Structure-Function Studies of the BTB/POZ Transcriptional Repression Domain from the Promyelocytic Leukemia Zinc Finger Oncoprotein

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ABSTRACT

The evolutionarily conserved BTB/POZ domain from the promyelocytic leukemia zinc finger (PLZF) oncoprotein mediates transcriptional repression through the recruitment of corepressor proteins containing histone deacetylases in acute promyelocytic leukemia. We have determined the 2.0 Å crystal structure of the BTB/POZ domain from PLZF (PLZF-BTB/POZ), and have carried out biochemical analysis of PLZF-BTB/POZ harboring site-directed mutations to probe structure-function relationships. The structure reveals a novel αβ-homodimeric fold in which dimer interactions occur along two surfaces of the protein subunits. The conservation of BTB/POZ domain residues at the core of the protomers and at the dimer interface implies an analogous fold and dimerization mode for BTB/POZ domains from otherwise functionally unrelated proteins. Unexpectedly, the BTB/POZ domain forms dimer-dimer interactions in the crystals, suggesting a mode for higher-order protein oligomerization for BTB/POZ-mediated transcriptional repression. Biochemical characterization of PLZF-BTB/POZ harboring mutations in conserved residues involved in protein dimerization reveals that the integrity of the dimer interface is exquisitely sensitive to mutation and that dimer formation is required for wild-type levels of transcriptional repression. Interestingly, similar mutational analysis of residues within a pronounced protein cleft along the dimer interface, which had been implicated previously for interaction with corepressors, has negligible effects on dimerization or transcriptional repression. Together, these studies form a structure-function framework for understanding BTB/POZ-mediated oligomerization and transcriptional repression properties.

INTRODUCTION

The PLZF gene was first identified as part of a t(11;17) chromosomal translocation with the RARα gene forming the PLZF-RARα fusion protein in APL (1). Unlike the more common APL t(15;17) translocation forming the PML-RARα fusion protein (2, 3), patients harboring the t(11;17) chromosomal translocation are resistant to treatment with pharmacological doses of RAs (4).

The PLZF moiety of the PLZF-RARα fusion protein contains a 120 residue BTB/POZ domain, named for its presence in the Drosophila proteins BTB (5), and its homology with several POZ (6). This domain has been found in an increasing number of proteins in poxvirus, Caenorhabditis elegans, Drosophila, and humans and is generally found at the NH2 terminus of either actin-binding or, more commonly, nuclear transcriptional regulatory proteins (7). Functional studies have shown that the BTB/POZ domain mediates histone deacetylation (6, 8, 9), heteromultimerization between different BTB/POZ-harboring proteins (6, 10), and transcriptional repression in the case of several DNA regulators harboring BTB/POZ domains (10–16).

Much of the mechanistic detail for the function of BTB/POZ domains has come from the study of the PLZF and LAZ3/BCL6 (lymphoma-associated zinc finger 3/B cell lymphoma 6) oncoproteins (10, 11). In these cases, the BTB/POZ domain has been shown to promote transcriptional repression through the recruitment of corepressor proteins such as N-CoR and SMRT (17, 18). More recently, the BTB/POZ domain of PLZF has been shown to interact with a protein complex containing N-CoR/SMRT, mSin3A, and the histone deacetylase, HDAC1, to mediate transcriptional repression (19–21). Moreover, this recruitment has been found to play a major role in the pathogenic effect of the PLZF-RARα fusion protein and for its resistance to treatment with RA. Specifically, a model has been proposed whereby the PLZF-RARα fusion protein acts as a potent transcriptional repressor through the ability of both the RARα (22) and BTB/POZ moieties to recruit the SMRT/N-CoR deacetylase transcriptional repression complex (23, 24). Because RA induces the release of this corepressor complex from RARα (22) but not from PLZF, this model is consistent with the RA resistance of APL patients harboring the PLZF-RARα translocation (25, 26).

Here we present the high resolution crystal structure of the BTB/POZ domain from PLZF and characterize the biochemical properties of PLZF proteins harboring site-directed mutations. The structure provides general insights into the architecture and mode of multimerization for the evolutionarily conserved BTB/POZ domain. Moreover, a correlation of the BTB/POZ domain structure with the dimerization and transcriptional repression properties of PLZF proteins harboring site-directed mutations establishes a structure-function paradigm for understanding the dimerization and transcriptional repression properties of proteins harboring BTB/POZ domains. Finally, the insights provided here provide a framework from which to design PLZF-specific inhibitory molecules that may be used to treat APL patients harboring the PLZF-RARα translocation.

