

Mutation of a Nuclear Respiratory Factor 2 Binding Site in the 5' Untranslated Region of the *ADSL* Gene in Three Patients with Adenylosuccinate Lyase Deficiency

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Adenylosuccinate lyase (*ADSL*; also called “adenylosuccinase”) catalyzes two steps in the synthesis of purine nucleotides: (1) the conversion of succinylaminoimidazolecarboxamide ribotide into aminoimidazolecarboxamide ribotide and (2) the conversion of adenylosuccinate into adenosine monophosphate. *ADSL* deficiency, a recessively inherited disorder, causes variable—but most often severe—mental retardation, frequently accompanied by epilepsy and/or autism. It is characterized by the accumulation, in body fluids, of succinylaminoimidazolecarboxamide riboside and succinyladenosine, the dephosphorylated derivatives of the two substrates of the enzyme. Analysis of the *ADSL* gene of three unrelated patients with *ADSL* deficiency, in whom one of the *ADSL* alleles displayed a normal coding sequence, revealed a $-49\text{T}\rightarrow\text{C}$ mutation in the 5' untranslated region of this allele. Measurements of the amount of mRNA transcribed from the latter allele showed that it was reduced to ~33% of that transcribed from the alleles mutated in their coding sequence. Further investigations showed that the $-49\text{T}\rightarrow\text{C}$ mutation provokes a reduction to 25% of wild-type control of promoter function, as evaluated by luciferase activity and mRNA level in transfection experiments. The mutation also affects the binding of nuclear respiratory factor 2 (NRF-2), a known activator of transcription, as assessed by gel-shift studies. Our findings indicate that a mutation of a regulatory region of the *ADSL* gene might be an unusually frequent cause of *ADSL* deficiency, and they suggest a role for NRF-2 in the gene regulation of the purine biosynthetic pathway.

Introduction

Adenylosuccinate lyase (*ADSL*; also called “adenylosuccinase” [Enzyme Commission number 4.3.2.2]) catalyzes two steps in the synthesis of purine nucleotides: (1) the conversion of succinylaminoimidazolecarboxamide ribotide (SAICAR) into aminoimidazolecarboxamide ribotide (AICAR), the eighth step in the de novo synthesis of IMP, and (2) the conversion of adenylosuccinate (S-AMP) into adenosine monophosphate (AMP), the second step in the conversion of inosine monophosphate into AMP. *ADSL* deficiency (MIM 103050), first described by Jaeken and Van den Berghe (1984), is an autosomal recessive disorder characterized by the accumulation, in body fluids, of succinylaminoimidazolecarboxamide riboside (SAICARiboside) and succinyladenosine (S-Ado), the dephosphorylated derivatives of the two substrates of

ADSL. To date, ~60 patients with *ADSL* deficiency have been diagnosed. Most of them display severe mental retardation, often accompanied by epilepsy and/or autism (Van den Berghe and Jaeken 2001). The *ADSL* gene has been mapped to chromosome region 22q13.1-13.2 in humans (Van Keuren et al. 1987; Delattre et al. 1991; Fon et al. 1993). It is 23 kb long and was entirely sequenced by Kmoch et al. (2000) (GenBank accession number AF106656). The human coding sequence comprises 1,452 nucleotides, encoding a protein of 484 amino acids (European Molecular Biology Laboratory [EMBL] Database accession number X65867).

Molecular analysis of 31 affected families has revealed the existence of 30 different mutations (Adenylosuccinate Lyase Mutations Database Home Page). Most of them are found in compound heterozygous form. The large majority are missense mutations, among which a predominant mutation, R426H, is found in 13 families. A splicing error (Marie et al. 1999) and a nonsense mutation (Kmoch et al. 2000) have also been identified. The present article describes the identification, in three unrelated patients, of the first mutation found in the 5' UTR of the *ADSL* gene, as well as its functional evaluation as a disease-causing gene.

