Received: 8 September 2021 | Accepted: 11 November 2021

DOI: 10.1111/liv.15099

Liver INTERNATIONAL WILEY

MINI-REVIEW

Gamma-Glutamyl Transferase (γ-GT) – an old dog with new tricks?

Paul N. Brennan[1,2] | John F. Dillon[2,3] | Elliot B. Tapper[4,5]

[1]Centre for Regenerative Medicine, University of Edinburgh, Edinburgh, UK

[2]Division of Molecular and Clinical Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK

[3]NHS Tayside, Ninewells Hospital and Medical School, Dundee, UK

[4]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan, USA

[5]Gastroenterology Section, VA Ann Arbor Healthcare System, Ann Arbor, Michigan, USA

Correspondence
Paul N Brennan, Centre for Regenerative Medicine, University of Edinburgh, 5 Little France Dr., Edinburgh EH16 4UU, UK.
Email: pbrenna2@ed.ac.uk

Funding information
The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors relating to this work. PNB has received lecture honoraria from Takeda. JFD has received research grants and lecture honoraria from MSD, Abbvie, and Gilead. EBT receives funding from the National Institutes of Health through the NIDDK (1K23DK117055). EBT has served as a consultant to Novartis, Kaleido, Axcella, and Allergan, has served on advisory boards for Mallinckrodt, Rebiotix, and Bausch Health, and has received unrestricted research grants from Gilead and Valeant.

Handling Editor: Luca Valenti

Abstract

Gamma-Glutamyl Transferase (γGT) is a key transferase involved in the transpeptidation of functional gamma-glutamyl groups to various receptor moieties. It performs important roles in antioxidant defence mechanisms, particularly glutathione recycling, xenobiotic metabolism, but analogously may also have a pro-oxidant role.

γGT is very sensitive for the diagnosis of liver injury, although it has poor specificity for particular aetiologies. It has been used to reflect temporal changes as a form of monitoring depending on aetiology.

Given its cellular role in antioxidant function, it has been investigated as a surrogate biomarker of oxidative stress. It has also been found to be a predictor of mortality across a spectra of non-hepatic disease pathologies, from metabolic and cardiovascular risk to chronic kidney disease and neoplasia. Similarly, it also remains of interest to the insurance industry given an apparent ability to predict mortality, in addition to a historical interest from law enforcement as a marker of chronic alcohol ingestion.

Here, we review some of the unique characteristics of this important enzyme, previously considered as a mere specific marker of liver dysfunction, but now with clear extra-hepatic implications and novel applications and utility.

KEYWORDS
cholestasis, gamma-glutamyl transferase (γGT), glutamyl cycle, glutathione, prognostication

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transferase; ArLD, alcohol-related liver disease; AST, aspartate transaminase; GSH, glutathione; GSSH, glutathione disulfide; hsCRP, high-sensitivity c-reactive protein; LTC4, leukotriene C_4; MetS, metabolic syndrome; ROS, reactive oxygen species; γ-GC synthetase, γ-glu-cysH synthetase; γGT, gamma-glutamyl transferase.

© 2021 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

1 | INTRODUCTION

Gamma-glutamyl transferase (γGT) is a key transferase involved in the transpeptidation of functional gamma-glutamyl groups to receptor molecules. Biologically, γGT is very sensitive for the diagnosis of liver injury, although enzyme induction can lead to loss of specificity for damage and it has poor specificity for particular aetiologies. More recent evidence has suggested that it also plays an important role in antioxidant defence and xenobiotic metabolism, as well as offering tantalising associations across a continuum of disease states including cardiovascular disease and cancer. In this mini-review, we explore the structure and function of γGT, some of the historic applications of γGT, as well as its evolution beyond a simple marker of cholestasis. We have summarised some of the key aspects of γGT's unique physiology in Table 1, but we are keen to suggest readers may wish to access a number of additional insightful recent reviews on the topic.[1,2]

Key Points

- An important enzyme for transpeptidation
- Sensitive biomarker for many liver pathologies
- Not specific for any individual liver disease or of direct liver injury
- γGT increases in response to oxidative stress and glutathione depletion
- Indirect biomarker for cardiovascular and metabolic risk