MATERIALS AND METHODS

Protein Expression and Purification for Crystallization. Residues 6–123 of PLZF harboring the BTB/POZ domain and containing the NH2-terminal 6xHis tag sequence MRGSHHHHHHGS (herein called PLZF-BTB/POZ) was overexpressed using a pQE30 T5-polymerase based expression vector in Escherichia coli S9 cells and purified using a combination of anion-exchange (Q-Sepharose) and gel filtration (Superdex-75) chromatography as described elsewhere (8).

SeMet-derivatized PLZF-BTB/POZ protein was prepared by growing pQE30/PLZF-BTB/POZ-transformed E. coli strain B834 (DE3; Novagen) in 4-morpholinopropanesulfonic acid-based minimal media (27) supplemented with 50 mg/l L-SeMet and other amino acids at the suggested concentrations. Cells were grown at 28°C to an A600 of 0.4 and induced with 1 mM isopropyl-1-thio-β-D-galactopyranoside to an A600 of ~1.0. The PLZF-BTB/POZ protein was isolated essentially as described for the derivatized protein. Quantitative...
amino acid analysis of SeMet-derivatized PLZF-BTB/POZ protein confirmed that >90% of the methionine residues had been replaced. After purification, SeMet-derivatized PLZF-BTB/POZ was concentrated to ~50 mg/ml by centrifugation using a Centricon-10 microconcentrator (Amicon) in a buffer containing 40 mM Tris (pH 8.5), 100 mM NaCl, and 1 mM β-mercaptoethanol and frozen as 50-μl aliquots at ~70°C before crystallization. Frozen protein aliquots were thawed for use in crystallization as needed.

Crystalization and Data Collection. Crystals of underivatized and SeMet-derivatized PLZF-BTB/POZ were prepared using 2-μl hanging drops containing 10 mg/ml PLZF-BTB/POZ, 8% isopropanol, 600 mM MgCl₂, 50 mM Tris (pH 8.5), and 50 mM HEPES (pH 6.5) equilibrated over a reservoir containing two times the concentration of salts, buffer, and precipitating agent. Crystals were transiently transferred (for ~5 min) to a harvest solution composed of salts, buffer, and precipitating agent at the same concentrations as the reservoir solution with the addition of 25% glycerol to facilitate X-ray data collection at cryogenic temperature (~170°C).

MAD data were collected from cryoprotected SeMet-derivatized PLZF-BTB/POZ crystals that were flash frozen in liquid nitrogen prior to data collection at 110 K. MAD data were collected at NSLS using beamline X42A equipped with an R-Axis IV image plate detector. The inverse-beam method was used to record Bijvoet differences from each of four different wavelengths to optimize dispersive differences: upstream remote (λ₁ = 0.9878 Å), the downstream remote (λ₅ = 0.9667 Å), the inflection (λ₂ = 0.9796 Å), and the maximum of X-ray absorption (λ₄ = 0.9795 Å). The MAD data were processed with DENZO and SCALEPACK (Ref. 28; Table 1).

Structure Determination and Refinement. The structure was determined to 2.3 Å resolution using the MAD data collected from SeMet-derivatized PLZF-BTB/POZ crystals. SeMet positions were identified and refined using difference Patterson and difference Fourier synthesis with the PHASES package (Ref. 29; Table 1). Two SeMet sites were unambiguously identified using difference Patterson maps produced with two sets of dispersive signals and three sets of Bijvoet signals, and two additional SeMet sites were confirmed using cross-difference Fourier maps using the first two sites. Phase refinement, using four SeMet sites using all Bijvoet and dispersive differences, and solvent flattening procedures were carried out with the program PHASES (29). The resulting electron density map was of very high quality (Fig. 1C) and allowed for straightforward tracing of the polypeptide chain with the program O (30) using the SeMet positions as landmarks.

