SHORT COMMUNICATION

Sequence-Tagged Sites (STSs) for a Set of Mapped Markers on Chromosome 21

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Sequence tagged sites (STSs) have been proposed as a "common language" for comparing physical and genetic maps of the human genome produced by a variety of techniques. We have produced 44 STSs from 38 mapped loci on human chromosome 21. The STSs represent most of the loci designated as genetic reference or ordered physical framework markers, along with a number of others chosen to span all regions of 21q. Of the STSs, 12 are from gene segments, including 4 from exons of the *APP* gene encoding the amyloid β protein precursor, and 32 mark anonymous DNA loci. These STSs make each of the corresponding loci readily accessible to the research community without the need for exchange of clones. These sites also represent multiple start points for the isolation of YAC clones that should permit overlapping the entire chromosome 21 long arm as cloned DNA. © 1992 Academic Press, Inc.

The mapping of individual human chromosomes using recombinant DNA techniques has been pursued for the past decade, but only recently have technological developments made the promise of complete maps and overlapping clone sets a realistic expectation. To facilitate comparison of the data derived from different physical mapping procedures, as well as from genetic linkage mapping, Olsen *et al.* (13) have proposed the development of sequence-tagged sites (STSs), or unique polymerase chain reaction (PCR)-amplifiable stretches of single-copy DNA. PCR amplification currently represents the preferred method for screening yeast artificial chromosome (YAC) libraries, suggesting that the development of STSs represents a crucial first step toward developing overlapping YAC clone sets for individual chromosomes.

Chromosome 21, the smallest human autosome comprising only 1.7% of the genome (12), is an ideal target for the development of an overlapping clone set due to its small size and its importance in medical genetics. A large number of single-copy probes and known genes from chromosome 21 have been isolated (22, 23, 27) and ordered by pulsed-field gel mapping (7, 14), mapping with irradiation-reduced or other hybrids (4, 5, 8, 24), and/or genetic linkage analysis (16, 22, 23, 25). A set of "reference linkage markers" and other mapped loci have been gathered into an "ordered marker framework" proposed as the foundation for developing a complete physical map of the chromosome (5). We have targeted the reference and framework markers, along with a number of other loci for the development of STSs. The 44 STSs generated provide well-spaced starting points in all cytogenetic regions of 21q. Isolation of YACs for these loci and development of new STSs from the ends of these would be expected to lead to an overlapping clone set for 21q.

The list of those loci selected for STS generation, along with the primer pair and predicted size of the amplification product for each resulting STS, is presented in Table 1. For all genes and *D21S3*, sequences used for STS production were drawn from published data (*APP*∗1 [exon 2], *APP*∗2 [exon 7], *APP*∗3 [exon 15], *APP*∗4 [exon 18], 29; *BCEI*∗1, 10; *CD18*∗1, 11; *Co16A2*∗1, 20; *GART*∗1, 2; *ETS2*∗1, 26; *MX1*∗1, 1; *MX2*∗1, 1; *SOD1*∗1, 9; *D21S3*∗1, 28). We generated several hundred basepairs of sequence from the edge of the indicated clone to design primers, which were chosen to have a roughly equal GC/AT ratio. STSs were named by adding ∗ followed by a sequential identification number to the locus symbol.

STSs were tested using human genomic DNA (placental or lymphoblast), DNA from WAV17, a human × mouse hybrid line containing only human chromosome 21 (19), and DNA from LTK^{-1}, the mouse parent. Figure 1 shows five examples of this analysis, yielding three different patterns of amplification. In three cases, *D21S17*∗1, *MX2*∗1, and *APP*∗3 (Figs. 1A, 1B, and 1C), intense bands were evident in the human and WAV17 amplifications, but not in the product of the mouse reaction. For *APP*∗2 (Fig. 1D), intense bands of different sizes were amplified from human and mouse DNA, and