2 | γGT BIOLOGY

Gamma-glutamyl transferase (γGT) is a glycosylated microsomal enzyme that catalyses the transfer of a gamma-glutamyl group to acceptor peptides and L-amino acids, particularly cysteine.[3,4] γGT is relatively ubiquitously expressed in human tissue and cell types, except within myocytes, and with some variability in expression profiles between cell types. It is most abundant on the luminal surfaces of cells with secretory or absorptive properties but can also be found on the basolateral surfaces of renal epithelial cells.[5] Alternate gamma-glutamyl targets include γGT1 substrates, including Glutathione di-sulfide (GSSH), leukotriene C4 (LTC4)[6] and *S*-nitroso-glutathione[7] and GSH-xenobiotic adducts. As such, γGT plays a prominent role in the homeostasis of glutathione production and recycling, inflammatory and nitric oxide signalling, as well as oxidative stress amelioration.

3 | γGT AND GLUTATHIONE

Glutathione exists as a tripeptide, γ-L-glutamyl-L-cysteinyl glycine, present in all mammalian tissues, with the highest intracellular concentrations found in the liver.[8] Here, as the most abundant non-protein thiol, it is responsible for oxidative stress mitigation. It exists in a thiol-reduced state (GSH), as the most prominent form (>98% of total), and as a disulphide-oxidised (GSSG) variant.[9] Within eukaryotic cells, GSH resides principally in the cytosol (80%-85%), with 10%-15% in the mitochondria, whilst the endoplasmic reticulum has a minute reservoir of GSH. GSH principally is derived from hepatocytes, with most being excreted into plasma and bile.[10] GSH is unique in its structure whereby the gamma-carboxyl portion of glutamate links to cysteine, rather than traditional α-carboxyl dipeptide formation. It is this unique characteristic that means this bond can only be hydrolysed by γGT.

TABLE 1 Physiological associations of γGT in disease

Organ/Tissue system	Physiological associations of γGT
Cardiovascular	• Evidence of co-localisation of γGT with typical foam cells and CD68+ macrophages, in addition to LDL in atherosclerotic deposits. • Increased incidence of congestive cardiac failure in those with higher serum values of γGT. • May be reflective of adaptative sequelae post-myocardial infarct
Lung	• Incompletely understood • γGT produced by type II pneumocytes and secreted into epithelial lining fluids (ELF); which may have a pathogenic effect. • Increased levels of ELF γGT are found in cystic fibrosis (CF) and probably reflect secretion from neutrophils within chronically inflamed airways.
Neoplasia	• Biologically plausible that γGT expressive tumours would have survival advantage in mitigating levels of oxidative stress in high cellular turnover state • γGT may protect certain cell lines from pro-oxidant chemotherapeutic regimes
Neurological	• Animal models of inflammatory CNS disease states implicate γGT and GSH pathways • γGT appears to have pro-oxidant signature, whereby blockade appears to ameliorate inflammatory effect.
Skeletal	• May behave as a damage-associated molecular pattern (DAMP), inducing RANKL and causing osteoclastogenesis
Renal	• Ischaemia/perfusion deficit to renal tubules results in increased γGT activity and reduced GSH concentrations. • Injurious effect of γGT-related cell toxicity is probably related to membrane lipid peroxidation.

Another fundamental aspect of GSH homeostasis relates to cysteine cycling, which is required for de-novo intracellular GSH synthesis, a process enzymatically facilitated by γGT. γGT also coordinates the transfer of the gamma-glutamyl moiety of glutathione S-compounded to mercapturic acid, thereby releasing cysteinyl glycine.[11] Importantly, cysteinyl glycine may interact with free iron species, thereby inducing the Fenton reaction and consequent superoxide production, a potent ROS, which may have a pathogenic role in a number of human diseases.[1]

