Acid α-glucosidase, the product of a housekeeping gene, is a lysosomal enzyme that degrades glycogen. A deficiency of this enzyme is responsible for a recessively inherited myopathy and cardiomyopathy, glycogenosis type II. We have previously demonstrated that the human acid α-glucosidase gene expression is regulated by a silencer within intron 1, which is located in the 5′-untranslated region. In this study, we have used deletion analysis, electrophoretic mobility shift assay, and footprint analysis to further localize the silencer to a 25-base pair element. The repressive effect on the TK promoter was about 50% in both orientations in expression plasmid, and two transcriptional factors were identified with antibodies binding specifically to the element. Mutagenesis and functional analyses of the element demonstrated that the mammalian homologue 1 of Drosophila hairy and Enhancer of split (Hes-1) binding to an E box (CACCGG) and global transcription factor-YY1 binding to its core site function as a transcriptional repressor. Furthermore, the overexpression of Hes-1 significantly enhanced the repressive effect of the silencer element. The data should be helpful in understanding the expression and regulation of the human acid α-glucosidase gene as well as other lysosomal enzyme genes.

The lysosomal acid α-glucosidase (GAA,1 acid maltase, EC 3.2.1.20) hydrolyzes 1,4-α-glucosidic and 1,6-α-glucosidic linkages in glycogen, maltose, and isomaltose (1, 2). Recessively inherited deficiency of the enzyme leading to abnormal glycogen accumulation in lysosomes causes glycogen storage disease type II, which in its most severe form presents as a rapidly progressive myopathy and cardiomyopathy (Pompe disease) (3). The GAA gene has been localized to chromosome 17q21-23. The cDNA sequence has been reported, and the gene sequence has been partially characterized (4, 5). The gene spans ~20 kb and is composed of 20 exons including a 5′-noncoding exon 1 that is separated by an ~2.7-kb intron from exon 2, the site of the initiator (ATG) codon. Although its promoter region has characteristics of housekeeping gene promoters (5), the GAA gene expression varies extensively during development and maturation (6). To date, very little is known regarding the transcriptional control of this gene or the majority of lysosomal enzyme genes.

In a mini-gene model system, we have previously demonstrated that an ~2.7-kb intron 1 of the human GAA gene contains a negative regulatory element (7). In the experiments reported here, we have employed an in vitro transfection assay in human hepatoma cells (Hep G2) and DNase I footprinting to localize the negative regulatory element within intron 1 to a 25-bp region ~1.7 kb downstream from the exon 1/intron 1 boundary. Within this region there are two tandem E boxes and a potential core Ying Yang 1 (YY1) binding site in juxtaposition. Electrophoretic mobility shift assay (EMSA) with specific antibodies showed that a transcriptional repressor Hes-1, the mammalian homologue 1 of D. hairy and Enhancer of split (E(spl)), binds to the downstream E box (CACCGG) and in collaboration with YY1 contributes to the repressive effect.

**EXPERIMENTAL PROCEDURES**

**Plasmid Constructs for Deletional Analysis of Intron 1 Fragment—** The various intron 1 fragments of the human GAA gene were generated by polymerase chain reaction. The wild type oligonucleotide corresponding to the 25-bp silencer element was 5′-ATCTCATCTGGCACGCGGCACTCCGGGTT-3′. Double-stranded wild type and mutant oligonucleotides were generated by heating the primers at 90 °C for 10 min followed by slow cooling at room temperature; the oligonucleotides were purified on a 20% polyacrylamide gel. The DNA fragments were subcloned into the expression vector phBLCAT2 upstream of the TK promoter and CAT gene in both orientations. For cotransfection with Hes-1 expression plasmid, four copies of wild type or mutant 25-bp element were subcloned into pBLCAT2 to generate 4×wtHes-1/TK-CAT and 4×mutHes-1/TK-CAT. The integrity of the plasmids was verified by restriction endonuclease digestion and sequencing.

