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RESEARCH

Fine Mapping of the Autosomal Dominant Juvenile Open Angle Glaucoma (GLC1A) Region and Evaluation of Candidate Genes

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Juvenile Open Angle Glaucoma (GLC1A) is an autosomal optic neuropathy that has been localized previously to chromosome 1q. Here we report the fine mapping of the disease region using YACs and a high density of polymorphic microsatellite markers. This study utilized two large JOAG pedigrees genotyped at 36 loci from chromosome 1q21-q31 to refine the GLC1A locus to a ~3-cM region flanked by YAC-derived microsatellite markers DIS3665 and DIS3664. The candidate genes LAMC1, NPRI, and CNR2 were excluded from the region by linkage. Four other genes, SELE, SELL, TXGPI, and APTILG1, were determined to lie within the critical region through YAC content and linkage mapping. The YAC-STS content map of the critical region provides the groundwork for the construction of a transcription map and the identification of the disease-causing gene.

Glaucoma is an optic neuropathy characterized by cupping of the optic nerve head with resultant visual field loss, usually in the presence of increased intraocular pressure. Primary open angle glaucoma (POAG) is the most common form of glaucoma with the age of onset generally over 40 (Leske 1983). The molecular mechanisms of POAG are unknown, and it is likely to be a genetically heterogeneous disease with a variety of biochemical causes. Autosomal dominant juvenile open angle glaucoma (JOAG) is a less common, early-onset form of the disease. Identification of the gene that causes JOAG may provide important clues to the biochemical mechanisms underlying the more common, late-onset form of the disease. The GLC1A locus responsible for JOAG originally was localized to chromosome 1q21-q31 by genetic linkage analysis of a single large pedigree (Sheffield et al. 1993). Linkage to chromosome 1 has been confirmed in other JOAG families, and the region has been narrowed by identification of recombination events in

those families (Richards et al. 1994; Wiggs et al. 1994; Morissette et al. 1995).

Following the original linkage study, we analyzed other members of the same family and an additional large family segregating the JOAG phenotype. Affected family members had normal-appearing trabecular meshworks, very high intraocular pressures, and presented with symptoms at an early age. The present study was designed to exploit the power of these large families, combined with yeast artificial chromosome (YAC)-sequence tagged site (STS) content mapping and targeted microsatellite development for narrowing the disease region. In addition, a high-resolution genetic map of the region was developed, and several genes were evaluated as putative candidates for GLC1A.

RESULTS

Fine Mapping

Three dinucleotide-containing sequences were subcloned from YACs in the region via marker addition through subtraction (MATS; Chen et al. 1995). Two of these (DIS3665 and DIS3664)

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were informative in at least one JOAG family. The third, D1S3666, was monomorphic in the JOAG families in this study. A trinucleotide (ATA) repeat was found in the right-end subclone from YAC 74AA9. This short tandem repeat polymorphism (STRP) (D1S3663) was polymorphic within both JOAG families. The genetic map of 36 STRPs from 1q21-q31 is shown in Figure 1. Due to the density of polymorphic markers in the region, the exact genetic order of some STRPs could not be determined. Based on the genetic map, a YAC content map of the region between D1S431 and D1S480 was constructed to further determine marker order (Fig. 2). Additional STSs reported by the Whitehead Institute (1996) to be in the region and YAC-end sequences were also included in the STS content map. The order of STRPs determined by a combination of linkage and physical mapping is as follows (STRPs in parentheses could not be ordered relative to each other): D1S194, D1S196, (D1S431, D1S318), D1S397, D1S445, D1S443, AFM126yd8, D1S1569, (D1S3665, D1S3464), (D1S452, D1S210), D1S2851, D1S2815, (D1S1619, D1S1165), APT1LG1, 8AFM107YG1, TXGP1, D1S3664, AT3, D1S2634, (D1S2814, D1S1589),