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Patients, Material, and Methods

Patients

The three patients were from unrelated families, and they presented with profound psychomotor delay and convulsions. Diagnosis was based on the detection of SAICARiboside and S-Ado by HPLC analysis of cerebrospinal fluid and/or urine. The clinical features of patient 1, an Italian American girl, have been published elsewhere (Nassogne et al. 2000). Patients 2 and 3 are from Norway and Australia, respectively. In all three patients, one of the *ADSL* alleles displayed a normal coding sequence. On the other allele, a missense mutation was found: R426H in patient 1, S447P in patient 2, and P318L (D. M. Cowley and I. McGown, personal communication) in patient 3. In accordance with findings in other patients (Race et al. 2000), measurements of the activity of *ADSL* in cultured skin fibroblasts showed 33%, 50%, and 28% of control activity (2.51 ± 0.17 nmol/min per mg of protein) with S-AMP, and 33%, 46%, and 10% of control activity (1.95 ± 0.24 nmol/min per mg of protein) with SAICAR, in patients 1, 2, and 3, respectively.

Cloning and Sequencing

Total RNA was extracted from two 75-cm² flasks of cultured fibroblasts from the patients through use of TRIZOL reagent (Life-Technologies). M-MLV-Reverse transcriptase (Life-Technologies) was used to obtain the cDNA. PCR was performed at 64°C through use of *Pwo* polymerase (Roche) and two *ADSL*-specific primers: S1, starting 47 bp upstream of the ATG codon (−47 CCGC-TCTTCCCTGGTCCAGTC −27); and AS1, starting 26 bp downstream of the stop codon (+1483 GATTTTCG-TTTAATTCTCTTCCAAC +1458) (coding sequence positions are given with respect to EMBL sequence X65867).

Genomic DNA was extracted from one flask of cultured fibroblasts, using the QIAamp DNA kit from QIAGEN. Two primers were used to amplify ~400 bp of the 5' flanking region of the gene: S2 (−398 GAGGGTCTC-CCTGTGTTGCCAG −376) and AS2 (+34 TCGGG-CGAACCATGATCGCCTC +13)

PCR products were either cloned in the pBluescript plasmid (pBS; Stratagene) and sequenced using the ThermoSequenase fluorescent labeled primer cycle sequencing kit (Amersham) with a 4000L automatic sequencer (LiCor), or they were directly sequenced using the CEQ 200 Dye Terminator cycle sequencing kit with a capillary automatic sequencer from Beckman Coulter.

Measurements of Relative Amounts of *ADSL* mRNA Transcribed from the Patients' Two Alleles

Quantification of *ADSL* mRNA harboring the 5' UTR mutation, as compared with *ADSL* mRNA carrying the patients' missense mutations, was performed by PCR amplification of specific allele (PASA), as described by Bottema and Sommer (1998). For each of the three patients, two different pairs of oligonucleotides (numbered "1" and "2" below) were used at the following annealing temperatures: for patient 1, (1) WT-426 (+1300 AAGTAGGCATCAACCTGGATAC +1279) and P1-2, and (2) Mut-426 (+1300 AAGTAGCATCAACCTGGATAT +1279) and P1-2, at 68°C; for patient 2, (1) WT-447 (+1361 GGCACGACCAGTGAAAGAAGA +1341) and P1-2, and (2) Mut-447 (+1361 GGCACGACCAGTGAAAGAAGG +1341) and P1-2, at 70°C; for patient 3, (1) WT-318 (+975 GGACAGATGCTGTCTGTAGCG +955) and P3, and (2) Mut-318 (+975 GGACAGATGCTGTCTGTAGCA +955) and P3, at 66°C. The sequence of P1-2, used in the analysis of patients 1 and 2, is +558 TTGAAGC-GTGTCCGAGATGACC +579, and the sequence of P3, used in the analysis of patient 3, is +370 TTCTTAGAAATGCACTTGACCTGCT +394. Amplification of ribosomal protein S26 was used as an internal control, with the following primers (Vincent et al. 1993): +50 TCGTGCCAAAAAGGGCCGCG +69 (sense strand) and +376 GCTCCTTACATGGGCTTTGGTGG +354 (antisense strand).