Model refinement was carried out with the program X-PLOR (31) using data collected from SeMet-derivatized PLZF-BTB/POZ crystals at the upstream remote wavelength (0.9878 Å). Before refinement, a randomly selected set of data (10%) was omitted from the refinement and used as a “free data set” to monitor subsequent calculations (32), and the model was refined against the remaining data (90%, working data set). Conventional position refinement was initially carried out at 3.0 Å with X-PLOR. After this procedure, iterative cycles of positional refinement with X-PLOR (33) and manual model building with O (30) using Sigma-weighted 2Fo-Fc and Fo-Fc difference maps were extended in steps to resolution limits of 2.7, 2.5, 2.3, and 2.0 Å. The later stages of refinement using both simultaneous annealing (34) and torsion angle dynamics (35) as implemented in X-PLOR. Also at the later stages of refinement, a bulk solvent correction was applied (36), tightly constrained atomic B-factors were adjusted, and water molecules were built into regions that showed strong Fo-Fc peaks and made stereochemically feasible hydrogen bonds. The correctness of the model was checked against simulated annealing omit maps (37) over the entire structure by omitting 15 residues at a time, and the model was adjusted appropriately. A last round of refinement resulted in a model with good geometry (RMSbond length = 0.005 Å, RMSbond angle = 0.862°) and a working R factor of 25.2% with a free R factor of 27.3% using all reflections between 20 and 2 Å (Table 1). The final model includes residues 7–122 of PLZF-BTB/POZ and 61 water molecules. Residue 6, the NH₂-terminal 6xHis-tag and the COOH-terminal residue are not visible in the electron density map. A Ramachandran plot showed no residues of the protein in disallowed regions (38).

Site-directed Mutagenesis. The plasmids containing the BTB/POZ domain of PLZF (residues 6–123) were constructed by PCR using the plasmid pQE30-PLZF as a template (8). A 5’ oligonucleotide (5’-GGA TCC ACC ATG GGC ATG ATC CAG CTG CAG-3’) with a BamHI site immediately 5’ to a consensus Kozak sequence (ACC) at methionine 6 and a 3’ oligonucleotide (5’-GAT GGA TCC CTA CTC CAG CAT CTG CAG ACA GCA CG-3’) with a stop codon (TAG) and BamHI site after amino acid 123 were used to amplify the desired sequence. Single amino acid point mutations within the BTB/POZ domain of PLZF were created using standard PCR-mediated mutagenesis. The mutagenic primers contained the following codons: L21A, CTG to GCG; D35N, GAT to AAT; H64A, CAC to GCC; N66A, AAT to GCT; and Q68A, CAA to GCA. BamHI-digested PCR products were ligated into BamHI-digested pSP73 for in vitro transcription and pM2 for in vivo expression. All PCR-derived plasmids were subjected to automated DNA sequencing of both strands to confirm the incorporation of appropriate mutations and integrity of surrounding sequences.

Gel Filtration Analysis of Wild-Type and Mutant PLZF Proteins. Fifty μl of [35S]metionine-labeled, in vitro-translated PLZFres1-123proteins (SP6 TrnT; Promega) were analyzed by gel filtration with a Superdex 200 HR 10/30 column (Pharmacia Biotech, Inc.) equilibrated in PBS (10 mM Na₂HPO₄, 1.4 mM KH₂PO₄, 137 mM NaCl, and 2.7 mM KCl, pH 7.0). The column was run at 4°C at a flow rate of 0.3 ml/min, and 1-ml fractions were collected. The...
protein from each fraction was concentrated by deoxycholate-trichloroacetic acid precipitation (39). The precipitated protein was resuspended in 100 μl of 0.1 M NaOH. Thirty μl of the resuspended protein sample were resolved on a 12% Laemmli SDS-PAGE gel, and PLZF –123 proteins were visualized by fluorography.

Transient Transfection/Luciferase Assays. Stable expression of heterologous GAL4-PLZF –123 fusion proteins was confirmed by transfection in COS-1 cells. One μg of a rabbit anti-GAL4 DBD polyclonal IgG (Santa Cruz Biotech) was used to detect expression of GAL4 fusion proteins by immunoprecipitation of [35 S]methionine-labeled cell extracts (40). All transcription/luciferase assays were done in NIH/3T3 cells as described elsewhere (40).

RESULTS AND DISCUSSION

The Overall Structure of the PLZF-BTB/POZ Dimer Is Unique. The BTB/POZ domain of PLZF (PLZF-BTB/POZ) crystallizes as a dimer in space group I222 with one protomer per asymmetric unit with a crystallographic 2-fold passing through the functional dimer. The final model contains residues 7–122 of PLZF, which includes the complete evolutionarily conserved BTB/POZ domain (Fig. 1, A and B). Each subunit is comprised of 5 β-strands and 6 α-helices that associate to form a globular dimer (Figs. 1D and 2). The dimer has approximate dimensions of 20 Å × 30 Å × 60 Å and has the appearance of a “butterfly,” with each subunit forming most of each of the wings (Fig. 2, A and B). The β strands lie on the top and bottom of each of the subunits, and the helices fill the interior and flank the sides of the dimer. There are two pronounced clefts at the top and bottom of the dimer, where the two subunits intersect (Fig. 2C). The smaller upper cleft has a relatively shallow groove, whereas the larger lower cleft is 20 Å long with a width and depth of 5 and 6 Å, respectively. A search through the structural database with either the monomer or dimer shows no significant homology with other protein structures, suggesting that the PLZF-BTB/POZ domain contains a novel protein fold.