4 | γGT INDUCTION

It has been consistently reported that serum γGT increases in patients taking anticonvulsant drugs. A number of older anticonvulsant therapies are well recognised as enzyme-inducing moieties including phenytoin and phenobarbitone, which are again associated with deranged serum γGT levels. There appears to be a synergistic effect on the modulation of alcohol and ingestion of phenytoin in incrementing serum γGT levels. In another study by Herzberg,[12] 40% of patients exposed to commonly used medications including α-methyldopa, quinidine, digoxin, diazepam and furosemide demonstrated a sustained rise in γGT which suggests induction of hepatic microsomal enzymes by these commonly prescribed compounds. Evidence extrapolated from some studies demonstrated that serum γGT incremented following a reduction in hepatic glutathione secondary to drug induction.[13] This would indirectly support the supposition that γGT mediates hepatic glutathione homeostasis. Interestingly, phenobarbital (a potent enzyme inducer) paradoxically increases both γGT and glutathione. However, a trial combination of cysteine and phenobarbital resulted in a nonsignificant decrease in γGT relative to control. This infers that γGT undergoes induction when enzyme-inducing drugs decimate hepatic glutathione levels; γGT induction may therefore subsequently result in higher than normal glutathione as a consequence. As a corollary, if glutathione does not fall, γGT is not induced, which provides important insight into how this might be exploited translationally.

5 | γ-GLUTAMYL CYCLE

The γ-glutamyl cycle comprises six enzymatically catalysed reactions that maintain glutathione homeostasis, which is summarised in Figure 1. Within the gamma-glutamyl cycle, inherited genetic defects have been described in four enzymes: γ-glu-cysH Synthetase (γ-GC synthetase), GSH synthetase, 5-oxoprolinase and γ-glutamyl transpeptidase.[14] Impaired GSH-synthetase and γ-GC synthetase functionality cause relative GSH deficiency. GSH synthetase deficiency is characterised by excess production of 5-oxoproline, which is manifested biologically as metabolic acidosis, 5-oxoprolinuria, haemolytic anaemia and neuromuscular disorders.[15,16] In patients with isolated γ-GC synthetase deficiency, haemolytic anaemia predominates, with or without hepatosplenomegaly. Importantly,

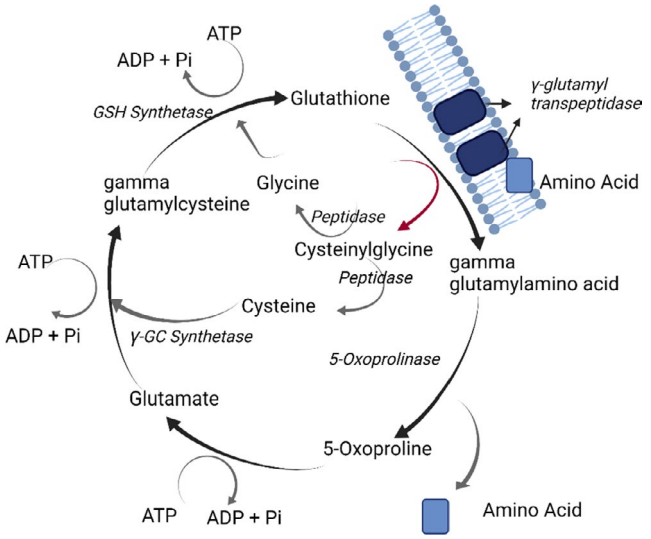

FIGURE 1 Overview of gamma-glutamyl cycle

isolated erythrocytic GSH-synthetase deficiency results in haemolytic anaemia but not 5-oxoprolinuria. Treatment is principally focused on acidosis correction, high concentrate supplementation of vitamins C and E and avoidance of precipitating haemolytic crises.[14]