Samples were withdrawn after 18, 21, 24, 27, and 30 cycles of PCR. Reaction products were resolved on 1.5% agarose gels. Pictures of the gels were scanned, and PCR products were quantified by densitometry with the NIH Image program.

Cell Transfection and Luciferase Assays

A series of DNA constructs were prepared in the pGL2-basic plasmid from Promega, containing the firefly luciferase gene (*F-luc*) in the absence of any promoter. Various lengths of the promoter region of the *ADSL* gene, including the 5' UTR, were inserted in front of the firefly luciferase reporter gene. Site-directed mutagenesis was performed by PCR amplification. The 5' flanking region cloned into pBS was amplified using *Pwo* DNA polymerase and two back-to-back primers, one of them containing a single modified base to generate one of three mutants, −49T→C, −46C→T, or −40T→C. The PCR-amplified plasmids were purified on 0.8% agarose gels and were ligated after phosphorylation of the 5' ends with ATP and polynucleotide kinase. Clones were checked by sequencing, and the mutated sequences were subcloned into the pGL2-basic plasmid.

HEK-293 cells were seeded at 3×10^5 cells per well

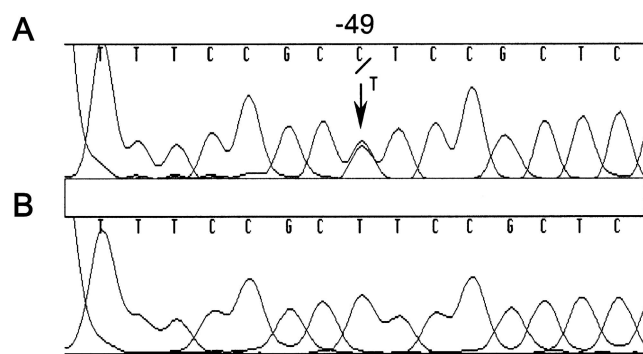


Figure 1 Sequence analysis of patient 1 DNA (A) and control DNA (B).

in six-well plates. After 24 h, through use of calcium phosphate precipitation, cells were cotransfected with 2 μ g of the pGL2 plasmid, containing the *F-luc* constructs, and with 20 ng of the pRL-CMV reference plasmid, containing the *Renilla* luciferase gene (*R-luc*) under the control of the cytomegalovirus promoter. *F-luc* and *R-luc* activities were assayed 48 h later, through use of the dual-luciferase reporter assay system from Promega and a DLR Turner Design luminometer. Luciferase activity was expressed as the ratio of *F-luc* and *R-luc* values. Similar experiments were performed with NIH-3T3 cells that were seeded at 5×10^4 cells per well in 24-well plates and transfected with 2 μ g of *F-luc* constructs and 20 ng of pRL-CMV.

Gel-Shift Experiments

Nuclear extracts from HEK-293 cells were prepared as described by Ausubel et al. (2000, pp. 12.1.1–12.1.3). HeLa cell nuclear extracts were purchased from Promega. Double strand oligonucleotides were labeled using T4 polynucleotide kinase and γ [32 P]-ATP. Protein-DNA binding reactions were performed in a total volume of 20 μ l containing 3 μ g of nuclear extract, 1 μ g poly(dI-dC), 10 mM Hepes (pH 7.6), 1 mM dithiothreitol, 5 mM MgCl₂, 0.1 mM EDTA, 50 mM KCl, 10% glycerol (v/v), and 5×10^4 cpm of 32 P-labeled oligonucleotide. Incubation was for 20 min on ice. For competition experiments, 20 or 50 ng of cold oligonucleotide were added at the same time. Protein-DNA complexes were resolved by electrophoresis on 6% native polyacrylamide gels for 3 h at 200 V. Gels were dried and subjected to autoradiography.