The Core of the PLZF-BTB/POZ Domain Is Conserved within the BTB/POZ Domain Family. Most of the secondary structural elements of the PLZF-BTB/POZ subunit contribute to stabilization of the hydrophobic core (Fig. 3A). The only exceptions are strands β1 and β5 and the NH2 terminus of helix α1, which contribute largely to...
that stabilize the core are also highly conserved among BTB/POZ proteins (Fig. 1B). Taken together, the conservation of residues that stabilize the core of the PLZF-BTB/POZ subunit strongly suggests that other BTB/POZ domains have a homologous subunit tertiary fold.

**Dimerization by PLZF-BTB/POZ Implicates a Conserved Mode of Dimerization by Other BTB/POZ Domain Proteins.** Previous studies in our laboratory have used a variety of biophysical techniques to show that the BTB/POZ domain of PLZF forms a dimer with an apparent $K_d < 200$ nM (8). The structure of the PLZF-BTB/POZ dimer is consistent with the high degree of dimer stability. Overall, there are 23 residues from each subunit that contribute to dimer formation, forming a solvent excluded surface of 2400 Å² for the dimer (Figs. 1B and 2C).

The principle dimer contacts between the PLZF-BTB/POZ subunits are mediated by the $\beta_1$ and $\beta_5$ strands and the $\alpha_1$ helix, which are the only secondary structural elements that do not contribute significantly to the subunit core (Fig. 3, B and C). The $\beta_1$ strand and the NH$_2$..
and Met 27 make a series of van der Waals interactions with residues in the core above (\(\beta 1\) and \(\beta 5\) strands) and in the central portion of the butterfly (\(\alpha 1\) helix). For simplicity of discussion, we will refer to the symmetry-related subunit of the dimer with a primed (\(\prime\)) designation. The \(\beta 1\) strand is wedged between the \(\beta 5\)’ strand and the \(\alpha 6\)’ helix of the opposing subunit, making sheet interactions with the \(\beta 5\)’ strand and van der Waals and hydrogen-bond interactions with other regions of the primed subunit (Fig. 4B). Specifically, Ile\(^{9}\) makes van der Waals interactions with Leu\(^{29}\) of \(\alpha 5\)’, Ala\(^{96}\) in the loop between \(\beta 5\)’ and \(\alpha 6\)’ and Met\(^{121}\) of \(\alpha 6\)’; Ile\(^{11}\) makes van der Waals interactions with Tyr\(^{113}\), Leu\(^{114}\), Glu\(^{117}\), and Cys\(^{118}\) of helix \(\alpha 6\)’; and the N82 of Asn\(^{113}\) hydrogen bonds to the side-chain hydroxyl of Tyr\(^{96}\) in helix \(\alpha 4\)’.

The \(\alpha 1\) helix and the proceeding loop is situated between the \(\alpha 1\)’ and \(\alpha 2\)’ helices and makes mostly van der Waals interactions with residues within these helices as well as with the \(\alpha 3\)’ and \(\alpha 4\)’ helices (Fig. 3C). Specifically, \(\alpha 1\)-helix residues His\(^{16}\), Pro\(^{17}\), Leu\(^{20}\), Leu\(^{21}\), and Met\(^{27}\) make a series of van der Waals interactions with residues from helices \(\alpha 1\)’, \(\alpha 2\)’, \(\alpha 3\)’, and \(\alpha 4\)’. In particular, Leu\(^{21}\) from \(\alpha 1\)’, Cys54 from \(\alpha 2\)’, and Ala\(^{80}\) from the loop between \(\alpha 4\)’ and \(\beta 5\)’ play important roles in stabilizing the dimer. Thr\(^{32}\), Leu\(^{33}\), and Asp\(^{35}\) in the loop proceeding helix \(\alpha 1\) also contribute to dimer stability. His\(^{64}\) from \(\alpha 3\)’ plays a particularly important role in this regard.

