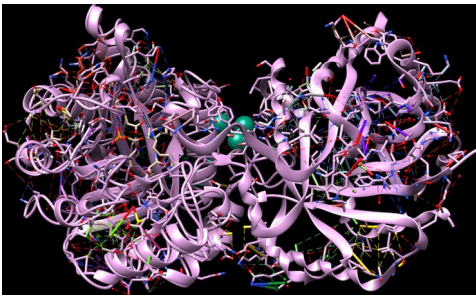


TRIOSEPHOSPHATE ISOMERASE (TPI) COMBINES THE EFFECTS OF HIS95 AND LYS13 FOR GLU165 THREE CRUCIAL CATALYTIC RESIDUES WHICH FORM THE ENEDIOL INTERMEDIATE NECESSARY FOR THE INTERCONVERSION REACTION CATALYZED BY TPI.

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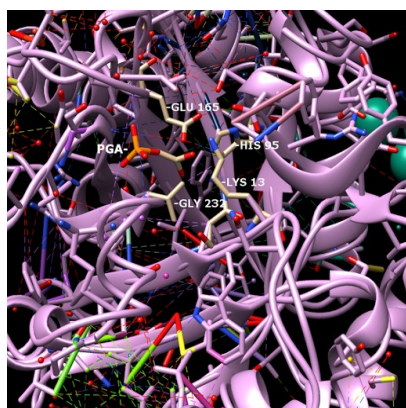
Triosephosphate isomerase (TPI, EC [5.3.1.1](#)) is essential to glycolysis, catalyzes the fifth step in the glycolysis pathway the reversible conversion of dihydroxyacetone phosphate (DHAP) into glyceraldehyde-3-phosphate.. TPI is a homodimer formed by two identical dimeric molecules of a single structural locus : [12p13.31](#).¹ TPI has only 1 functional gene with a molecular mass of 29 kDa, that after refinement are products of a distinct single structural locus. The variant phenotype of identical subunits are expressed in both red cells and circulating [lymphocytes](#),² catalyzing the interconversion of one of the two products breakdown by reversible conversion. The TPI substrate by [deprotonation](#)³ the transition state reaction of dihydroxyacetone phosphate ([DHAP](#))⁴ substrate yields one product of the glycolytic pathway, is a [trend](#)*⁵ (Kcat) that persists creating the initial complex microcompartmentation of TPI to give ([G3P](#))⁶ glyceraldehyde-3-phosphate which seems to be the [isomerase](#)*⁷ activity, release is slower than its conversion to DHAP in normal and TPI deficient cells. [TIM](#)⁸ with its natural substrates has [not been](#)⁹ (•) crystalized**.¹⁰ TPI is a dimeric enzyme and contains 7 exons interrupted by six introns.



The crystallographic structure of (HsTPI) human triosephosphate isomerase PDB:1HTI is one dimer per asymmetric unit subunit 1 and subunit 2 are in the open and closed conformations in the 3-dimensional symmetry space group P 2(1) which is specific to the Monoclinic with minimization on the entire structure In the presence of substrate analogues and its surrounding residues supporting possible regions targeted for drug design.

TPI deficiency (TPID) a disorder of glycolysis, occurring in haplotypes of specific alleles heterogeneous to clinical [TPI](#)¹¹-[deficiency](#),¹² with a rare homozygous [deficiency](#)¹³ the resulting [genetic](#)¹⁴ defects is the cause of a null variant incompatible with [life](#)¹⁵ by abnormally high [levels](#)¹⁶ of [DHAP](#)¹⁷ which degrades spontaneously into the toxic ([MG](#))¹⁸ [methylglyoxal](#),¹⁹ due to [deamidation](#)²⁰ of asparagine (Asn15-71)²¹ to [form](#)²² aspartic and glutamic acid. [Loop 6](#)²³ plays a role in preventing the breakdown yield of [methylglyoxal](#)²⁴ ([fMG](#))²⁵ one of the of the three products of enzyme-bound enediol(ate) [phosphate](#),²⁶ towards [elimination](#)²⁷ of ([fMG](#))²⁸ inorganic phosphate. TPI deficiency is due to the common aberrant dimerization (or the dissociation into inactive monomers) of mutation TPI [1591C](#),²⁹ encoding a Glu104-to-Asp³⁰ (glutamate-to-aspartate) substitution in the TPI [variant](#)³¹ found in cases of hemolytic anemia [coupled](#)³² with [neurodegeneration](#),³³ the Glu104-to-Asp³⁴ substitution is the most [common](#)³⁵ disease allele inherited, when compared to wild-type TPI's [three](#)³⁶ (residues from the same [subunit](#))³⁷ similar but not identical interactions between the inhibitor and catalytic residues, Glu 167³⁸ (or 165)³⁹ forms a stable dimer and provides the [rationale](#)⁴⁰ for production of structurally normal enzyme in humans, the E104D⁴¹ mutation, provides the [amyloid-resistant](#)⁴² structure of human triosephosphate isomerase (HsTPI).⁴³ [Water-protein](#)⁴⁴ molecules [join](#)⁴⁵ two catalytically active monomers which is only in its dimeric form, as [monomers](#)⁴⁶ of TIM are not functional. Within a hydrophobic catalytic [pocket](#)⁴⁷ of the native enzymes the binding and catalysis of TPIs in