Results

Sequence and Mutation Analysis of the 5' UTR of the Human ADSL Gene

The putative transcription initiation start point of the human *ADSL* gene was localized, 55 nucleotides up-

stream of the ATG codon, by Kmoch et al. (2000). When we analyzed the 5' UTR, we found an additional G in position -51 (fig. 1), bringing its length to 56 bp. Analysis of 400 bp of the 5' flanking region of the DNA of patient 1 revealed a T \rightarrow C substitution that was 49 bp upstream of the ATG codon and thus was located in the 5' UTR. As shown in figure 1, patient 1 is a T/C heterozygote at position -49 , which contains T in the control DNA. The -49 T \rightarrow C mutation was also found in the heterozygous state in the mother's DNA. The same mutation was found in patient 2 from Norway and in patient 3 from Australia, as well as in her father. It was not found in a series of 121 control DNAs.

Measurements of the Relative Amounts of mRNA Transcribed from the Two Alleles of the Patients

Since the -49 T \rightarrow C mutation is located too close to the 5' end of mRNA, oligonucleotides that would be specific for the mutated allele (-49 C) or the normal allele (-49 T) could not be used. Three different pairs of oligonucleotides, one for each missense mutation—R426H, S447P, or P318L—were therefore designed, as described in the "Patients, Material, and Methods" section, so as to match

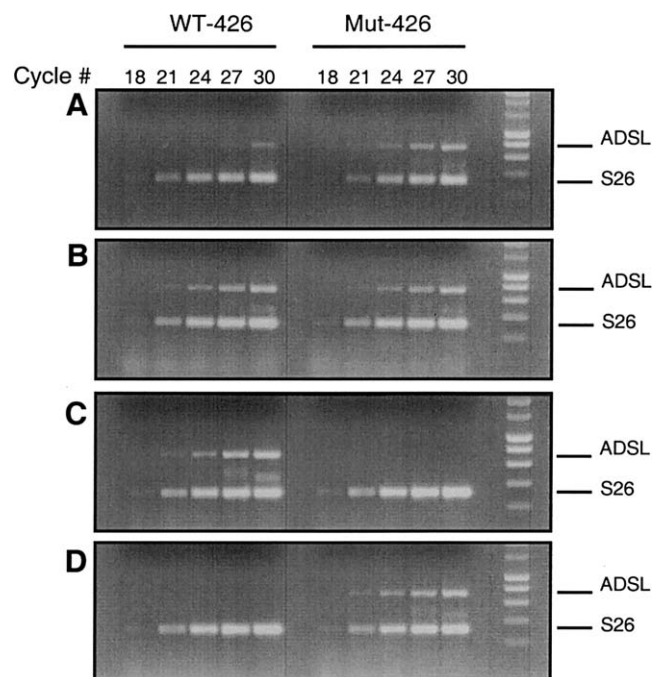


Figure 2 PASA in patient 1. cDNAs from patient 1 (-49 T \rightarrow C/R426H) (A), a heterozygote (WT/R426H) (B), a control (WT/WT) (C), and a homozygote (R426H/R426H) (D) were amplified by PCR with one oligonucleotide specific for the WT allele (WT-426) and one oligonucleotide specific for the mutated allele (Mut-426), as described in the "Patients, Material, and Methods" section. PCR products were analyzed at several numbers of cell cycles, as indicated at the top of the figure. Ribosomal protein S26 was used as an internal control.