Nearly 80% of the residues that stabilize the PLZF-BTB/POZ dimer show conservation within the BTB/POZ domain family (Fig. 1A). In particular, His\(^{16}\) and Leu\(^{21}\) in helix \(\alpha 1\) and Asp\(^{35}\) in the loop proceeding the \(\alpha 1\) helix are highly conserved and play important roles in dimer stability. All but the aspartic acid play a hydrophobic role in dimer stability. Asp\(^{35}\), in contrast, makes a direct hydrogen bond to Arg\(^{99}\) (moderately conserved within the BTB/POZ family) and a water-mediated hydrogen bond to Asp\(^{35}\’\). Taken together, the degree of conservation within residues that stabilize dimer formation suggests that BTB/POZ domains from otherwise unrelated proteins will form dimers with similar quaternary arrangements. Correlating well with our findings, there are several BTB/POZ domains that have been shown to form homodimers. Among them are PLZF (8), ZID (6), Ttk (6), bab (9), and BAZF (11). Indeed, the BTB/POZ domain appears to be an ideally suited dimerization module.

**Dimer-Dimer Interactions in the Crystals Implicate a Propensity for Higher Order Oligomerization by BTB/POZ Domains in Vivo.** Comparison of the PLZF-BTB/POZ structure derived here with that of the recently published PLZF-BTB/POZ structure determined by Ahmad et al. (42) shows a high degree of structural similarity between the protein dimers with an RMS deviation between all atoms of 1.1 Å\(^{2}\). Strikingly, this comparison also shows that although the two structures were obtained in different crystal lattice environments, both show structurally homologous dimer-dimer interactions in the crystal lattice (Fig. 4A). These dimer-dimer contacts bury a total of 1200 Å\(^{2}\) of solvent excluded surface and is largely mediated by 2 4-stranded antiparallel \(\beta\)-sheet involving \(\beta 1\) and \(\beta 5\)’ from one dimer with the corresponding segments of the symmetry related dimer. In addition, Ala\(^{96}\) in the loop between \(\beta 5\)’ and \(\alpha 5\)’ makes a van der Waals contact with Met\(^{121}\) at the COOH-terminus of \(\alpha 6\)’ in the symmetry related dimer. The \(\alpha 6\)-mediated interactions at the dimer-dimer interface are somewhat more extensive in the PLZF-BTB/POZ structure described by Ahmad et al. (42) because their \(\alpha 6\)’ helix contains an additional turn of secondary structure. It is interesting to note that the mode of dimer-dimer interaction observed in the crystals does not prohibit the formation of extended dimer-dimer interactions, which would result in the formation of even higher order multimers (Fig. 4, B and C). Taken together, these observations suggest that the BTB/POZ domain may mediate the formation of higher-order multimers in vivo.

Correlating well with our findings, two recent studies have shown that the BTB/POZ domain of the GAGA transcription factor directly mediates the formation of higher-order oligomers to bind multiple GAGA sites that are found in natural target promoters in vivo (41, 43). Moreover, the formation of these higher-order oligomers have been shown to be correlated with the cooperative nature of GAGA transcription factor binding to multiple DNA-binding sites and correlated with the finding that this cooperativity is strictly dependent on the presence of the GAGA BTB/POZ domain. Interestingly, natural GAGA promoters display a large degree of variability between GAGA sites, also correlating well with the relatively flexible dimer-dimer interactions seen in the crystals.

Our findings of higher-order BTB/POZ oligomers may also explain other studies that find that the BTB/POZ domains from some proteins mediate specific hetero-oligomers. For example, Tik can form oligomers with itself and with the GAGA protein but not with the BTB/POZ region of ZID (6). In addition, BAZF has been shown to form oligomers with itself and with BCL6 (11). Taken together, the BTB/POZ domain appears to be an ideally suited module for both homo and hetero protein multimerization.
Biochemical Analysis of PLZF Proteins Harboring Site-directed Mutations Shows That Dimerization Is Required for Transcriptional Repression. The recent study by Ahmad et al. (42) has suggested that a pronounced cleft along the bottom of the PLZF dimer (Fig. 2C) may be a site of corepressor interaction. To directly test this hypothesis and to directly probe the functional significance of dimer formation by PLZF, we carried out site-directed mutagenesis coupled with biochemical analysis of these mutant proteins. We prepared five different site-directed mutations that fell into two subgroups (Fig. 2C). The first two (L21A and D35N) involved residues that play critical roles in dimerization; and the second group (H64A, N66A, and Q68A) involved residues in the pronounced cleft at the base of the PLZF-BTB/POZ domain dimer. Each of the mutants were tested for both dimerization and transcriptional repression properties. To evaluate the effects of these mutations on the dimerization of the BTB/POZ domain, the wild-type PLZF6–123 and each mutant described herein were in vitro translated and then subjected to gel filtration (Fig. 5). Consistent with expectations, the wild-type PLZF6–123 protein, as well as each of the proteins harboring mutations in the cleft region, eluted from the sizing column at a molecular weight consistent with a dimeric PLZF-BTB/POZ species. In addition, proteins harboring mutations in the dimerization interface of PLZF-BTB/POZ eluted in two peaks, one near the void volume (Mₐ ≈ 670,000), indicative of protein aggregates and another at a position consistent with a monomeric PLZF-BTB/POZ domain (Mₐ, 17,000). These results indicated that the L21A and D35N mutant proteins were defective in dimer formation.