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TABLE 1

Description of Chromosome 21 Sequence-Tagged Sites

STS	Sequence	PCR product size (bp)	PCR primer sequences
*APP**1	PS	267	5′ TGCCTTGGAGCTATGGATACT 3′ 5′ AACAAATGCATGTGATCCAAC 3′
*APP**2	PS	224	5′ ATGCTAAATGTGGTTCCCCA 3′ 5′ CAGAGTCATGGCGAGAGAGA 3′
*APP**3	PS	188	5′ AAGGAGACAACGTCTGCTCG 3′ 5′ GCCACGACTTACCGATCTTG 3′
*APP**4	PS	543	5′ GCAGCCTCTGAAGTTGGACAGCAA 3′ 5′ GCAGAAGCAGCAATCTGTACAGTA 3′
*BCEI**1	PS	222	5′ CATGTAGCTTGACCATGTCTAGG 3′ 5′ GATCACCTTGTTCTCCATGGTGGC 3′
*CD18**1	PS	225	5′ GTTTGCTGAGAGTTAGGAGC 3′ 5′ ATGCAAAGACTGTGCCAGTC 3′
*COL6A2**1	PS	266	5′ AAGCTGGTGCACAGGGACATCGTGG 3′ 5′ GACTGGAAGATGCAGCCGCAGCAA 3′
*GART**1	PS	202	5′ GTAGCTGAAGATGTGGATGC 3′ 5′ GGCTTCATTCCTCTTTAACC 3′
*ETS2**1	PS	356	5′ CAGAACTTGCTGGGGTTCACGCCCGAGGAAC 3′ 5′ CCCGTCCCACGGACTGCCAGGCGCCAGGAC 3′
*MX1**1	PS	252	5′ TGCTCAGTAGTCAGACTGGATAGTCC 3′ 5′ AGCTGTGATGTTCAGCATGTGTCAGT 3′
*MX2**1	PS	228	5′ GTGCTGTGTAAGTGATGGAGATAC 3′ 5′ TAACAGAACAATGGAAGCTCATCATA 3′
*SOD1**1	PS	1191	5′ GCCAAATGAATGACGGGCCTATAAGTAAGGTA 3′ 5′ GATACTGAAAACTAGTCGAGACTCCATTTATATGT 3′
*D21S3**1	pPW231C	303	5′ CTGAACATGGCTTCCTCTTC 3′ 5′ CTGCCAGCATGTTGGCATTG 3′
*D21S11**1	pPW236B	314	5′ TCCTGCCCTAGTGTAAGTCAG 3′ 5′ CAGCAATGACTAGACAATG 3′
*D21S12**1	pPW267C	160	5′ AGCTGAAGCTTTTTAAAATCTTTCCTTGAC 3′ 5′ TCTGCGTAGTTGAATCTGAGCAATCATTTT 3′
*D21S13**1	pGSM21	276	5′ GGGAAGTCACCTAACATACAGCAGTGGACT 3′ 5′ GGGAATCCAGATAGCCTCACTTGTCACAATTCTGTC 3′
*D21S15**1	pGSE8	218	5′ GAGGATAAACCGATTCACAGCTAGGAATAC 3′ 5′ GTGCACGTAATTAATGACCATGATATTGCT 3′
*D21S16**1	pGSE9	238	5′ TTCCATGCCCAGACTGAAGTTCTGGACTGA 3′ 5′ CCTATCACCAATGGAGAAAGCCCATAAGGA 3′
*D21S17**1	pGSH8	210	5′ CCAGGATAGTCAATGGCAGAATGGGAGCAA 3′ 5′ GGCTGATTGCACCAATGGGAATGGAAGTTG 3′
*D21S18**1	pGSB1	284	5′ AGCACAACAGAGCATCCAC 3′ 5′ ACTGACTCATGTGCCTGCTG 3′
*D21S19**1	pGSB3	305	5′ AAACACATCTGTTTCATGGTGTAAGTTACT 3′ 5′ CCACATTAGCACAGGAAATATTGGTTGGTT 3′
*D21S23**1	pPW244D	169	5′ TCACTAGCAGTATATGAGAGTTCCAGTTGT 3′ 5′ AGGAAGGCAAGCAGGCAGGCAGGCAGGCAG 3′
*D21S52**1	pPW511-1H	221	5′ GCTTATCATCGATAAGCTTCC 3′ 5′ GAAGAGGAATTTGGCTTGG 3′
*D21S53**1	pPW512-18P	134	5′ ATACTGTTCATCCATCATACCCTG 3′ 5′ CAGAGCTCTGTTATTCATGCATCT 3′
*D21S53**2	pPW512-5R	208	5′ AGCTGCCACTTCTCACTCGAAGG 3′ 5′ TCAGAAGAAGCCATCCAGGC 3′
*D21S54**1	pPW513-5H	176	5′ CCATTCTTCTTACTATTGCTG 3′ 5′ GATGGATATATTCTCCTAGGG 3′
*D21S55**1	pPW518-1R	208	5′ GGTTTGAGGGAACACAAAGCTTAACTCCCA 3′ 5′ ACAGAGCTACAGCCTCTGACACTATGAACT 3′
*D21S55**2	pPW518-8B	159	5′ AGGCTCCTTCACCTCTTGAC 3′ 5′ CATCCTCTTTGCATTAGG 3′
*D21S56**1	pPW520-10R	204	5′ CTCCAGCACACAGGACGGAGA 3′ 5′ TCTGTCTTCTCTGTTTCTAGA 3′
*D21S58**1	pPW524-5P	407	5′ GGAGTGGTCTTTATGCCGGTCCCTGCTCTG 3′ 5′ GGTCTGAATCCTTGCTCAGCCACTCATGAC 3′
*D21S59**1	pPW552-3H	153	5′ GGAAGTCTGTGGGAAAACGAC 3′ 5′ GAAAGATCTGTGTCAATGAC 3′
*D21S59**2	pPW552-2B	224	5′ AGCTTTCCCAGAATCCCTAG 3′ 5′ GTGGCAAGTATGTTAGTTG 3′

