



REVIEW ARTICLE

Glucose 6 phosphatase dehydrogenase (G6PD) and neurodegenerative disorders: Mapping diagnostic and therapeutic opportunities

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KEYWORDS

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Abstract Glucose 6 phosphate dehydrogenase (G6PD) is a key and rate limiting enzyme in the pentose phosphate pathway (PPP). The physiological significance of enzyme is providing reduced energy to specific cells like erythrocyte by maintaining co-enzyme nicotinamide adenine dinucleotide phosphate (NADPH). There are preponderance research findings that demonstrate the enzyme (G6PD) role in the energy balance, and it is associated with blood-related diseases and disorders, primarily the anemia resulted from G6PD deficiency. The X-linked genetic deficiency of G6PD and associated non-immune hemolytic anemia have been studied widely across the globe. Recent advancement in biology, more precisely neuroscience has revealed that G6PD is centrally involved in many neurological and neurodegenerative disorders. The neuroprotective role of the enzyme (G6PD) has also been established, as well as the potential of G6PD in oxidative damage and the Reactive Oxygen Species (ROS) produced in cerebral ischemia. Though G6PD deficiency remains a global health issue, however, a paradigm shift in research focusing the potential of the enzyme in neurological and neurodegenerative disorders will surely open a new avenue in diagnostics and enzyme therapeutics. Here, in this study, more emphasis was made on exploring the role of G6PD in neurological and inflammatory disorders as well as non-immune hemolytic anemia, thus providing diagnostic and therapeutic opportunities.

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Abbreviations: MS, multiples sclerosis; DOPA, L-3, 4-dihydroxyphenylalanine; G6 PD, glucose 6 phosphatase dehydrogenase; PPP, pentose phosphate pathway; EC, enzyme commission; ROS, reactive oxygen species; pQ, poly-glutamine; MND, motor neuron disease; RBCs, red blood cells; ALS, Amyotrophic lateral sclerosis.

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Introduction

The enzymes are the most versatile bio-molecules in biological world with a precise affinity for their substrate.¹ However, there is a growing belief that these molecules can also work in many prospects referred as enzyme promiscuity.² There is preponderant research data suggesting the diagnostic and therapeutic potential of these bio-molecules.^{3,4} These molecules are associated with various disorders including cancer, inflammation, blood vascular disorder and much more.⁵⁻⁷ Enzyme based therapeutics are considered as one of the most effective and advanced area of modern medicine available for the management of various life threatening diseases and disorders.⁸⁻¹⁰ In physiological milieu, harnessed energy and its consumption remain in a dynamic balance, which further defines tissue homeostasis.¹¹ Every living being possesses several bio-molecules playing a crucial role in maintaining energy balance.^{12,13} The complex metabolic pathways associated with the harnessing of energy in the form of energy-rich molecules such as ATP, NADPH and FADH are governed by many enzymes^{14,15} (see Figs. 1 and 2).

These enzymes are basal proteins and are expressed constitutively. The abnormal expression and altered enzyme activity alone or both result in an imbalance of energy cycle, which is the onset of various metabolic diseases and disorders.¹⁶ The key energy harnessing pathways

such as glycolysis, pentose phosphate pathways, Krebs cycle (tricarboxylic acid) and electron transport System (ETS) are comprised of a group of complex enzymes. Among these enzymes, many of them are rate limiting, and they centrally regulate a particular metabolic cascade.¹⁷ Hence, if a critical enzyme is disabled, or the control mechanism for a metabolic pathway has been affected, it will result in the onset of diseases/disorders. Over last few decades; researchers worldwide have characterized a number of enzymes associated with numerous metabolic disorders.¹⁸ Among these enzymes, G6PD associated with hemolytic anemia has been studied enormously over last few decades.¹⁹ Here, the current was a study designed to map diagnostic and therapeutic opportunities of G6PD associated with hemolytic anemia.