**Cell Culture and Transient Transfection Assay—** Hep G2 cells, human hepatoma cell line (ATCC, Manassas, VA), were cultured in Dulbecco’s modified Eagle’s medium (Life Technologies, Inc.) supplemented with heat-inactivated 10% fetal calf serum (HyClone, Logan, UT) and 100 μg/ml penicillin-streptomycin (Life Technologies, Inc.). Hep G2 cells were transfected with 4.0 μg of purified DNA (Qiagen, Valencia, CA) with 10 μl of LipofectAMINE reagent (Life Technologies, Inc.) in serum-free medium for 5 h. Then the cells were re-fed with original medium and harvested for assay 48 h posttransfection. In all experiments, cells were cotransfected with 0.5 μg of pRGH5 (human growth hormone gene expression plasmid) as an internal control of transfection efficiency. Plasmid pUC19 was used to compensate the amount of DNA. For cotransfection experiments, the ratio of reporter gene constructs 4×wtHes-1/TK-CAT or 4×mutHes-1/TK-CAT and pcDNA3 or pcDNA3-WT Hes-1 was 1:3. Cell culture medium was collected for hGH activity assay (hGH enzyme-linked immunosorbent assay kit, Roche Molecular Biochemicals), and cell lysates were assayed for CAT activity (CAT enzyme-linked immunosorbent assay kit, Roche Molecular Biochemicals). Protein concentration was determined using a dye binding assay (Bio-Rad).

**DNase I Footprinting Analysis—** Nuclear extracts from cultured cells were prepared as described (8) and kept at −80 °C. DNase I footprint...
ing experiments were carried out as described (9). The noncoding strand of the 90-bp DNA fragment (1711–1800 bp from the exon 1/intron 1 boundary) was 3′-end-labeled with [32P]dCTP using the Klenow fragment of DNA polymerase. The binding reaction was carried out in a 50-μl volume with 1.0 ng of probe and 60 μg of nuclear extract of Hep G2 cells for 30 min at room temperature. After incubation, 50 μl of cofactor buffer (10 mM MgCl2, 5 mM CaCl2) was added, and the reaction mixtures were digested with a different amount of DNase I (Sigma) for 2 min at room temperature. The reaction was stopped with 100 μl of stop buffer (200 mM NaCl, 20 mM EDTA, pH 8.0, 1% SDS, 40 μg/ml tRNA). The mixture was extracted once with phenol and pelleted with ethanol. DNA pellet was resuspended in 4.0 μl of loading buffer, denatured at 95 °C for 3 min, and subjected to 8% polyacrylamide sequencing gel electrophoresis.

Electrophoretic Mobility Shift Assay—The 25-bp oligonucleotides were end-labeled with [32P]dCTP using the Klenow fragment of DNA polymerase, and EMSA was performed as described (10). 1.0 ng of labeled probe was incubated with 50 μg of nuclear extracts of Hep G2 cells in a 20-μl volume reaction containing 100 mM Hepes, pH 7.9, 200 mM KCl, 5 mM MgCl2, 10 μg of bovine serum albumin, 0.5 mM EDTA, 2.5 mM dithiothreitol, and 50% glycerol for 30 min at room temperature. For competition experiments, the nuclear extract was incubated with competitors at 100-fold molar excess at room temperature for 30 min before adding the probe. For immunosupershift assay, the nuclear extract was incubated with 1.0 μl of 1:500 diluted anti-Hes-1 antiserum and anti-MyoD antibodies (Santa Cruz Biotechnology, Santa Cruz, CA) at room temperature for 30 min before adding the probe. The anti-Hes-1 antisera have been successfully used to recognize overexpressed Hes-1 in human lung cancer cells (11). The protein-DNA complexes were run on a 5% polyacrylamide gel and visualized by autoradiography.