TABLE 1—*Continued*

STS	Sequence	PCR product size (bp)	PCR primer sequences
D21S63∗1	pPW517-3R	200	5′ TATGGTGTAAACTGTGTTGCAA 3′ 5′ CATAACGACTCAAGTGCTATGA 3′
D21S64∗1	pPW551-8P	167	5′ CTGCAGGGTATGGTAAGAG 3′ 5′ AGGAGCCATCATTCTCATCG 3′
D21S65∗1	pPW525-5H	191	5′ GTGGACTTGCAATGAGAATG 3′ 5′ AGGTGAACTGGTGTTCGAAG 3′
D21S71∗1	pPW519-14R	139	5′ CTAGCAAAGAGGTGAGGGTGAG 3′ 5′ TGTAGAGTCTGCCTGGCAGAAC 3′
D21S82∗1	FR-8-77	432	5′ TAGGATAGCAAGTGAGTTCTC 3′ 5′ CTACAATGGGAGATAGCATC 3′
D21S93∗1	pJG77	323	5′ GGAAGGCTGCGGTTGGCTGAAGGCCGACTCCTG 3′ 5′ CCACCTACTGCAAATGCCACTGCTGCATAAGCT 3′
D21S110∗1	p21-4U	258	5′ CTGCCAATATGCTGACTTTGAAAGAGGTCT 3′ 5′ CTAAGTGTTATCTAAGTGGCAAGTGGCAGT 3′
D21S111∗1	PS	301	5′ TGACCAGAAAGATGTAATTGCCTGTAACAATTACC 3′ 5′ CTGCTAGAACATGAAGAGTTTGCTTCTGTGCC 3′
D21S112∗1	CRI4-427	282	5′ TTCCAGTTGCAGTGACTCC 3′ 5′ TTGGCCAGTGTGTGCCTGGAC 3′
D21S113∗1	pMCT15	358	5′ GATCCACCAAGCATCATGCAG 3′ 5′ ACAGGTAGCTCTGTCTCAG 3′
D21S120∗1	pUTB37	291	5′ GGATGGGATTCACTCCTTAATTCAACAGAT 3′ 5′ CCTCATTTAACCTTAATTACCTCCTAGAGCC 3′
D21S237∗1	pPW265D	191	5′ AGAGTGATAGTTGTTAGAAGA 3′ 5′ TGCTGCTACAGAGACATCACT 3′

Note. PS, published sequence.

both products were amplified from WAV17 DNA. In the final example, *D21S53*∗1 (Fig. 1E), a fragment of similar size was amplified from both mouse and human DNA.