G6PD

G6PD (EC 1.1.1.49) is critical to the maintenance of NADPH pool and redox homeostasis in the health individual.²⁰ The enzyme acts as a classical oxidoreductase, if it is acetylated by ELP3 at Lys-403, the acetylation would inhibit its homodimerization and enzyme activity; if it is deacetylated by SIRT2 at Lys-403, the deacetylation would stimulate its enzyme activity.²¹ G6PD catalyzes the synthesis of D-ribose 5-phosphate from D-glucose 6-phosphate (oxidative

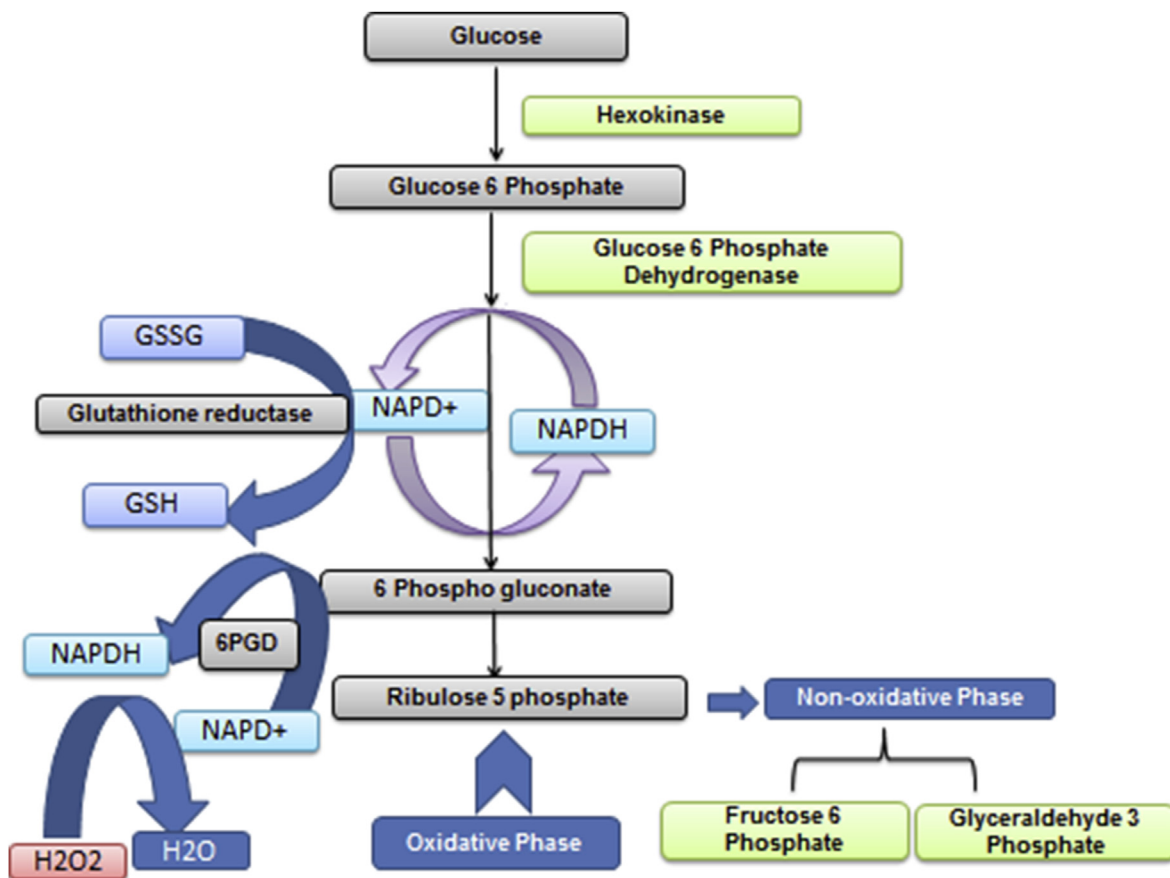


Figure 1 Schematic representation of the involvement of G6PD in energy harnessing and as an antioxidant. The enzyme acts differently in oxidative and nonoxidative phase with different outputs.