6 | γGT AS A LIVER FUNCTION TEST

γGT has been adopted as a liver function test since the 1960s. A seminal paper by Szczeklik[16] demonstrated mean values in differing aetiologies of liver disease, highlighting variation in serum γGT over time, and contrasting with other enzymatic trends including aldolase, phosphohexose isomerase and aspartate and alanine transferases. γGT demonstrates high sensitivity for liver damage, being abnormal in the majority of patients with liver disease irrespective of pathogenesis, however, extremes of upper limits are most commonly seen in patients with cholestasis. Conversely, there is an inherent lack of specificity in γGT, especially given other contributing diseases and conditions including pancreatitis, diabetes mellitus, obesity, excessive alcohol, enzyme-inducing drugs.[13] An interesting observation in patients with chronic active hepatitis, was that γGT tended to normalisation in remission and in those undergoing treatment, however, this never reached statistical significance but may provide a useful insight into treatment response.[17]

Importantly, while the normal reference range for γGT remains relatively consistent across age, there is inherent male–female variation in serum concentrations. Additionally, there are a number of demographic, physiological and inducible factors which affect γGT so there is heterogeneity in defining the reference interval. The standard reference thresholds for γGT in adult humans as recommended by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) are presented in Table 2.18

There have been incident case reports of isolated high serum gamma-glutamyl transferase levels in the absence of other

TABLE 2 Proposed IFCC γGT standard ranges

Gender	Upper reference limit (U/l)	90% confidence intervals (U/l)
Women	38	37-39
Men	55	53-58

predisposing factors within an extended Italian familial series. This condition has an autosomal dominant mode of inheritance and does not confer any disease-specific risks.[3]

Conversely, there is a spectrum of related cholestatic conditions which manifest as low – normal γGT, collectively termed *low gamma-GT familial intrahepatic cholestasis*, with disease severity which may range from mild to severe.[19] These forms of inherited cholestatic disease appear to be inherited in an autosomal recessive manner. There are a number of other disease variants within this continuum, however, it is beyond the scope of this article to cover in more detail.

7 | DIAGNOSTIC UTILITY IN LIVER DISEASE

After perfecting the methodology for measuring serum γGT,[20] Orlowski evaluated the diagnostic potential of γGT in ~100 conditions felt probably to alter serum levels.[21] In a mixed cohort, patients with alcohol-related liver disease (ArLD), viral hepatitis, carcinomatosis and malabsorption were compared with those with no hepatic or renal pathology. γGT was markedly elevated in hepatobiliary disease as well as ArLD and carcinomatosis, whilst transaminases and alkaline phosphate remained within normal limits.[22] The authors concluded that serum γGT may therefore be useful in the clinical assessment of ArLD and primary and secondary forms of hepatic neoplasia.

Whilst γGT is relatively ubiquitously expressed across tissues as previously described, its principle utility has been a part of the extended panel of liver function tests, including as a composite of a number of non-invasive algorithms of liver fibrosis assessment.[23] It is well established as a very sensitive marker of hepatobiliary disease, with lower specificity than aspartate aminotransferase (AST) and alanine aminotransferase (ALT) for diagnosis of liver disease,[24] however, it is more sensitive than ALT and AST in anicteric, non-alcohol related parenchymal disease. Despite the introduction of a standardised measurement methodology for γGT, there have not been more contemporaneous studies to determine if new diagnostic reference thresholds should be derived. A broad clinical approach to determining the cause of an elevated γGT is provided in Figure 2.

8 | ALCOHOL-RELATED LIVER DISEASE

In 1976, the Blennerhassett Committee recommended the identification of high-risk individuals among those persons convicted of driving under the influence of alcohol.[25] There was increasing interest in prospectively identifying high-risk offenders and supporting assessment by clinicians from the Department of Transport in determining evidence of alcohol dependence. There was widespread enthusiasm in the clinical utility of γGT as a prospective biomarker of problem alcohol ingestion. Given its enzymatic activity is not considerably raised following a single bout of drinking, it was seen to represent an obvious candidate.[26]