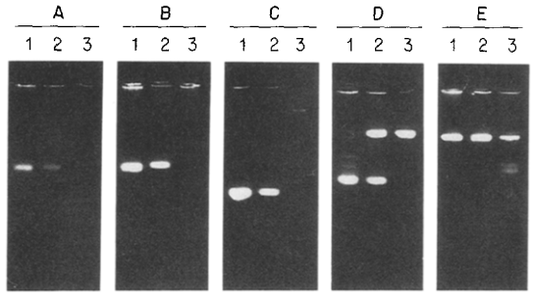

FIG. 1. Specificity of representative human chromosome 21 STSs. Ethidium bromide-stained 3% Nusieve/1% agarose gel containing representative PCR products amplified from (1) human genomic DNA; (2) the human chromosome 21-specific mouse–human somatic cell hybrid, WAV17 DNA; and (3) LTK^{-1} mouse DNA. **A,** *D21S17*∗1; **B,** *MX2*∗1; **C,** *APP*∗3; **D,** *APP*∗2; **E,** *D21S53*∗1. See Table 1 for PCR product sizes and primer sequences used. The shadow bands in **D** and **E** most likely represent additional low-level amplified products and primer dimer, respectively. DNA sequence was obtained by the procedure of Sanger *et al.* (21). Primers were synthesized using a Biosearch Cyclone DNA synthesizer or an Applied Biosystems DNA synthesizer. PCR was carried out in a 50-μl reaction containing 10 m*M* Tris–HCl, pH 8.2, 1.5 m*M* $MgCl_2$, 50 m*M* KCl, 200 μ*M* dNTPs, 50 p*M* primers, 1 unit *Taq* DNA polymerase (Perkin–Elmer Cetus, Boehringer/Mannheim, Promega, or gift of David Engelke), and 300–500 ng genomic DNA. After a 10-min incubation at 94°C, the reactions were subjected to 30 cycles of 1′ at 94°C, 1′ at 58°C, 2′ at 72°C (except *D21S111*∗1, 30 cycles, 1′ at 94°C, 1′ at 65°C, 2′ at 72°C), followed by 10′ incubation at 72°C; amplification product not shown.

Figure 2 shows typical examples of PCR amplification products from human genomic DNA for several of the STSs reported here. All primer and predicted amplification product sequences were used to search GenBank using the BLAST network service at the National Center for Biotechnology Information (3). Even though all of the clones listed in Table 1 have been used successfully as single-copy probes in Southern blot experiments, three of the STS sequences (*D21S23*∗1, *D21S54*∗1, and *D21S82*∗1) revealed some similarity to low-level repeats.

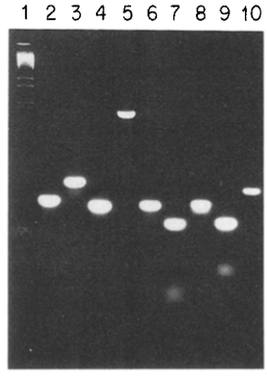

FIG. 2. Representative human chromosome 21 STS PCR products. Ethidium bromide-stained 1.8% SeaKem agarose gel containing PCR products amplified from human genomic DNA. **1,** λ/*Bst*EII marker; **2,** *D21S19*∗1; **3,** *D21S58*∗1; **4,** *D21S13*∗1; **5,** *SOD1*∗1; **6,** *D21S18*∗1; **7,** *D21S55*∗1; **8,** *D21S120*∗1; **9,** *D21S17*∗1; **10,** *D21S113.* See Table 1 for PCR product sizes and primer sequences used.