To evaluate any effects these mutations may have on the transcriptional repression function of the PLZF BTB/POZ domain, heterologous fusions between the DNA binding domain of GAL4 (amino acids 1–147) and each of the BTB/POZ domain mutants described herein were created (Fig. 6). Each fusion protein demonstrated stable and comparable nuclear-localized expression in COS-1 cells (Fig. 6B), suggesting comparable DNA-binding properties for each of our protein fusions. The wild-type GAL4-PLZF₆₋₁₂₃, BTB/POZ domain and each mutant version thereof were cotransfected with 2 TK-luciferase reporter downstream of four copies of the GAL4 consensus UAS in NIH/3T3 cells (Fig. 6A). The wild-type GAL4-PLZF₆₋₁₂₃ protein demonstrated significant repression of the luciferase reporter gene activity (Fig. 6C). Expression of the of the D35N mutant protein, which fails to dimerize properly (Fig. 5B), demonstrated a significantly impaired repression function (Fig. 6C). To a lesser extent, the repression function of the L21A mutant protein was also impaired (Fig. 6C). All other mutants (H64A, N66A, and Q68A) demonstrated negligible effects on the repression function of the BTB/POZ domain of PLZF (Fig. 6C). Significantly, these data suggest that the repression function of the PLZF-BTB/POZ domain is strictly dependent upon
homodimerization. Moreover, these data suggest that the cleft region of the PLZF-BTB/POZ domain may not play a significant role in the transcriptional repression property of PLZF.

Recently, Huynh and Bardwell (10) have carried out a site-directed mutagenesis study of the BTB/POZ domain of BCL6 with the goal of disrupting corepressor function. In this study, the authors targeted NH2-terminal residues that are highly conserved in proteins that showed interaction with the corepressor proteins N-CoR and SMRT and that mediated transcriptional repression (BCL6, PLZF, ZID, GAGA, and vaccinia virus SaFI7R). Mutations were made to the corresponding residues of the BTB/POZ harboring protein, Protein A from the mod(mdg4) gene, which failed to show binding to N-CoR and SMRT and which failed to mediate transcriptional repression. A correlation of the phenotype of these mutations with the PLZF-BTB/POZ structure shows that the two mutations that disrupt corepressor binding and function (Leu to Ser at position 21, and Met-Arg to Cys-Cys at position 47) did not have a detectable effect on N-CoR and SMRT interaction or transcriptional repression. The structure of the PLZF-BTB/POZ region shows that the two mutations that disrupt corepressor binding and function (Leu to Ser at position 21, and Met-Arg to Cys-Cys at position 47) did not have a detectable effect on N-CoR and SMRT interaction or transcriptional repression. The structure of the PLZF-BTB/POZ region shows that the two mutations that disrupt corepressor binding and function (Leu to Ser at position 21, and Met-Arg to Cys-Cys at position 47) did not have a detectable effect on N-CoR and SMRT interaction or transcriptional repression. The structure of the PLZF-BTB/POZ region shows that the two mutations that disrupt corepressor binding and function (Leu to Ser at position 21, and Met-Arg to Cys-Cys at position 47) did not have a detectable effect on N-CoR and SMRT interaction or transcriptional repression. The structure of the PLZF-BTB/POZ region shows that the two mutations that disrupt corepressor binding and function (Leu to Ser at position 21, and Met-Arg to Cys-Cys at position 47) did not have a detectable effect on N-CoR and SMRT interaction or transcriptional repression. The structure of the PLZF-BTB/POZ region shows that the two mutations that disrupt corepressor binding and function (Leu to Ser at position 21, and Met-Arg to Cys-Cys at position 47) did not have a detectable effect on N-CoR and SMRT interaction or transcriptional repression.
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