This premise was applied across a number of cohort studies in Tayside, Scotland. A quarter of drivers convicted of drink driving had abnormal γGT activity at time of arrest. Dunbar and colleagues surmised that overall γGT activity demonstrated that blood ethanol level in isolation is poorly predictive of wider-alcohol related issues among drunk drivers (other than those associated with driving under the influence). Serial γGT levels also suggested that up to one-third of these persons may be problem drinkers.[27] They did, however, note a strong association between raised γGT activity and accidents in older offenders. Among young drivers, the traditional association between blood alcohol concentration and accidents was strongly associated. Focusing solely on measured blood alcohol concentration may therefore disguise a relation between chronic, rather than acute, alcohol abuse and accidents.[28] Whilst γGT proved very sensitive for chronic alcohol use, it's specificity was relatively poor, with 17% of persons having abnormal levels in the context of no identifiable cause. Despite its relative sensitivity, these limitations continue to limit γGT as a reliable and definitive biomarker of alcohol-related disease. Given the historical nature of these studies, there would probably be significant interest in revisiting the wider applicability of γGT in chronic alcohol use, especially where it might be combined with novel serum and urine alcohol metabolites.

9 | CHOLESTASIS

γGT has been reported as a marker of biliary disease, in part owing to its association with alkaline phosphatase, another indirect biochemical marker of cholestasis. This association was demonstrated by Whitfield and colleagues[29] in a large cohort of patients with liver disease and healthy controls. Average serum activities of γGT and alkaline phosphatase (ALP) were three to six times greater in biliary disease compared to parenchymal aetiologies. In mixed parenchymal and biliary diseases, the ratios of mean γGT to ALP were approximately equivalent. Within this cohort, they also noted that γGT elevations often resolved corresponding to overall liver recovery, whether primary biliary or hepatocyte in origin.

Similar findings were subsequently reported by Cushieri and Baker,[17] whereby patients with extrahepatic biliary obstruction had significant elevations of γGT and ALP, which resolved on the removal of the offending lesion. They noted an appreciable lag time in reduction of γGT, particularly in cases of significant jaundice pre-procedure.

10 | GENERAL PROGNOSTICATION

Beyond the interest in using γGT to identify those at risk of alcohol-related vehicle accidents, there is increasing curiosity around the utility of γGT in risk stratification relating to cardiovascular disease