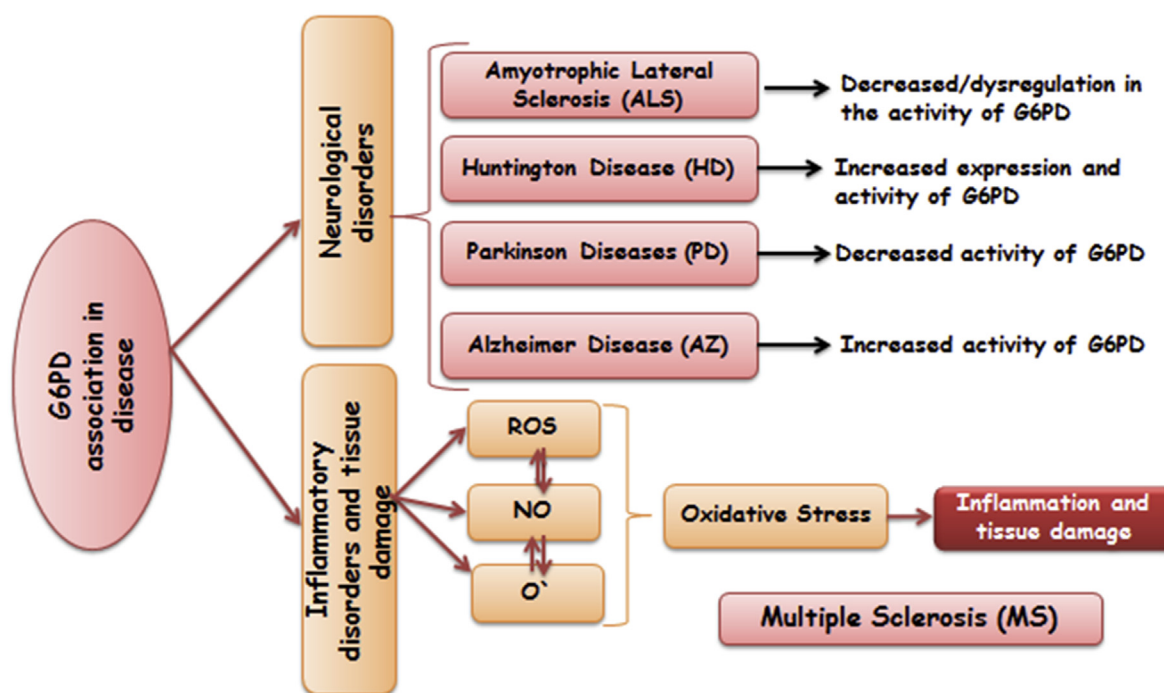


Figure 2 Schematic representation of the role of G6PD in various inflammatory and neurodegenerative disorders. The enzyme G6PD is associated with several neurodegenerative disorders directly and indirectly as well.

stage). The frequent mutation in the gene encoding G6PD at different sites blocks binding affinity to its native substrate and limits production and synthesis of D-ribulose 5-phosphate.²² The Molecular weight of a complete, mature enzyme is 59.25 kDa with an isoelectric point: 6.39 encoded by G6PD gene lies as two distinct isoforms. The enzyme is highly susceptible for the phosphorylation and is believed to be one of the major reasons for the loss of enzyme activity leading to hemolytic anemia.²³ Besides the hemolytic anemia, the G6PD is associated with a different number of pathological events. It has been widely reported that the G6PD deficiency alters the redox homeostasis, and affects dysfunctional cell growth and signaling, anomalous embryonic development, and also changes the susceptibility to infection.²⁴

G6PD based hemolytic anemia affects more than 500 million people worldwide with a gene frequency nearly 0.5. G6PD deficiency is a genetic disorder that occurs most often in males.²⁵ The work carried out by Persico et al. and Takizawa et al. in 1986 have identified and successfully cloned G6PD gene independently.^{26,27} The G6PD gene is located on the long arm of the X chromosome (Xq28), and consists of 13 exons. G6PD locus is thought to be one of the most polymorphic loci among humans with almost 300 allelic variants reported. The G6PD enzyme monomer consists of 515 residues with over 59 kDa molecular weight. It was reported that the enzymatically active form of G6PD is either a dimer or a tetramer of a single polypeptide subunit according to cellular pH.²⁸ This condition mainly affects red blood cells (RBCs), which carry oxygen from the lungs to tissues throughout the body. In affected individuals, a defect in the enzyme called G6PD causes RBCs break down prematurely.²⁹ This destruction of RBCs is called hemolysis. Further, G6PD is also a significant cause of

mild to severe jaundice in newborns. Although most affected individuals are asymptomatic, exposure to oxidative stresses such as certain drugs or infection, can elicit acute hemolysis.³⁰

