

SSIEM
ANNUAL SYMPOSIUM
ISTANBUL 2010

31 Aug -3 September 2010



Registrant : Peter Bross

Ref.ID : FUJACC-486427-103071-SSIEM2010

Abstract Session : Standard Abstract (includes Dieticians' Workshop)

Abstract Type : Oral / Poster

Abstract Title

Title Dominant negative effect of a mutation in the glutaryl-CoA de-hydrogenase gene associated with an apparently dominantly inherited form of glutaric aciduria type I

Category 20. Molecular Mechanisms

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Other Requirements

Details

None

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YES NO

Details

None noted

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A patient with suspected glutaryl-CoA dehydrogenase (GCDH) deficiency, a usually autosomal recessively inherited defect of mitochondrial amino acid metabolism, was identified by elevated glutarylcarnitine (C5DC) during neonatal screening. Further biochemical analysis of blood and urine from the proband and low GCDH activity (20% of normal mean) in cultured fibroblasts were consistent with a glutaric aciduria type I phenotype with high residual enzyme activity. Subsequent genetic analysis detected a 18 bp deletion (c.553_570del18) resulting in deletion of 6 amino acids (p.Gly185_Ser190del) in one allele of the GCDH gene and no sequence changes in the other allele. Recombinant expression of the mutant variant in *E. coli* showed that the GCDH-(p.Gly185_Ser190del) protein was expressed; however, its ability to assemble into the active tetrameric structure was severely impaired. To investigate the hypothesis that expression of the mutant allele negatively affects a co-expressed wild type allele, we engineered a prokaryotic expression system with two plasmids carrying the two GCDH variants under control of arabinose- and IPTG-inducible promoters, respectively. Cells expressing both wild type and the GCDH-(p.Gly185_Ser190del) protein displayed increased levels of total GCDH protein compared to cells expressing wild type GCDH only, but the levels of GCDH tetramer and activity were significantly decreased. These experiments suggest that the GCDH-(p.Gly185_Ser190del) protein interferes with tetramer formation of the wild type protein and are thus consistent with the notion that the presence of the GCDH-(p.Gly185_Ser190del) protein significantly reduces the formation of active GCDH enzyme from wild type monomers thus explaining the biochemical phenotype of the heterozygous patient.