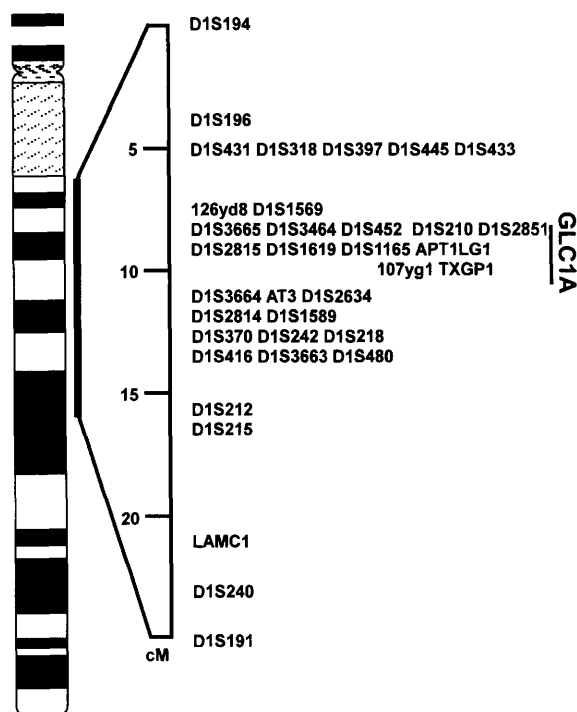


Figure 1 Linkage map of polymorphisms in the GLC1A region. Loci listed on the same line could not be ordered by linkage.

(D1S370, D1S242, D1S218), D1S416, (D1S3663, D1S480), D1S212, D1S215, LAMC1, D1S240, D1S191. An apparent gap in the YAC contig exists between D1S1165 and D1S2496. None of the seven YACs positive for D1S1165 amplifies D1S2496. Similarly, neither of the D1S2496-containing YACs amplifies D1S1165. Radiation hybrid mapping of markers flanking the gap indicate the size is ~250 kb. The region between D1S416 and D1S3663/D1S480 has been excluded from containing GLC1A and has not been characterized as extensively but contains another apparent gap. The physical size of the critical region was not determined empirically, but it is less than 5 Mb based on the sizes of the YACs comprising a minimum tiling path, plus the maximum size of the apparent gap.

Linkage Results

Family B (Fig. 3) was genotyped with STRPs from the region to test for linkage to GLC1A. Family B was shown to be segregating the disease at GLC1A, with a maximum lod scores at $\Theta = 0$ of 6.27 (AT3), 6.12 (D1S445), and 5.92 (D1S210). Family A was the original family in which the GLC1A region was defined (Sheffield et al. 1993) with a maximum lod score at $\Theta = 0$ of 6.5 for D1S212. Analysis of the disease haplotype segregating in family B (Fig. 4) revealed that individual V-4 had a recombinant haplotype for STRPs D1S215, D1S240, and D1S191, indicating that GLC1A lies proximal to D1S215. Individual III-17 from family A further narrowed the interval on the distal side, having recombinant haplotypes for D1S3664 and other distal markers. Several individuals from family A exhibited a recombinant haplotype for STRPs proximal to D1S445. Family A member IV-10 was found to have a recombination event between 126yd8 and D1S3665, indicating the disease lies distal to 126yd8. Family A member IV-3 was also determined to be recombinant at 126yd8 by examination of the haplotypes inherited from each parent. Individual IV-8 of family B did not possess the affected allele for D1S3665 and other proximal STRPs. Thus, the disease must lie in the region defined by one recombinant-affected individual for D1S3665 and one recombinant-affected individual for D1S3664, a genetic distance of 2.5–3.5 cM.