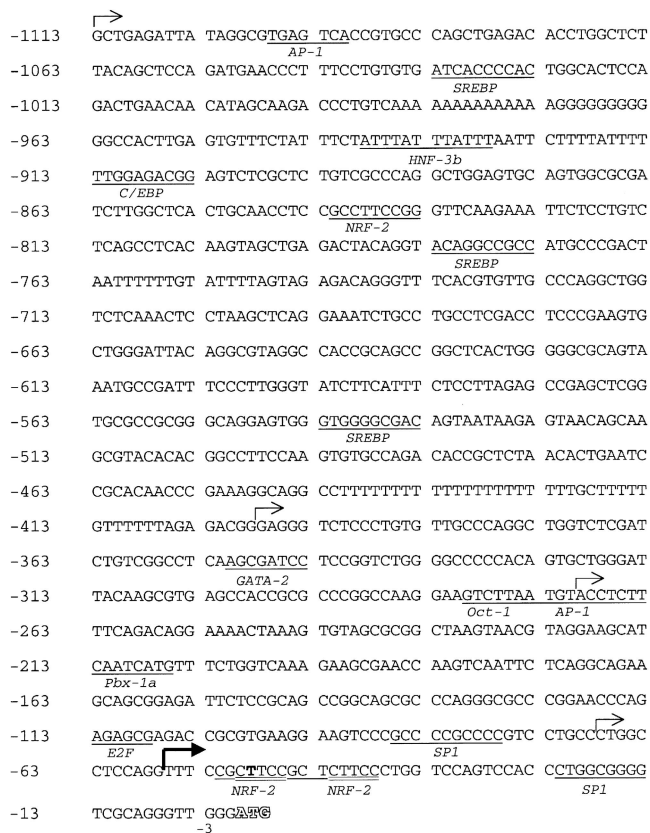


Figure 3 Sequence of the 5' flanking region of the human *ADSL* gene. Bases are numbered by reference to the ATG codon. The bold arrow indicates the start point of the initiation of transcription. Thin arrows indicate the start points of the different constructs used for luciferase assay. Potential binding sites for nuclear factors are underlined. The core sequence of the tandem NRF-2 sites are double-underlined. Base -49T within the -52/-44 NRF-2 site is indicated in boldface.

perfectly with the normal sequence (WT-oligo) or the mutant sequence (Mut-oligo) of *ADSL*. In all cases, WT-oligo amplified the mRNA with mutation -49T→C.

Figure 2 shows the results obtained in the study of patient 1, who carries mutations -49T→C and R426H, with the oligonucleotides specifically amplifying her two alleles. As shown in panel A, distinctly less mRNA was transcribed from the patient's -49T→C allele (amplified with WT-426) than from her R426H allele (amplified with Mut-426). Quantification after 27 and 30 cycles showed that the amount of mRNA transcribed from the -49T→C allele reached 30% and 35%, respectively, of that transcribed from the R426H allele. In contrast (fig. 2B), in an individual heterozygous for the R426H mutation, equal amounts of mRNA were transcribed from the WT and R426H alleles. The specificity of the two oligonucleotides at 68°C is shown in the bottom panels of figure 2: the cDNA from control cells (C) was am-

plified only with the WT-426 oligonucleotide, and the cDNA from a patient homozygous for mutation R426H (D) was amplified only with the Mut-426 oligonucleotide. Results similar to those depicted in panel A were obtained for patients 2 and 3, with WT- and Mut-447 and with WT- and Mut-318 oligonucleotides, respectively (not illustrated).

Mapping of the Promoter Region of the Human ADSL Gene

Analysis of the 5' UTR sequence in the transcription factor database TRANSFAC showed that mutation -49T→C is located within the consensus sequence CNCTTCCGGT (core sequence underlined) of a potential binding site for nuclear respiratory factor 2 (NRF-2), a stimulatory regulator of transcription (Virbasius et al. 1993). To test the effect that a mutation of this potential binding site has on promoter function, we first analyzed the basal promoter activity of the 5' flanking region of the *ADSL* gene.