G6PD is a ubiquitously expressed enzyme that has a housekeeping role in all cells and it is particularly critical to the integrity and function of RBCs.³¹ The G6PD gene has many mutant alleles, which entail a decrease in enzyme activity, expressing the G6PD deficient phenotype.³² This trait is widespread in many human populations to whom several of the underlying mutant alleles present at variable polymorphic frequencies. G6PD deficiency selectively affects RBCs for two reasons. First, most known mutations cause a decreased stability of the enzyme, and since these cells cannot synthesize proteins, the enzyme level decreases as cells age during their 120 days lifespan in circulation.³³ Second, RBCs are exquisitely susceptible to oxidative stress from exogenous oxidizing agents in the blood as well as the oxygen radicals continuously generated as hemoglobin cycles between its deoxygenated and oxygenated forms.³⁴ When G6PD activity is deficient, they have a diminished ability to withstand stress, and therefore risks destruction (hemolysis).

G6PD and neurological (neurodegenerative) disorders

Another role of G6PD has been seen in neurological disorders. However, this enzyme affects differently to neurological disorders. Differential level of G6PD in particular disorder regulates the severity and decides further deterioration or prevention. Though the extensive role of G6PD in neurological disorders remains poorly explored, here, we

are presenting a descriptive analysis of current information.

Amyotrophic lateral sclerosis (ALS)

ALS, also known as motor neuron disease (MND) is a rare group of neurodegenerative disease that occurs due to the death of neurons controlling voluntary muscles. Messages from the motor neurons in the brain (upper motor neurons) are transmitted to neurons in the spinal cord (lower motor neurons) and from the spinal cord to the muscles. During ALS, upper and lower motor neurons undergo degeneration and thus fail to deliver coordination messages to muscles. This ultimately leads to progressively weakening muscle, muscle atrophy, and twitching. Eventually, the brain stops initiating and controlling voluntary muscle movements, and the ALS patients fail to do day-to-day activities such as eating, drinking, speaking, walking and even breathing. ALS can occur due to several reasons including enzymatic imbalance, and one of them is deregulated function of G6PD. In patients with ALS, levels and activities of G6PD were low, and their erythrocytes were correlated with increased lipid peroxidation in these cells. The level of G6PD is inversely correlated with the extent of lipid peroxidation.³⁵ However, the activity of G6PD was normal in posterior root ganglions of the spinal cords in patients suffering from ALS.³⁶ In spite of the fact that G6PD is involved in ALS, the extensive role of G6PD in generation and persistence of this disease is not much explored.

Huntington disease (HD)

This is a genetic disorder and can be inherited to several generations. This disease is named after the malfunction of a cellular protein called Huntingtin. The specific function of huntingtin has still not been assigned, however, this protein is important in brain-body development, as an absence of this leads to death in mice. Usually, Huntingtin is composed of poly-glutamine (pQ) repeats, wherein insertion of less than 36 pQ is considered to be protective. However, an enhanced insertion of poly-glutamine (pQ) residues in the Huntingtin protein causes malfunction of this protein and results in motor neuron dysfunction and cognitive disorders known as Huntington disease. Overexpression of G6PD in the *Drosophila* model of HD increases the lifespan of the flies by rescuing them from eye neuro-degeneration and locomotory deficits,³⁷ which proves the importance of glucose metabolism and G6PD in preventing HD. Similarly, the cybrid made with cells isolated from HD patients showed a decrease in G6PD activity with a decreased rate of PPP pathway³⁸; however, in few cases, the RBCs isolated from HD patients showed an increase in G6PD activities.³⁹ The role of G6PD in treating HD is still debatable, and it needs extensive research for using G6PD as a therapeutic measure for this disease.