Mapping and Exclusion of Candidate Genes

Two genes that map to the general region have

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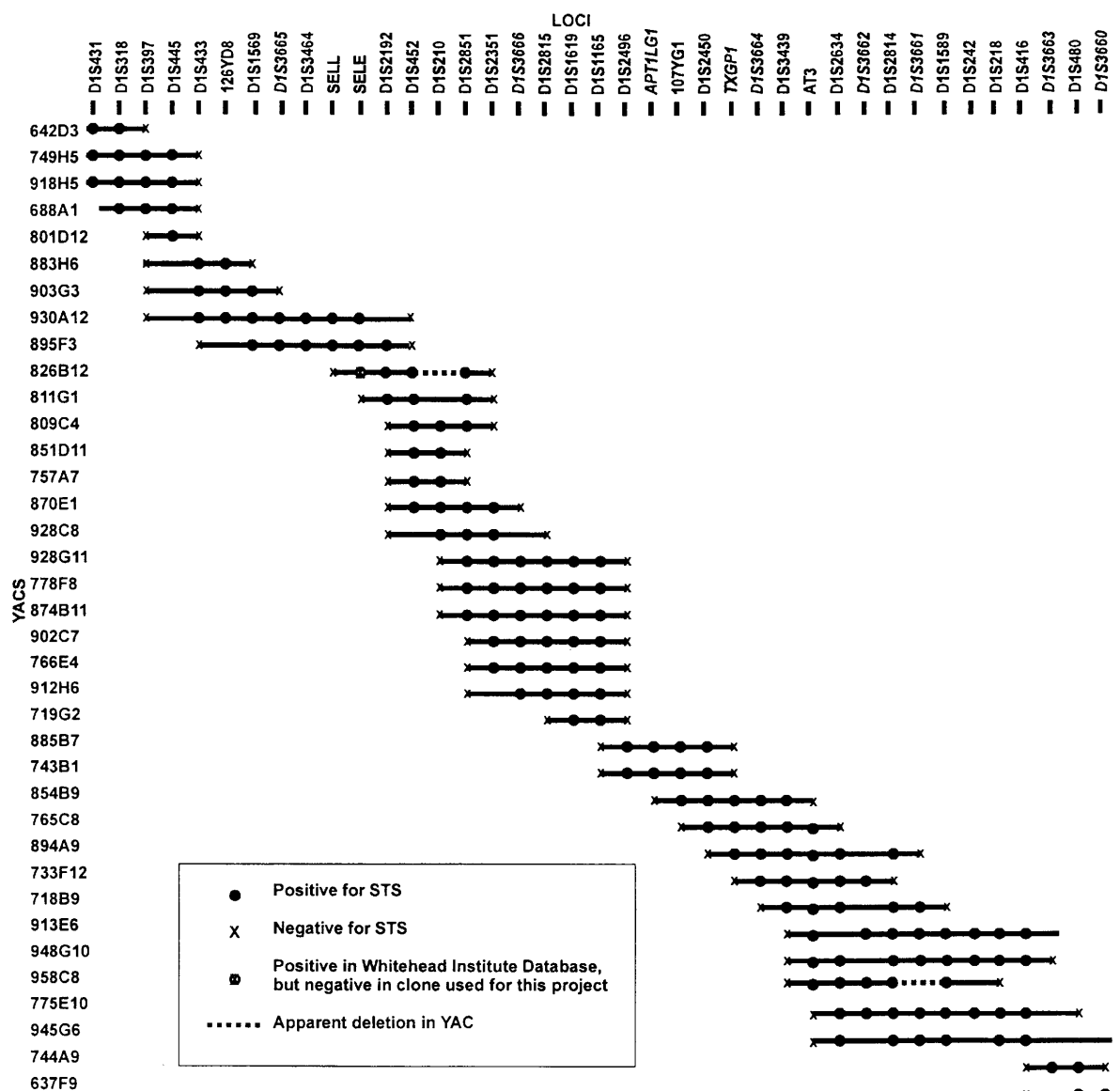


Figure 2 YAC contig of the GLC1A region. STSs listed in italics are newly reported and primer sequences are listed in Table 1.