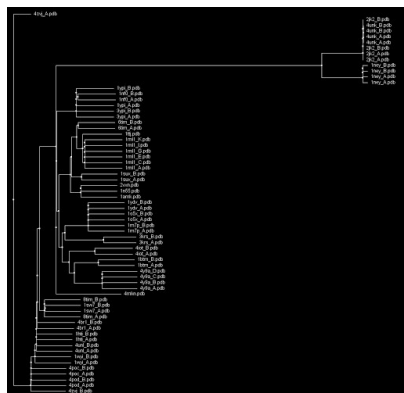
[hemolysates](#),⁴⁸ bind to the [red cell](#)⁴⁹ membrane. Molecular modeling using the human crystal structure of [TPI](#)⁵⁰ was performed to determine how these mutations could affect enzyme structure and function. The Amyloid [secondary](#)⁵¹ structure autoepitopes [antigen](#)-driven⁵² mechanism works toward recovery of the [anti](#)-triosephosphate⁵³ isomerase mutant TPI [peptide](#)**⁵⁴ antigens. This is the [scheme](#)⁵⁵ that allows function-enhancing the stability most significantly, the catalysis for deprotonation of DHAP or vice-versa GAP substrates of the TIM-barrel relative to TPI toward turnover of two-part substrate glycolaldehyde / phosphite dianion {GA + HPO₃²⁻ the transition state for this enolising enzyme substrate pieces.} Km/[obsd](#)*⁵⁶ group of the whole GAP substrate and [H95](#)⁵⁷ ([loop 4](#))⁵⁸ is also optimal for small mutational changes in or reflects its compatibility with amino acid residues which stabilizes the [enediolate](#) intermediate ([GA/HPO](#))⁵⁹ activity from change in the products [scheme](#)⁶⁰ (a proton transfer [mechanism](#))⁶¹ [DHAP/G3P](#)⁶² or interconversion of these intermediates.



Closed (activated for catalysis) of optimal WT (TPI) molecular modeling PDB 1HTI_B using the human crystal structure of TPI human triosephosphate isomerase (HsTPI) conformation 1hti_b, calculated to the incidence residue Water-protein molecules and the protein cage that interacts within a hydrophobic catalytic pocket isolated and examined which coded for human triosephosphate isomerase. [EC: 5.3.1.1]....