As shown in figure 3, several potential binding sites for nuclear factors are found in the 5' flanking region of the *ADSL* gene, including the NRF-2 site at position -52/-44. Of note, close to this site, at position -42/-38, a second potential binding site for NRF-2 is found with the essential core sequence CTTCC. To map promoter activity of the 5' flanking region of the *ADSL* gene, four DNA constructs were used. Fragments starting at positions -1113, -398, -270, or -68 and ending at position -3, with respect to the ATG codon (fig. 3), were cloned into the pGL2-basic plasmid for transient expression in HEK-293 cells. Figure 4 shows promoter activities obtained with these constructs, measured as relative light units (firefly luciferase activity/*Renilla* luciferase activity). Maximal promoter activity was obtained with the longest (-1113 bp) fragment, which displayed 400-fold more luciferase activity than the

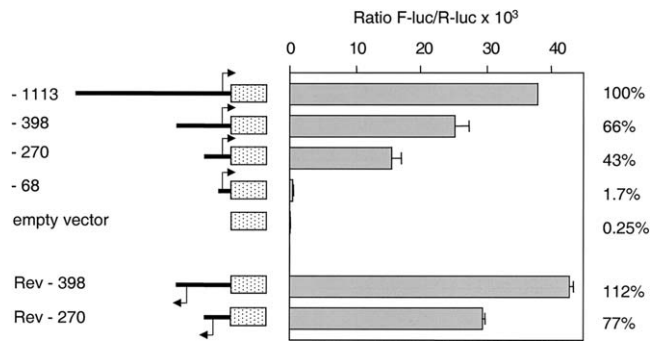


Figure 4 Promoter activity of 5' flanking region of the human *ADSL* gene. Lengths of constructions are indicated on the left, and activities of firefly luciferase are given on the right as a percentage of the 1,113-bp construct.

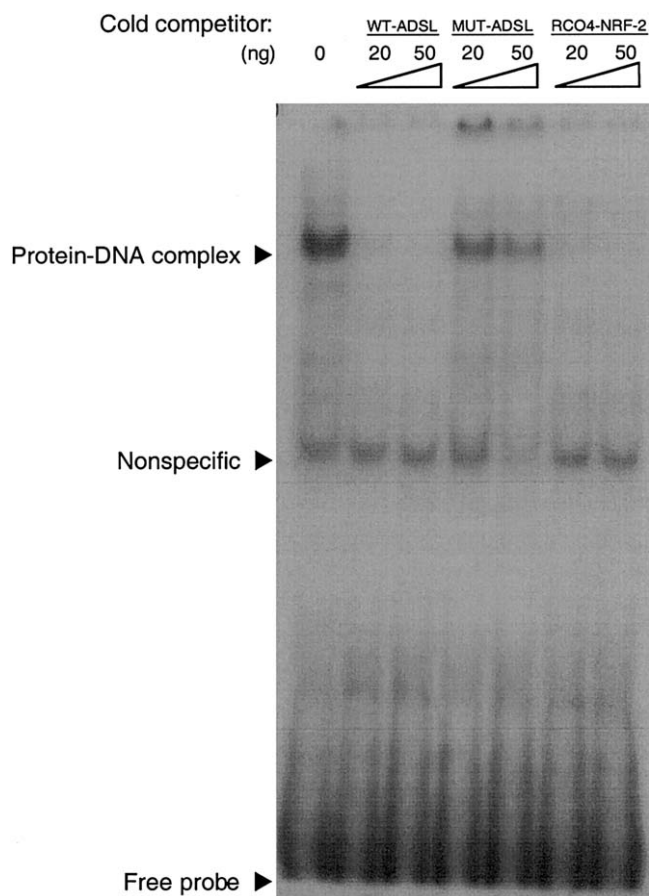


Figure 7 Gel-shift analysis of NRF-2 binding site of *ADSL*. Binding of nuclear proteins to labeled WT oligonucleotide is shown in the absence (0 ng) or in the presence of 20 and 50 ng of WT-*ADSL*, $-49T \rightarrow C$ mutated *ADSL* (Mut-*ADSL*), and cytochrome *c* oxidase (RCO4-NRF-2) cold competitor oligonucleotides.

the binding of NRF-2, a known activator of transcription. The studies also suggest a role for NRF-2 in the gene regulation of the purine biosynthetic pathway.