been suggested as candidates for JOAG: laminin C1 (LAMC1) and atrionatriuretic peptide receptor A precursor (NPR1). Both genes contain polymorphisms that are informative within the families investigated in this study. The LAMC1 microsatellite (Watkins et al. 1993) showed recombination with the disease phenotype in four individuals in the JOAG families and has been mapped distal to the critical region by linkage (CHLC v8c7 integrated map, <http://www.chlc.org>). An SSCP in the 3' untranslated region (UTR) of NPR1 was uninformative for the majority of both families, but was recombinant

in the affected members of family B, including VI-8, who is recombinant for the proximal portion of the interval. NPR1 has been mapped to 1q21-q22 (Lowe et al. 1990), supporting its placement proximal to GLC1A. A third gene, the peripheral cannabis receptor (CNR2; Munro et al. 1993), was evaluated as a candidate because of the reduction in intraocular pressure that cannabis causes in some patients with glaucoma. The gene was mapped to chromosome 1 by amplification of pooled DNA from the National Institute of General Medical Sciences (NIGMS) human-rodent single chromosome somatic cell hybrid

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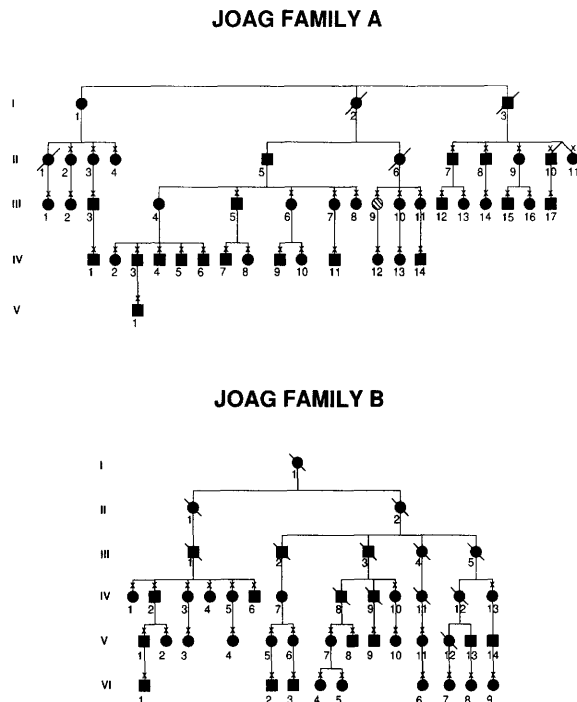


Figure 3 Pedigrees of three JOAG families used for this study. DNA samples were genotyped from individuals marked by "x." Only affected members are shown. Individual III-9 is phenotypically unaffected, although she possesses the complete disease haplotype and has a clearly affected daughter.

panel 2 as described previously (Sunden et al. 1996). A two-allele polymorphism was detected in the 3' UTR of the gene by SSCP. Typing in Centre d'Etude du Polymorphisme Humain (CEPH) reference families mapped the gene by linkage to 1p34-p36, between liver alkaline phosphatase (ALPL) and alpha-L-1 fucosidase (FUCA1), excluding the gene from the GLC1A interval.

Three STSs identified by the Whitehead genome center that amplify from YACs within the region correspond to genes. STS D1S3363, was developed from selectin E (SELE) sequence (GenBank accession no. M24736). This gene encodes a cell-surface glycoprotein that mediates the adhesion of blood neutrophils (Bevilacqua et al. 1989). STS D1S3431, which maps to the same portion of the contig, amplifies a portion of selectin L (SELL; GenBank accession no. M25280), another member of the selectin family (Tedder et al. 1989). STS WI-7792 corresponds to the tax-transcriptionally activated glycoprotein 1 gene (TXGP1, GenBank accession no. D90224), a membrane protein that is a member of the tumor necrosis factor (TNF) gene family (Miura et al.