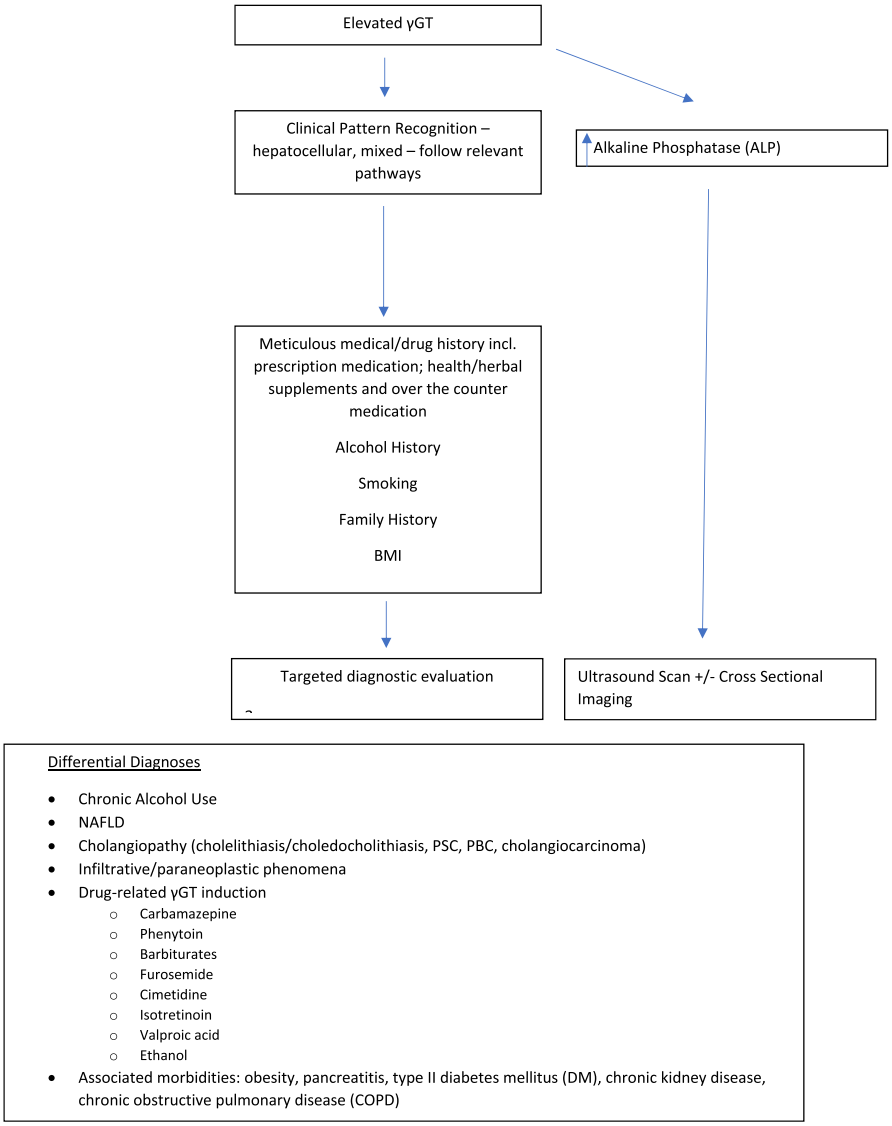

FIGURE 2 Suggested approach to elevated γGT

and malignancy. Clearly, this is of significant interest to clinicians and healthcare providers, however, additionally, it is of enormous interest to the insurance and life assurance industries.

Evidence from a number of epidemiological studies suggest that increased serum levels of γGT are associated with increased cardiovascular risk, including the addition of the various components of the metabolic syndrome (metS). Similarly, novel cardiovascular predictive determinants including hsCRP, fibrinogen and F2-isoprostanes also demonstrate a strong correlation with γGT.[30]

There has been significant dissonance regarding the mortality effect seen in those with increased γGT in cardiovascular disease. Parallel epidemiological studies were insufficient to delineate whether serum γGT simply reflected increased cardiovascular disease risk determinants, or, whether γGT had prognostic propensity beyond these individual risk strata.[30] The Framingham heart study was developed from the Framingham Offspring Study in 1971. Within this cohort, elevated γGT was associated with fatal and non-fatal incident cardiovascular events and predicted the development of the metS. This association was apparent even on correcting for additional variables including CRP, and additional risk factors when temporally modelled as covariates including fasting glucose and the other individual components of the metS.

Interestingly, moderate to high levels of serum γGT (50th-90th percentiles) has been demonstrated to significantly associate with the incidence of heart failure in a Finnish cohort.[31] Similarly, γGT appears to have a mechanistic role in reversing the down-regulation of K+ channels in the myocardium post-myocardial infarct and further scavenging ROS, which may aid cardiac remodelling.

Another area of increased interest is individual cancer risk stratification. Whilst there are relative predictors for cardiovascular disease (metabolic syndrome, hyperlipidaemia and diabetes), cancer risk profiling usually relies on clinical or family history and is generally less robust by underwriting standards. A number of clinical studies have attempted to model for cancer risk using laboratory markers and physical attributes, however, they often only demonstrate univariate risk factors. A large study by Palmier and Lanzrath[32] utilising 1.25 million insurance applicants who were matched to claims records, demonstrated that γGT positively

correlated with cancer mortality across most modelled ranges, albeit the apparent risk appeared to plateau at higher values. Alkaline phosphatase levels and relative risk appear to positively correlate with γGT in this cohort.

11 | CONCLUSION

γGT is an enzyme of many parts, vital to maintaining oxidative stress and signalling homeostasis. Once a mainstay of the liver function test panel, which in many areas it was discontinued as a cost-saving measure. It is now making a resurgence as a sensitive gateway test to early detection of chronic liver disease and as a prognostic marker for cardiovascular disease. These novel insights clearly represent exciting new avenues of research for this figurative 'old dog'.

CONFLICTS OF INTEREST

The authors have no competing interests relating to this work.