The observations that the $-49T \rightarrow C$ mutation decreased the amount of mRNA transcribed from this allele, to ~33% of that transcribed from the other allele (fig. 2A), and reduced luciferase activity to 25% of WT in transfection experiments (fig. 5) provide a strong indication that, in the patients' cells, the allele carrying this mutation produces a lower amount of the *ADSL* enzyme protein. Together with the *ADSL* lesion provoked by the mutation on the other allele, this would explain the *ADSL* deficiency.

The finding of reduced amounts of mRNA in both the studies of transcription and the transfection experiments performed with the 5' UTR mutation does not allow us to differentiate between a transcriptional or translational effect of the mutation. Indeed, decreased translation of the mRNA might render it less stable.

However, the finding that the $-49T \rightarrow C$ mutation is located within a potential binding site for the activating transcription factor NRF-2 is an argument in favor of a transcriptional effect. NRF-2 is a member of the Ets factor family (LaMarco et al. 1991; Thompson et al. 1991; Wasylyk et al. 1993) and is identical to the previously characterized GABP and E4TF1 (Virbasius et al. 1993; Suzuki et al. 1998). NRF-2 is known to activate the transcription of several nuclear and mitochondrial genes encoding mitochondrial respiratory proteins, such as cytochrome *c* oxidase subunits (Virbasius and Scarpulla 1991; Seelan et al. 1996; Wong-Riley et al. 2000) and succinate dehydrogenase iron protein (Au and Scheffler 1998). Components of the mtDNA transcription and replication machinery, such as mtTFA, are also controlled by NRF-2 (Virbasius and Scarpulla 1994). Of note, in all of these promoters, the NRF-2 binding site is frequently located within the 5' UTR, as in *ADSL*, or only a few nucleotides upstream of the transcription initiation site.

Our gel-shift experiments provide a good indication that NRF-2 is the factor that binds to the *ADSL* promoter. Indeed, the RCO4-NRF-2 oligonucleotide competes very well with the WT-*ADSL* oligonucleotide (fig. 7), indicating that they probably bind the same nuclear factor. The finding that the *ADSL* oligonucleotide with the $-49T \rightarrow C$ mutation is not able to compete with the wild-type sequence corroborates the functional importance of the mutation and indicates that the lack of NRF-2 binding may play a role in the decrease in transcription. The observation that the protein-DNA complex formed with WT-*ADSL* DNA comigrates with the complex formed with the RCO4-NRF-2 oligonucleotide (fig. 8), which was used to purify NRF-2 from HeLa cells (Virbasius et al. 1993), also indicates binding of

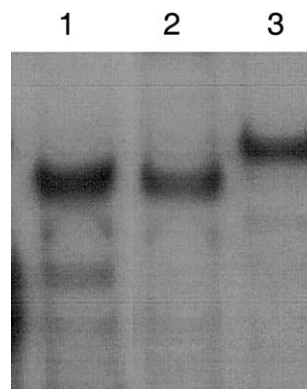


Figure 8 Comparison of protein-DNA complexes formed with WT and mutated *ADSL*, as well as with RCO4-NRF-2. Apparent sizes of protein-DNA complexes formed after incubation of nuclear extracts with labeled RCO4-NRF-2 (lane 1), WT-*ADSL* (lane 2), and $-49T \rightarrow C$ mutated *ADSL* (lane 3) oligonucleotides are shown.

NRF-2 to the *ADSL* promoter. The observation that, in binding assays with nuclear proteins (fig. 8), the oligonucleotide probe with the $-49T \rightarrow C$ mutation revealed a complex of higher molecular weight suggests that the mutation might also allow the binding of an unknown repressing factor.