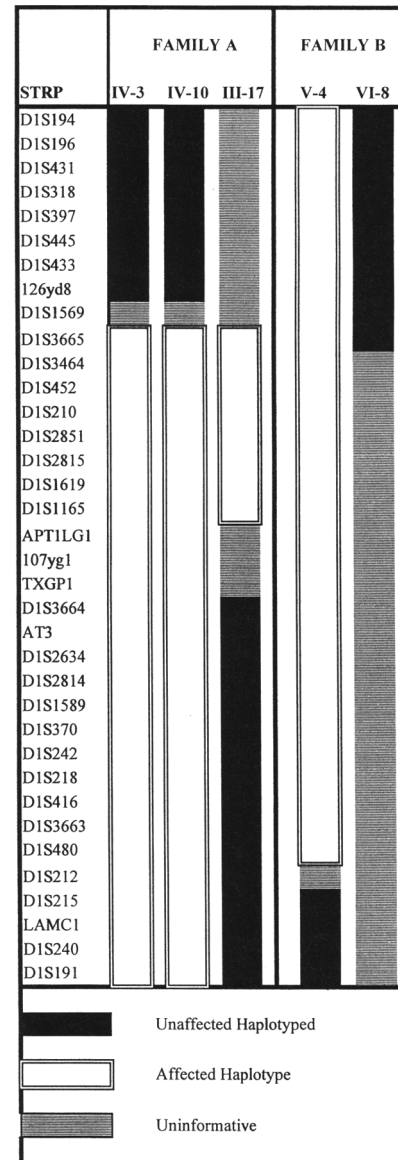


Figure 4 Haplotypes of selected individuals from JOAG families. Recombination events in family B VI-8 and family A 111-17 define the current interval.

1991). The 3' UTR of this gene contains a three-allele di-nucleotide repeat. The gene is completely linked in both families. Inheritance of the affected allele cannot be traced directly in family A member III-17, who defines the distal end of the region due to homozygosity of that person's affected parent for this locus. According to data from the YAC contig, TXGP1 lies inside the GLC1A critical region, just proximal to D1S3664.

One additional gene maps within the region by linkage and by YAC content. The apoptosis (APO-1) antigen ligand 1 (APT1LG1) is a small protein that is also a member of the TNF family

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and is important in apoptosis (Takahashi 1994). This gene contains a polymorphic dinucleotide repeat in the 3' UTR that is completely linked with the disease. The polymorphism for this gene has the same pattern of genotypes as TXPG1 in family A III-17. Consequently, whether this gene lies proximal or distal to the recombination breakpoints in this individual could not be determined. APT1LG1 maps to the distal portion of the GLC1A critical region on the YAC map, near D1S2496.

DISCUSSION

The identification of the gene causing JOAG has important implications for the understanding of this disorder and the more common adult POAG. At the time of the initial report of linkage of this disorder (Sheffield et al. 1993), only seven STRPs were mapped to the original 23-Cm region. Since that time, genome-wide mapping efforts by several groups (Gyapay et al. 1994; Murray et al. 1994; Sheffield et al. 1995; Utah Marker Development Group 1995) have produced large collections of di-, tri- and tetranucleotide repeat markers distributed across the human genome. Between STRPs made public by those groups and targeted microsatellite development in our own laboratory, there are now 36 STRPs in the region, ten of which lie between the new flanking markers D1S3665 and D1S3664. The additional markers make it possible to narrow the GLC1A interval.

The density of markers surrounding JOAG is such that exact ordering by linkage analysis is difficult. Fine-mapping STRPs from the region required physical mapping using YACs. Screening the CEPH mega-YAC library with STRPs from the region identified 37 clones that comprise the YAC-STS content map. Mapping of STRPs within this framework made it possible to identify YACs from which to develop additional microsatellite markers. The contig also makes it possible to screen candidate genes for inclusion within the region. The apparent gap between D1S1165 and D1S2469/ATP1LG1 prevents one from excluding genes from the region based on nonamplification of YACs from the current contig. As expected, there is general agreement between the linkage and physical maps. For regions of highest marker density, a best order could not be obtained by linkage, but determination of marker order could be made using the physical map.

Large families make it possible to utilize only affected members in the analysis, thus avoiding the possibility of erroneous narrowing of the region based on genotypic data from a nonpenetrant individual. Once the region containing the gene is narrowed and evaluation of candidate genes for mutation analysis commences, it is beneficial to have more than one unrelated family to screen for the mutation. In this way, one is more likely to distinguish between a rare polymorphism and a true disease-causing mutation.