**Statistical Analysis**—Statistical analyses were performed using the standard t test.

**RESULTS**

**Deletion Analysis of the Intron 1 Fragment**—To localize the silencer element, a series of intron 1 deletion fragments was introduced into a TK-CAT reporter plasmid, and the reporter activity was assayed in human Hep G2 cells. As expected, the 2.6-kb intron 1 fragment significantly repressed the TK promoter activity (Fig. 1). All the constructs (intron 1, F1–F4, F6, and F8) containing a 90-bp fragment of the intron 1 (1711–1800 bp from the exon 1/intron 1 boundary) showed a significant repressive effect on TK-CAT gene expression in both forward and reverse orientations. In contrast, the constructs without the 90-bp fragment (F5 and F7) did not repress the CAT activities (Fig. 1). Therefore, the results indicate that the 90-bp region contains the putative silencer element and that the transcriptional activity of the element is independent of position and orientation.

**Characterization of the Silencer Element within the 90-bp Region**—To further localize the functional silencer element, DNase I footprinting analysis of the 90-bp region was performed with nuclear extracts from Hep G2 cells. A 25-bp protected region (5′-ATCTCATGACGCCACATCCTTG-3′) was revealed including two E boxes (CANNTO) and a potential YY1 binding site (ACAT), which abuts the second E box (Fig. 2). The second E box is noncanonical (CAGCGG) and is a preferred site for hairy in *Drosophila* where it functions as a repressor (12). The YY1 site within the element is one of the two core sequences of YY1 binding sites (ACAT and CCAT) (13).

To test the transcriptional activity of the protected region, the element was introduced into pBLCAT2, and transient transfection analysis was performed. As expected, it had a significant repressive effect on TK promoter activity in both orientations similar to that of the 90-bp region (Fig. 3C). Thus, the silencer element was localized to the 25-bp element.

**Identification of the Proteins Binding to the 25-bp Element**—To detect the transcriptional repressor(s), the 25-bp element was used as a probe and incubated with nuclear extracts from Hep G2 cells. In EMSA, two proteins were shown to bind the element (Fig. 1). Therefore, the results indicate that the 90-bp region contains the putative silencer element and that the transcriptional activity of the element is independent of position and orientation.

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**Identification of the Proteins Binding to the 25-bp Element**—To detect the transcriptional repressor(s), the 25-bp element was used as a probe and incubated with nuclear extracts from Hep G2 cells. In EMSA, two proteins were shown to bind specifically to the DNA. The binding of both proteins was completely competed by unlabeled 25-bp oligonucleotide (Fig. 3B, lane 3) but not at all by a nonspecific DNA fragment (Fig. 3B, lane 8). Immunosupershift assay with rabbit polyclonal antisera to the Hes-1 C-terminal and N-terminal peptides showed that one DNA-protein complex band disappeared.

![Deletional analysis of intron 1 of the human GAA gene.](http://www.jbc.org/)

**Fig. 1.** Deletional analysis of intron 1 of the human GAA gene. The positions and sizes of the fragments within the intron 1 are marked on the graph, and the first base pair from exon 1/intron 1 boundary is taken as position 1. The orientations of intron 1 fragments in plasmids are indicated with arrows. CAT activities were standardized relative to human growth hormone activity as an internal control for transfection efficiency. The CAT activities are expressed relative to pBLCAT2, which is assigned a value of 100%. The bars represent mean ± S.E. *, p < 0.05; **, p < 0.01 compared with pBLCAT2. Numbers in parentheses indicate the numbers of repeated experiments. The dashed line indicates a change in scale.
In the same way, EMSA with anti-YY1 antibody or YY1 consensus oligonucleotide revealed that the second specific DNA-protein complex band was completely competed, and the second band disappeared (Fig. 4, lanes 5 and 6). In contrast, the control anti-MyoD antibody did not change the binding pattern (Fig. 4, lane 7). These results indicate that the proteins binding to the 25-bp element are the transcriptional factors Hes-1 and YY1.