Parkinson disease (PD)

PD is a chronic degeneration of central nervous system that affects the locomotion controlling neurons. Apart from

developing movement problems, a PD patient also develops neuropsychiatric disorders related to mood, cognition, and behavior. Genetic factors play a major role in the development of PD; however, in few cases, environmental factors also play a role. In few studies, the chronic degeneration of neurons in PD has been associated with deregulated glucose metabolism and oxidative stress. Unlike many another cell types of the body, neurons prefer to metabolize glucose from PPP pathway to maintain their anti-oxidant state. G6PD is a very important enzyme of this pathway, which acts as an anti-oxidant enzyme and helps protect neurons from oxidative stress. In PD patients, RBCs undergo oxidative damage due to decreased activity of anti-oxidant enzyme G6PD, which could be one of the possibilities of neuro-degeneration in PD patients.⁴⁰ A study of human brain samples isolated from autopsied PD patients showed a reduced level of G6PD in the cerebellum of both early and late stage PD patients, whereas in the putamen (limbs controlling structure in the brain) of only early stage PD patients.⁴¹ In contrast, the production of NADPH was high only in disease-affected areas of late stage PD, but not in early stage PD⁴¹. Interestingly, the G6PD level was unchanged in RBCs and Leukocytes of PD patients from different ethnic origin in comparison to their healthy controls.⁴²

Alzheimer disease (AD)

Similar to PD, Alzheimer's disease is also an outcome of chronic degeneration of neurons. However, unlike PD, the patients suffering from AD faces severe memory loss as they age. The neuro-degeneration happens due to the uncontrolled accumulation of amyloid- β peptides ($A\beta$) in the brain, which disrupts the calcium-ion homeostasis and induces cellular apoptosis. The accumulation of $A\beta$ also interferes with glucose metabolism and glucose uptake by the neurons. Apart from this, an increase in brain peroxide metabolism due to increased activity of anti-oxidant enzymes such as G6PD, of hexose monophosphate pathways in brains, may lead to neuro-degeneration thus causing Alzheimer's disease.⁴³ Alzheimer's brain is the outcome of an oxidative challenge, which leads to neuro-degeneration in several parts of brains.⁴⁴ A study done using brain samples of Alzheimer's patients showed an increase in activity of G6PD in several regions of brains, and those regions included hippocampus, para-hippocampal gyrus, parolfactory gyrus and cerebellum.⁴⁴

However, in few cases of Alzheimer, G6PD showed reduced activities in affected hippocampal regions.⁴⁵ The increased G6PD reductive activity and its overall cytoplasmic level in Alzheimer's brain is a result of homeostasis towards counterbalancing the oxidative stress and neuro-degeneration induced by amyloid- β peptide.^{46–48} However, the amyloid- β peptide does not directly induce the activity of G6PD in AD.⁴⁹ In AD, the severely affected component of the brain is the synapses of the frontal cortex, wherein the reduced activity of G6PD is diminished to a greater extent that leads to massive oxidative stress.⁵⁰ As G6PD gene is located in X-chromosome, studies suggest that Alzheimer's disease could be genetically inherited due to the accumulation of this critical enzyme in the offspring's

because of chromosomal breakage and partial transfer of X-chromosome genes.⁵¹ The activity of major anti-oxidant enzymes, such as glutathione peroxidase and glutathione reductase, remains normal in Alzheimer's disease, whereas the activity of G6PD and 6-phospho gluconate dehydrogenase increases in inferior temporal cortex of the Alzheimer's brain that results into deregulated (either increased or decreased) Fe²⁺/Ascorbate-induced lipid peroxidation.⁵² Additionally, a mice model of AD also showed increased activity of G6PD in the brain.^{53,54} Apart from the brain, the high G6PD activity is also detected in the serum of Alzheimer's patients, which indicates the diagnostic potential of this enzyme in AD.⁵⁵

G6PD and metabolic stress, protection against ROS generation & inflammation

As G6PD is a major enzyme responsible for NADPH generation and it creates a reductive environment in cells, the deregulated function of this enzyme leads to oxidative stress and damage. Here, we are briefly discussing the role of G6PD in metabolic stress, ROS generation, and inflammation.