The refinement of the GLC1A critical region presented here is an important step for the identification of the disease-causing gene, either through positional cloning or through the positional candidate gene approach. The number of polymorphic markers accurately mapped to the region is now large enough to maximize informativity for screening new families with juvenile or later onset forms of glaucoma for linkage to GLC1A. The high density of STRPs is also useful for comparison of haplotypes between presumably unrelated families for the detection of an ancestral haplotype and further narrowing of the disease gene region. The families included in this study do not show notable similarities in the disease haplotype within the critical interval. Additional targeted marker development for the region is under way to further delineate the interval defined by recombination. STRPs at both ends of the current region are uninformative in the individuals with recombination events that define the interval, indicating that the region may be narrowed further.

Four genes are known to lie within the GLC1A region. SELE is a cell-surface glycoprotein expressed in leukocytes (Collins et al. 1991). SELL is highly homologous to mouse lymph node homing receptor core protein (mLHRc), and its expression in humans appears to be largely limited to lymphoid tissues (Siegelman and Weissman 1989). Both SELE and SELL are cell surface molecules involved in the regulation of inflammatory and immunological events at the interface of vessel wall and blood (Bevilacqua et al. 1989). TXGP-1 and APT1LG1 are TNF family proteins, also involved in immunological events. Because of the limited number of candidate genes that currently are identified to lie within the region, our focus is on narrowing the interval genetically and completing the physical contig of the region with YACs and smaller-insert cloning reagents.

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Table 1. Primer Sequences for Newly Reported STRPs, SSCPs, and STSs

Locus	Source	Size (bp)	Forward primers sequence	Reverse primers sequence	Alleles
D1S3660	Right end of YAC 637F9	123	GGAATAAGTGGGAGAAA- ACCC	CCTGCATCCGACAAATGAC	1
D1S3661	Right end of YAC 718B9	206	AGGCAACTCCTAGCACTA- GCC	CAGGATCCCAAAGTGCTCAT	1
D1S3662	Right end of YAC 733F12	222	GGTTACCATCTGGCTCTCA- TCC	TGCTCAGACACCCTGAAAAG	1
D1S3663	Right end of YAC 744A9	250	TGGTTTAAAAGAAAAGCA- ATG	GGCCTTTGTTAACTACTATCCAA	4
D1S3664	YAC 854B9	145	AAGGCCTTAATATGGGTGGG	TGATTTTGTCTGCAAAGATGC	4
D1S3665	YAC 895F3	160	CAGTTTTAAAGGACAGGTCA- TGG	GCAGGTTTAAACAGTCGACTCT	8
D1S3666	YAC 928C8	230	AAGTCCTAAGATGCTAAGG- GCC	GGGCAAAACATTGCCACTAT	1
APT1LG1	3' UTR	217	ACTTCTAAATGCATATCCTGA- GCC	ATCTTGACCAAATGCAACCC	3
NPR1	3' UTR	245	GGCAAAGGCAAGGTTCCGG	CCATGCCAGTCCCCTCTCA	2
TXGP1	3' UTR	208	CCAAGGCACTCACAGAATCA	TTGCAGAACATGGTCAATAACA	3
CNR2	3' UTR	150	CTGACTCCTGGAAGACAGCC	GACTTCCAAGAGAACAACCC	2

METHODS**Patients**

The clinical features of the family that was the subject of the original linkage study (family A) have been described previously (Johnson et al. 1993). Twenty-one additional affected members have been evaluated. Twenty-eight affected members of a second family (family B) have also been ascertained and used for fine mapping of the region (Fig. 3). Clinical features of a related branch of this family were reported by Stokes (1940) and by Richards et al. (1994). Patients were classified as affected if they had intraocular pressures of greater than 30 mm Hg, if they had pressures above 21 mm Hg with glaucomatous optic nerve cupping or visual field loss, or if they had intermediate pressures and at least one affected offspring. The clinicians who determined the affectation status were masked to the genotypic data. Unaffected pedigree members were not used for defining the region or to calculate LOD scores.