The active flexible site loop must [open](#)⁶³ before product [release](#),⁶⁴ unliganded in trypanosomal [Tb](#)⁶⁵-[TIM](#)⁶⁶ glycerol phosphate ester to liganded [Glu167](#)⁶⁷ in the catalytic cycle and the enzymes substrate transition state between [open and closed](#)⁶⁸ to protect the substrate for the turnover of DHAP and G3P (GAP) the natural substrates, and inhibiting the formation of a [toxic](#)⁶⁹ by-product in the [absence](#)⁷⁰ of this equilibration reactions between dihydroxyacetone phosphate and glyceraldehyde 3-phosphate ([G3P](#))⁷¹ enzymes by mutations that impair biosynthesis transforming competent cells, in the presence of an [auxotrophic](#)⁷² effect with these differences generated for an inability of the host organism to synthesize an [essential](#)⁷³ compound during glycolysis in Tb-TIM. Trypanosomal-TIM is a glycolytic enzyme essential for the parasite [survival](#)⁷⁴ that causes [Chagas](#)*⁷⁵ disease, in this study [G. bellum](#)⁷⁶ from the genus related Geraniaceae and its phenolic compound are leads which generates an unstable [epimer](#)⁷⁷ of an enzyme [Geranin](#)⁷⁸ A-containing changes resulting from [ligand](#)⁷⁹ adducts in the active site to capture in addition a [source](#)⁸⁰ of [frustration](#)⁸¹ that becomes more favourable. [Glycolaldehyde](#)⁸² ([GA](#))⁸³ the simplest sugar-related molecules uptake of a proton by Glu167 preserves the small effect for inhibition by PGA (transition-state analog) [relative to](#)⁸⁴ substrate G3P, produces a triosephosphate isomerase with wild-type activity, [loop 6](#)⁸⁵ adopts the "closed" [desolvated](#)^{86, 87} conformation to [facilitate](#)⁸⁸ completion of catalysis by the formation of the > [Michaelis-Menten](#)⁸⁹ complex (on the < [micros-ms](#)⁹⁰ > time scale) utilization yields further corrected calculations to [54kD](#)*⁹¹ with corresponding (slower Kcat) motional rates Km increase are discussed in the context of the significance (Enzyme kinetics/Kcat) and may be estimated where the 'single-substrate' is locked in a protein cage [probably](#)⁹² because of an [active](#)⁹³ reaction site ([loop 6](#))⁹⁴ movement to the transition state for deprotonation; which are the on-average opened (substrate binding and release) and closed (activated for catalysis) of both monomers optimal WT (wild type) TIM conformations. [Lys-12](#)⁹⁵ < is expected to interact with both centers, where the enediol intermediate along with the catalytic [glutamate](#)⁹⁶ base and [histidine-95](#)⁹⁷ the catalytic electrophile stabilizes the [reversible](#)⁹⁸ reaction intermediate that polarizes the substrate [DHAP](#)⁹⁹ in the [Michaelis](#)¹⁰⁰ complex. Interconversion spans the [C-terminal](#)¹⁰¹ end of the [eight β](#)-

strands.¹⁰² For catalysis to occur [likley](#)¹⁰³ a low pKa value transition from DHAP - for the enolase reaction enzyme enhancement 'relative to'¹⁰⁴ the nonenzymatic reaction - (Bound [PGH](#)¹⁰⁵ - phosphoglycolohydroxamate mimics the (closed form) negative polarization (•)¹⁰⁶ [charge](#)••,¹⁰⁷ while [PGA](#)¹⁰⁸ (2-phosphoglycolate) the positively charged residues in the two active conformation sites.) is similar for the two conformers' in the [closed](#)¹⁰⁹ conformation, on [ligand](#)¹¹⁰ binding interacting with the reactive end's ([β](#))¹¹¹ the deprotonated substrate-bound structures to be protonated by a single-base (Glu-[165](#))¹¹² proton transfer^ mechanism.



Structure of human triose phosphate isomerase at the positions of introns in homologous TPI genes from a number of phylogenetically diverse species. The introns motif are identified as calculated in phylogeny. Phylogenetic trees constructed on the basis of sequence comparisons for triosephosphate isomerases analysis, TIM sequences were constructed based phylogeny with similarity, to those adopting the same structural fold of interest from different species for the taxonomic groups and the K13M mutations involvement in the [human](#) triosephosphate isomerase gene family¹¹³...

Interactions in the loop regions the combine the effects of His95 and Lys13 for Glu165 (loop [4, 1](#),¹¹⁴ and 6) are the three crucial catalytic residues in triose phosphate isomerase [all](#)¹¹⁵ form the [enediol](#) intermediate necessary for the interconversion reaction catalyzed by TIM resulting in the natural substrates G3P formation. The introns motif are identified as calculated in [phylogenic motifs](#).¹¹⁶ Poorly conserved residues as targets for [specific](#)••¹¹⁷ drug design are expected when compared to ([TPI](#))¹¹⁸ Triosephosphate isomerase (•), catalytic residues of the phylogenetic relationship pathways obtained by sequence based methods of specific key amino acids can than be calculated to the incidence residues and other TIMs which may influence the (human) HsTPI equilibrium.

Footnotes

Some Correlations are identified with Basic Punctuation or Bullet's: ^ , * and • , ••.
Triosephosphate isomerase Mar 20, 2016 [images: 7](#) – 3 MB

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