AUTHOR CONTRIBUTIONS

All authors reviewed the literature. PNB prepared the initial manuscript draft and all revisions. JFD and EBT revised the manuscript critically for important intellectual content. All authors approved the final draft of the manuscript.

PATIENT CONSENT FOR PUBLICATION

Not required.

PROVENANCE AND PEER REVIEW

Commissioned, externally peer-reviewed.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ORCID

Paul N. Brennan https://orcid.org/0000-0001-8368-1478
John F. Dillon https://orcid.org/0000-0002-2164-4476
Elliot B. Tapper https://orcid.org/0000-0002-0839-1515

REFERENCES

1. Koenig G, Seneff S. Gamma-Glutamyltransferase: a predictive biomarker of cellular antioxidant inadequacy and disease risk. *Dis Markers* 2015;2015:1-18. https://pmc/articles/PMC4620378/
2. Corti A, Belcastro E, Dominici S, Maellaro E, Pompella A. The dark side of gamma-glutamyltransferase (GGT): pathogenic effects of an 'antioxidant' enzyme. *Free Radic Biol Med*. 2020;160:807-819.
3. Bibas M, Zampa G, Procopio A, Guaitolini R. High serum Gamma-Glutamyltransferase concentrations in a family. *N Engl J Med*. 1994;330(25):1832-1833. 10.1056/NEJM199406233302518
4. Dalle-Donne I, Rossi R, Giustarini D, Colombo R, Milzani A. S-glutathionylation in protein redox regulation. *Free Radic Biol Med*. 2007;43(6):883-898. https://pubmed.ncbi.nlm.nih.gov/17697933/
5. Lieberman MW, Barrios R, Carter BZ, et al. γ-Glutamyl transpeptidase: what does the organization and expression of a multipromoter gene tell us about its functions? *Am J Pathol*. 1995;147(5):1175-1185. https://pmc/articles/PMC1869519/?report=abstract
6. Mayatepek E, Okun JG, Meissner T, et al. Synthesis and metabolism of leukotrienes in γ-glutamyl transpeptidase deficiency. *J Lipid Res*. 2004;45(5):900-904.
7. Angeli V, Tacito A, Paolicchi A, et al. A kinetic study of gamma-glutamyltransferase (GGT)-mediated S-nitrosoglutathione catabolism. *Arch Biochem Biophys*. 2009;481(2):191-196.
8. Lu SC. Glutathione synthesis. *Biochim Biophys Acta*. 2013;1830(5):3143-3153.
9. Kaplowitz N, Aw Y, Ookhtens M. The regulation of hepatic glutathione I. *Ann Rev Pharmacol Toxicol* 1985;25(1):715-744. www.annualreviews.org
10. Ookhtens M, Kaplowitz N. Role of the liver in interorgan homeostasis of glutathione and cyst(e)ine. *Semin Liver Dis*. 2008;18(04):313-329. doi:10.1055/s-2007-1007167
11. Zhang H, Forman HJ, Choi J. Gamma-glutamyl transpeptidase in glutathione biosynthesis. *Meth Enzymol* 2005;401:468-483. https://pubmed.ncbi.nlm.nih.gov/16399403/
12. Herzberg M, Fishel B, Wiener MH Hepatic microsomal enzyme induction and its evaluation in a clinical laboratory. *Isr J Med Sci*. 1977;13(5):471-476. https://europepmc.org/article/med/17578
13. Whitfield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci*. 2001;38(4):263-355. https://pubmed.ncbi.nlm.nih.gov/11563810/
14. Ristoff E, Larsson A. Patients with genetic defects in the γ-glutamyl cycle. *Chem Biol Interact*. 1998;111–112:113-121. https://pubmed.ncbi.nlm.nih.gov/9679548/
15. Beutler E, Moroose R, Kramer L, Gelbart T, Forman L. Gamma-Glutamylcysteine synthetase deficiency and hemolytic anemia. *Blood*. 1990;75(1):271-273.
16. Szczeklik E, Orlowski M, Szewczuk A. Serum γ-Glutamyl transpeptidase activity in liver disease. *Gastroenterology*. 1961;41(4):353-359.
17. Cuschieri A, Baker PR. Gamma-Glutamyl-Transpeptidase in Hepato-Biliary Disease – value as an enzymatic liver function test. *Br J Exp Pathol* 1974;55(2):110. https://pmc/articles/PMC2072525/?report=abstract
18. Gerhard S, Bonora R, Ceriotti F, et al. IFCC primary reference procedures for the measurement of catalytic activity concentrations of enzymes at 37 degrees C. International Federation of Clinical Chemistry and Laboratory Medicine. Part 5. Reference procedure for the measurement of catalytic concentration of aspartate aminotransferase. *Clin Chem Lab Med* 2002;40(7):725-733. https://pubmed.ncbi.nlm.nih.gov/12241022/
19. Thompson R, Strautnieks S. BSEP: function and role in progressive familial intrahepatic cholestasis. *Semin Liver Dis* 2001;21(4):545-550. https://pubmed.ncbi.nlm.nih.gov/11745042/
20. Orlowski M, Szewczuk A. Colorimetric determination of gamma-glutamyl transpeptidase activity in human serum and tissues with synthetic substrates. *Acta Biochim Pol* 1961;8:189-200. https://europepmc.org/article/med/13731220
21. Orlowski M. The role of gamma-glutamyl transpeptidase in the internal diseases clinic. *Arch Immunol Ther Experiment*. 1963;11:1-61. https://pubmed.ncbi.nlm.nih.gov/14062968/
22. Zein M, Discombe G. Serum gamma-glutamyl transpeptidase as a diagnostic aid. *Lancet*. 1970;296(7676):748-750. https://pubmed.ncbi.nlm.nih.gov/4195980/
23. Dillon JF, Miller MH. Gamma glutamyl transferase 'to be or not to be' a liver function test? *Ann Clin Biochem*. 2016;53(6):629-631. https://journals.sagepub.com/doi/full/10.1177/0004563216659887
24. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med*. 2009;342(17):1266-1271. doi:10.1056/NEJM200004273421707