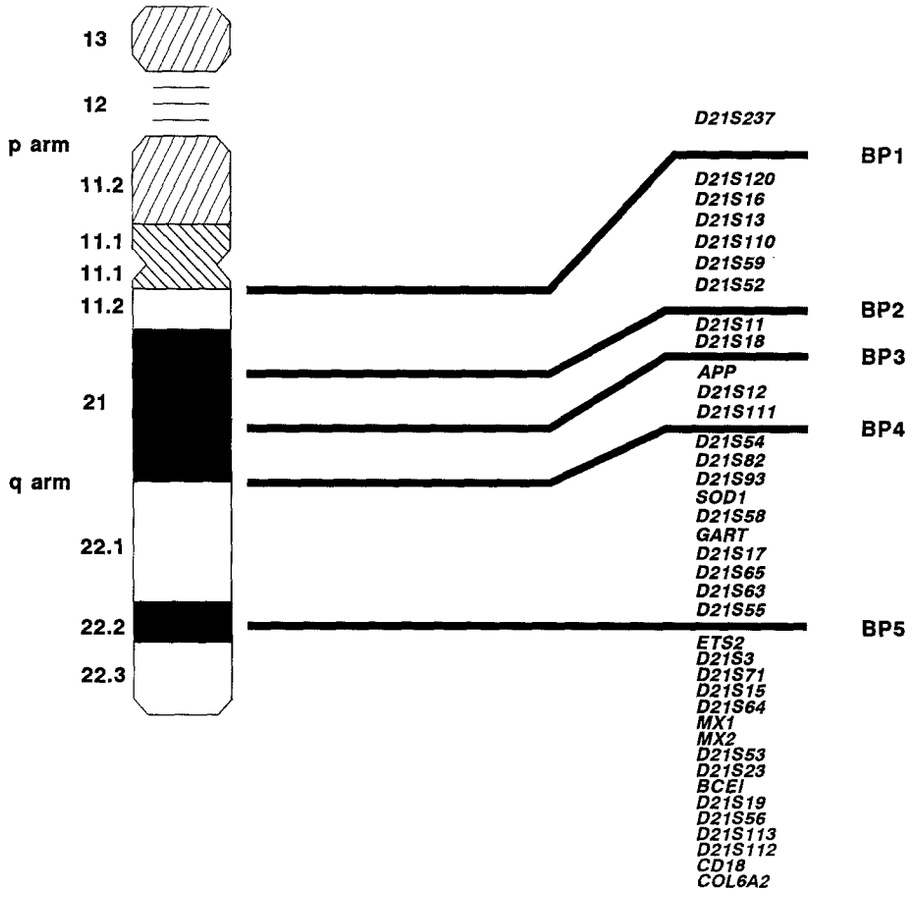

FIG. 3. Relative locations of the 38 chromosome 21 loci with STSs. The loci are assigned to six physical regions based on five reference hybrid breakpoints, designated BP1-BP5 (5). The loci are listed in approximate relative order based on physical, genetic, and hybrid cell mapping (4, 5, 7, 8, 14, 16, 22–25). Since physical and genetic mapping of *D21S111* relative to *APP* disagree (7, 25), the order of these markers has been shown as unresolved.

The relative location for each locus at which an STS has been generated is shown in Fig. 3. Of the 12 loci designated as unambiguously ordered polymorphic reference markers at Human Gene Mapping Workshop 10.5 (5), 9 are represented by STSs in Table 1. We have not yet generated an STS for *COL6A1,* but it is located less than 500 kb from the more distal *COL6A2* (7). The presence of another reference marker, *HMG14,* can already be assayed by PCR amplification of a unique polymorphic dinucleotide repeat sequence (17). *D21S8* is the remaining index marker without an STS. Twenty of the loci in Table 1, represented by 24 STSs, were also selected as part of the ordered marker framework of physically mapped loci. Of the remaining eight framework markers, five (*HMG14, CRYA1, PFKL, COL6A1,* and *S100B*) are cloned genes for which sequence data are already available. Moreover, like *HMG14, PFKL* can be assayed by amplification of a unique dinucleotide repeat (18). The other three are anonymous markers, *D21S1* [which is tightly linked with no crossovers to *D21S11* (22, 23)], *D21S4,* and *D21S8* [which is tightly linked to *APP* (22, 23)]. Twenty of the STSs in Table 1 represent additional loci not selected as framework markers but that have been previously mapped by physical and/or genetic methods (7, 14, 16, 22–25).

The construction and comparison of detailed genetic and physical maps of chromosome 21 will be facilitated by the availability of this large set of STSs distributed throughout the chromosome. However, of more immediate consequence, these STSs have afforded the opportunity to isolate YAC clones to ultimately assemble an overlapping clone set for the chromosome. All of the STSs reported here have already been, or are currently being, employed to isolate YAC clones (15). The majority of these have been obtained through the efforts of the Chromosome 21 Joint Yac Screening Effort, a collaborative initiative of the chromosome 21 community (5, 15). Generation of additional STSs from other loci on chromosome 21 and especially from the YACs currently being characterized can be expected to eventually produce an ordered clone set covering this chromosome.

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