**Mutagenesis and Functional Analysis**—To determine whether both Hes-1 and YY1 act as transcriptional repressors that bind to the element, site-directed mutagenesis analysis was carried out. The wild type and mutant sequences of the 25-bp element are shown in Fig. 3A. In EMSA, mutations in the element will lead to a decreased binding of transcriptional factors, and thus these mutants would no longer compete with the wild type probe. As shown in Fig. 3B (lanes 5 and 6), the element with the mutation in the second E box (M2) was not able to compete with the wild type probe for Hes-1 binding. Similarly, the element with mutation in the YY1 site (M3) could not compete with the wild type probe for YY1 binding. Moreover, the element with both the second E box mutation and the YY1 site mutation (M4) no longer competed for Hes-1 or YY1 binding (Fig. 3B, lane 7). In contrast, an oligonucleotide with a mutation of the first E box (M1) still competed with the wild type probe (Fig. 3B, lane 4).

To further examine the transcriptional activity of Hes-1 and YY1, the mutants of the element were subcloned into pBLCAT2 in both orientations, and transient transfection assays were carried out in Hep G2 cells. As shown in Fig. 3C, the mutation of the second E box (M2) or of the YY1 binding site (M3) diminished, and the mutation of both (M4) abolished the repressive effect of the element. Consistent with the EMSA results, the mutation of the first E box (M1) did not alter the repressive effect (Fig. 3C). Taken together, the results indicate that Hes-1 binds to the second E box (CACCGG) within the 25-bp element, whereas the activator-repressor YY1 binds to one of the most frequent core YY1 sequences (ACAT). Neither Hes-1 nor YY1 acts fully alone, but together they act as a transcriptional repressor.

**Cotransfection Analysis with Expression Plasmid for Hes-1**—To confirm that Hes-1 binds to the element and functions as a repressor, the plasmids pBLCAT2, 4×wtHes-1/TK-CAT, and 4×mutHes-1/TK-CAT were transfected alone or cotransfected
with empty vector pcDNA3 or expression plasmid-pcDNA3-WT Hes-1. Compared with transfection alone, overexpression of Hes-1 resulted in a significant decrease of reporter gene expression of the plasmid 4×wtHes-1/TK-CAT with four copies of wild type Hes-1 binding site (*p < 0.01) (Fig. 5). In contrast, the overexpression of Hes-1 did not affect the reporter gene expression of the plasmid 4×mutHes-1/TK-CAT containing four copies of the mutant Hes-1 binding site (*p > 0.05) (Fig. 5). Co-transfected empty plasmid pcDNA3 affected the reporter gene expression of neither plasmid 4×wtHes-1/TK-CAT (*p > 0.05) nor 4×mutHes-1/TK-CAT (*p > 0.05) (Fig. 5). These results showed that reporter gene expression was regulated by over-expressed Hes-1.

**DISCUSSION**

In this study, we have identified and characterized a negative regulatory element of 25 bp within intron 1 of the human GAA gene, which is position- and orientation-independent. Site-directed mutagenesis and functional analysis showed that transcriptional factors Hes-1 and YY1 collaborate to act as a transcriptional repressor of the human GAA gene in the Hep G2 cell line by binding to the element. Hes-1, a basic helix-loop-helix (bHLH) factor, binds to a C class E box site (CACCGG), and YY1 binds to a core YY1 binding site (ATAC) within the element.