25. Departmental Committee. Drinking drivers and the law. *BMJ*, London 1976. http://www.bmj.com/
26. Clark PM, Kricka LJ, Zaman S. Drivers, binge drinking, and gamma-glutamyltranspeptidase. *BMJ*. 1982;285(6355):1656-1657. https://pubmed.ncbi.nlm.nih.gov/6128053/
27. Problem drinking among drunk drivers. *BMJ (Clin Res Ed)*. 1983;286(6374):1319. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1547610/
28. Dunbar JA, Ogston SA, Ritchie A, Devgun MS, Hagart J, Martin BT. Are problem drinkers dangerous drivers? An investigation of arrest for drinking and driving, serum gamma glutamyltranspeptidase activities, blood alcohol concentrations, and road traffic accidents: the Tayside Safe Driving Project. *BMJ (Clin Res Ed)*. 1985;290(6471):827. https://pmc/articles/PMC1418594/?report=abstract
29. Whitfield JB, Pounder RE, Neale G, Moss DW. Serum γ-glutamyl transpeptidase activity in liver disease. *Gut*. 1972;13(9):702-708. https://gut.bmj.com/content/13/9/702
30. Lee DS, Evans JC, Robins SJ, et al. Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol*. 2007;27(1):127-133. https://pubmed.ncbi.nlm.nih.gov/17095717/
31. Wang Y, Tuomilehto J, Jousilahti P, et al. Serum γ-glutamyltransferase and the risk of heart failure in men and women in Finland. *Heart*. 2013;99(3):163-167. https://heart.bmj.com/content/99/3/163
32. Palmier J, Lanzrath BJ Laboratory and biometric predictors of cancer-related mortality in an insured population. *J Insur Med (New York, NY)*. 2012;43(3):162-168. https://europepmc.org/article/med/23451617

How to cite this article: Brennan PN, Dillon JF, Tapper EB. Gamma-Glutamyl Transferase (γ-GT) – an old dog with new tricks? *Liver Int*. 2022;42:9–15. doi:10.1111/liv.15099