It has been shown that NRF-2 binds as a dimer to its site, with one subunit containing the DNA binding domain and the other subunit modulating its affinity for DNA (Thompson et al. 1991; Virbasius et al. 1993). Moreover, the presence of two very proximal NRF-2 sites is a rather frequent situation in genes controlled by NRF-2 (Seelan et al. 1996; Wong-Riley et al. 2000). The presence of a tandem site allows the binding of NRF-2 as a tetramer, resulting in a stronger interaction between the factor and DNA. In the *ADSL* 5' UTR, we found a second core sequence of the NRF-2 binding site, CTGCC, at position $-42/-38$, very close to the $-52/-44$ site. This tandem site could thus bind NRF-2 as a tetramer. However, the observation in the luciferase experiments that mutation $-40T \rightarrow C$ within this second core sequence did not significantly affect transcription (fig. 5) leads us to suppose that this second site is not implicated in the binding of the factor.

In the course of our studies, we also observed that the *ADSL* promoter displays bidirectional activity. Divergent transcription has been reported for other genes, like *Surf* and collagen genes (Lennard and Fried 1991; Fischer et al. 1993). Two closely linked genes of the de novo pathway of purine synthesis—namely, *GPAT* and *AIRC*—are also divergently transcribed in chicken (Gavalas et al. 1993; Gavalas and Zalkin 1995), human (Brayton et al. 1994), and rat (Iwahana et al. 1995). *GPAT* encodes glutamine 5'-phosphoribosyl-pyrophosphate amidotransferase, catalyzing step 1 of the de novo purine synthesis, and *AIRC* encodes a bifunctional enzyme, 5'-phosphoribosyl-aminoimidazole carboxylase/5'-phosphoribosyl 4-(N-succinocarboxamide)-5-aminoimidazole synthetase, catalyzing steps 6 and 7. Interestingly, another nuclear respiratory factor, NRF-1, implicated in the expression of several genes whose products function in the mitochondria (Evans and Scarpulla 1990; Chau et al. 1992), has been shown to play a key role in the bidirectional transcription of the human *GPAT-AIRC* genes (Chen et al. 1997). A potential NRF-1 binding site was also found in the rat *GPAT-AIRC* promoter (Iwahana et al. 1995) but not in the chicken promoter (Gavalas et al. 1993). Whereas the NRF-1 site of the *GPAT-AIRC* promoter was found to be implicated in the transcription in both orientations, this was not the case for the NRF-2 site in the *ADSL* promoter, since we found that mutations in the latter site did not affect the transcription in the reverse direction. Also of note, the identity of the neighbor gene of the *ADSL*

gene is not known, even though the entire sequence of human chromosome 22 is available.

Taken together, our studies suggest that a mutation of a regulatory region of the *ADSL* gene might be an unusually frequent cause of *ADSL* deficiency. Indeed, regulatory mutations account for <1% of all mutation types (Human Gene Mutation Database), whereas a disease-causing mutation of the 5' UTR has now been identified in 3 of 31 families with the *ADSL* enzyme defect. On the other hand, in vertebrates, little is known about gene regulation in purine nucleotide synthesis. Our observation that NRF-2 plays a role in the transcription of *ADSL* lends further support to the proposal that nuclear respiratory factors may play a role in the coordination of respiratory metabolism with biosynthetic and degradative pathways (Seelan et al. 1996; Scarpulla 1997).

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

Adenylosuccinate Lyase Mutations Database Home Page, <http://www.icp.ucl.ac.be/adslldb/>
 European Molecular Biology Laboratory (EMBL) Nucleotide Sequence Database, <http://www.ebi.ac.uk/embl/index.html> (for the *ADSL* gene [accession number X65867])
 GenBank, <http://www.ncbi.nlm.nih.gov/Genbank/> (for the *ADSL* coding sequence [accession number AF106656])
 Human Gene Mutation Database, The, <http://www.uwcm.ac.uk/uwcm/mg/hgmd0.html>
 Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> (for *ADSL* [MIM 103050])

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