Detection of Polymorphisms

DNA was prepared from blood using a standard protocol (Grinsberg et al. 1989). Amplification of STRP from chromosome 1q were performed in 8.4- μ l reactions containing 10–40 ng DNA, 1.5 \times *Taq* polymerase buffer (Boehringer Mannheim), 200 μ M each dCTP, dATP, dGTP, and dTTP, 1 pmole each primer, and 0.25 units *Taq* polymerase (Boehringer Mannheim). Samples were subjected to 35 amplification cycles of 94°C for 30 sec, 55°C for 30 sec, and 72°C for 30 sec. STRP PCR products were electrophoresed on 6% denaturing polyacrylamide gels (7.7 M urea). Single-strand conformation polymorphisms (SSCP) were detected with

room temperature electrophoresis in 6% (49:1) nondenaturing arylamide gels containing 5% glycerol. Gels were stained with silver (Bassam et al. 1991; Sunden et al. 1996) and permanent records created by exposure of the gels to duplicating film (Typon APC film, Promega). STRPs developed and assigned to chromosome 1 by the Cooperative Human Linkage Center (CHLC) using a somatic cell hybrid panel (Sunden et al. 1996) were screened for linkage to the GLC1A region by comparing amplification patterns of pooled DNA from affected individuals with pooled DNA from their unaffected siblings as in Sheffield et al. (1994). STRPs that showed differential intensity of amplified alleles between pools were tested for linkage by genotyping individuals in the families.

Identification, Preparation, and STS Content Mapping of YAC Clones

YAC clones were selected in two ways. Approximately half the clones in the contig were identified from the CEPH YAC library via amplification of STRPs from the region between D1S218 and D1S196 using pooled DNA (Research Genetics). We also evaluated clones identified as positive by the Whitehead Institute's Human Genome Mapping Project (Whitehead Institute 1996). Individual clones were obtained (Research Genetics), and single colonies from each clone were selected for analysis after streaking on selective (URA-TRP) media. Total DNA was prepared from 5-ml cultures for individual clones. All clones were tested by PCR amplification of STSs using the same conditions as used for genomic DNA except that only 5–10 ng total clone DNA was used per reaction. STSs with weak signals were amplified in the presence of *Taq* Extender (Strata-

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gene) to enhance amplification. PCR products were electrophoresed on polyacrylamide gels as described for genomic STRP analysis, except that PCR reactions were loaded in a staggered fashion to eliminate false positives from bleed-over between lanes. Each amplification was performed at least twice, independently, to verify results.

Targeted Development of STRPs and STSs

Ends of YACs were subcloned using circularization and inverse PCR following digestion of total clone DNA with *Hae*III (Joslyn et al. 1991). PCR fragments containing YAC ends were purified and sequenced using fluorescent Dye Terminators (Applied Biosystems, Inc.). Primers were selected from the insert portion of the fragment with Primer 0.5 (Daly et al. 1991). Dinucleotide STRPs were selected from YACs using MATS (Chen et al. 1995) and sequenced using an ABI automated sequencer with Dye Primer chemistry. Primers flanking each microsatellite were then selected using Primer 0.5 (Daly et al. 1991). Primer sequences for newly developed STRPs, SSCPs, and STSs are listed in Table 1.

Linkage Mapping

A subset of STRPs (D1S431, D1S318, D1S433, 126yd88, D1S3464, D1S2851, D1S452, D1S1165, D1S210, D1S1619, AT3, ATA4E02, and D1S3663) were typed in 12–25 CEPH families. Genotypes were analyzed using CRI-MAP 2.4. STRPs were inserted one at a time into an initial framework map consisting of D1S318, D1S452, and D1S1589. Alternative locus orders were evaluated using the FLIPS routine. Double-recombinant individuals within the interval were identified with the CHROMPIC option and retyped for verification or correction. The resulting map was integrated with a map of CHLC and other published STRPs (Cooperative Human Linkage Center, unpubl.) to obtain a map of 36 STRPs in the region.

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