat neuroblastoma (*31*), *neu*, has recently been shown to be the rat homologue of c-*erb*B-2 (*32*). Thus, a number of genes related to but distinct from oncogenes transduced by retroviruses have been implicated in the neoplastic process. Our detection and partial isolation of *arg*, a gene closely related to *abl*, should make it possible to determine if amplification or rearrangement of this gene can be linked to any human malignancy.

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