Hes-1 is a mammalian bHLH transcription factor related to *D. hairy* and *E(spl)*. It belongs to a repressor gene family (12, 14) that acts in opposition to the activator bHLH genes. The bHLH transcription factors have been divided into three classes based on the recognized E box sequences (CANNTG): canonical class A (CACCTG or CACCTG), canonical class B (CACGTG or CATCTG), and noncanonical class C (CACCGG or CACGAG) (12). In *Drosophila*, the C class E box (CACCGG) is the optimal binding site for the hairy protein. *E(spl)* repressors prefer a canonical B class E box (CACCTG) over the class C core and a slightly different C class E box, which has been termed N box (CACNAG) (15–19). Furthermore, *hairy* mediates transcriptional repression over a distance of more than 1.0 kb (20). In mice, Hes-1 can bind to C class E box (CACCGG), but it prefers the N box (CACNAG). Targeted disruption of the *Hes-1* gene in mice is lethal and leads to severe defects of the neural tube and arrest of T-cell development in the thymus (21, 22), whereas expression of the *Hes-1* gene prevents differentiation of mammalian neurons in the central nervous system and neural retina (23, 24).

Although *Hes-1* is essential to several developmental processes, few target genes have been identified particularly in humans. In mice, it has been shown that *Hes-1* blocks neurogenesis by suppressing the expression of the MASH-1 gene (25), the mammalian homologue 1 of *Drosophila achaete-scute* gene that is essential for neural development (26). In human *hASH1* (human *achaete-scute* homolog-1) expressing small cell lung cancers that do not express *Hes-1*, the introduction of *Hes-1* results in a dramatic reduction of *hASH1* mRNA through a direct binding of *Hes-1* to a class C site within its promoter (11).

Here we present evidence that a completely different gene, the human lysosomal acid α-glucosidase gene, that is unrelated to the transcriptional activators is a downstream target of *Hes-1*. Furthermore, the C class E box binding site is located in the intron 1 of the GAA gene rather than in the promoter as in other targets. Hes-1 binds to a single C class E box site of the protected DNA region (5′-ATCTCATCATGGACGACATC-TTGG-3′) within intron 1; the underlined E box and flanking sequences match closely with the *hairy* binding sequences (5′-GGCCCGGAC-3′) in the *D. achaete* gene promoter (18). These results indicate that the binding sequences of *Hes-1*, *hairy*, and *E(spl)* are conserved from *Drosophila* to humans. In addition, in the human GAA gene the *Hes-1* binding site (1761–1785 bp from the exon 1/intron 1 boundary) is located more than 1.8 kb from the promoter region (5), indicating that *Hes-1* is a long range repressor in human cells.

It has been demonstrated that the *Hes-1* gene and its homo-
logenues are immediate downstream genes of the Notch signaling pathway from invertebrates to vertebrates (27, 28). Notch is a transmembrane protein and is related to the proliferation and differentiation of many cell types (29, 30). Whether or not the human GAA is involved in the signaling pathway needs to be further investigated.

YY1, a C2H2-type zinc finger DNA-binding protein, is a multifunctional transcriptional factor that can act as an activator, a repressor, or an initiator-binding protein. The two most common binding core sequences are CCAT and ACAT (13). Several studies have shown that YY1 binds to the promoter and intron regions of housekeeping genes and can regulate their expression (31, 32). In this study, we have shown that YY1 binds to one of the conserved sites (ACAT) within intron 1 of the human GAA gene and functions as a partner of Hes-1 for repressive effect. The established mechanisms of repression by YY1 include activator replacement, interference with activator function, and recruitment of a corepressor (13). Our data suggest that YY1 is acting in a new way by collaborating with Hes-1.

In summary, we have demonstrated that the regulation and expression of the human GAA gene is in part controlled at the transcriptional level by a silencer element within its first intron. The identification of the transcription factors affecting the GAA expression may have another practical application. A majority of patients (~80%) with a milder adult form of glyco- gen storage disease type II have a markedly reduced level of an entirely normal gene product as a consequence of a point mutation in the polypyrimidine tract of intron 1 (-13t-g) (7, 33). Pharmacological or genetic interference with either the binding of the transcriptional factors or the interaction between them may be used to up-regulate the gene expression.

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Transcriptional Regulation of the Human Acid α-Glucosidase Gene: IDENTIFICATION OF A REPRESSOR ELEMENT AND ITS TRANSCRIPTION FACTORS Hes-1 AND YY1
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