G6PD in metabolic stress and ROS generation

A balanced level of G6PD is required for the normal function of cells, whereas, increased or decreased level causes cell damages due to oxidative stress.^{21,56–59} As G6PD is a major enzyme that produces NADPH, it plays a crucial role in many essential metabolic pathways, such as lipid, fatty acid or cholesterol biosynthesis, and it is also involved in controlling the generation of ROS and inflammation.^{21,58,59} Hence, deregulation of this enzyme causes severe metabolic stress and inflammation evidenced as neurodegenerative disorders, arthritis, muscle dystrophy, blood vessel damage, and hormonal imbalance and so on. The cellular antioxidant system plays a central role in regulating both metabolic stress and inflammation, wherein oxidative molecules are directly controlled by the reducing nature of NADPH.^{21,60} In the cellular antioxidant system, NADPH is required for reducing the oxidized-glutathione, which otherwise fails to control the production of ROS and thus causes oxidative damage to cells.^{60,61} Studies have shown that mice deficient in G6PD showing enhanced sensitivity to even mild oxidative stress.^{62,63} These findings further suggest the importance of G6PD in the synthesis of NADPH, controlling metabolic stress & ROS generation and thus preventing cell damages. Furthermore, altered activity and levels of G6PD has been considered as one of the markers of inflammation and many age related diseases including neurological disorders as described in this review.^{64–69}

Multiple sclerosis (MS)

Multiple sclerosis is an outcome of degenerated nerve fibers due to the loss of myelin sheath (nerve fiber covering sheath), which results in the interrupted transmission of brain messages to muscles. It is important for cranial nerves to receive, analyze and process information instantly, and

hence all the cranial nerves having myelin sheath allow 1000 higher information via a node of Ranvier. As a result of this, various locomotory and visionary associated problems occur. Though researchers are unable to confirm a molecular reason behind the generation of MS, auto-immunity against the myelin sheath is considered to be one of the major factors in the development of this disease. Apart from this, G6PD deficiency is one of the alarming factors in MS.⁷⁰ Additionally, a direct correlation of genetic deficiency in G6PD and the prevalence of MS has been seen in some of the geographical regions of the world.⁷¹ This indicates that G6PD could be considered as a diagnostic element, and the supplementation of G6PD could help ameliorate MS symptoms.

Diagnostic and therapeutic opportunities of G6PD

As I have reviewed here, the enzyme (G6PD) is associated with major neurodegenerative disorders and can be used as an early diagnostic marker. It has been demonstrated that the deregulated function of G6PD could be a cause of amyotrophic lateral sclerosis (ALS)-a nervous system disorder leads to the weakness of muscles and impaired physiology. Now understanding the molecular etiology and genetics of ALS in the context with G6PD will be useful to map the gene and enzyme for diagnostic opportunities. Similarly, in case of MS, G6PD gene expression and profiling of enzyme allow us to setup diagnostic standards. G6PD gene expression and glucose metabolism have a direct link with the onset of HD demonstrated in *Drosophila*. However, in case of human G6PD, ambiguous results show increased and decreased level of enzyme, which needs a further molecular investigation to correlate HD and G6PD. Currently, PD and AD are leading neurodegenerative disorders associated with chronic degeneration of neurons. Though the onset of PD and role of G6PD is not understood completely, however, the enzyme involves in the progression of disease due to the oxidative damage of RBCs. G6PD acts as a potent anti-oxidant, and in case of PD, altered G6PD activity against hexose monophosphate pathways facilitates neuronal tissue damages.

Again there is little information available that could link PD and G6PD precisely. Hence, a detailed molecular study is essential to map and correlate PD and enzymes. ROS act as a trigger for tissue damage including neurodegeneration, here G6PD plays a vital role in the regulation of energy harnessing and control of ROS generation. Now, profiling of ROS production with G6PD activity will provide direct evidence for possible tissue damage including neuro degradation. Such data from a healthy diseased individual will be useful in designing diagnostic kits and tools. Eventually, all kinds of degenerative disorders are associated with inflammation and ROS production that disables native inflammation resolution mechanisms. Now, an aberrant G6PD gene expression and altered enzyme activity are combined together for an additive output, leading to distorted energy balance. Further, chronic inflammation resulted from a failed resolution mechanism affects energy homeostasis and component associated, such as G6PD. Hence, the profiling of ROS and inflammatory mediators

allow us to sketch the link towards degenerative disorders including neurological diseases.

Conclusion

G6PD has been studied extensively over last few decades in the context of its genetics and hemolytic anemia. Certainly, G6PD deficiency remains a major health issue worldwide, affecting male population comparatively more. Researchers worldwide are seeking novel molecular approaches to overcome such life threatening disorders. At the same time, the role of G6PD in neurological and inflammatory disorders via the generation of ROS, and its potential as the diagnostic marker was least studied. There is limited literature available demonstrating the lack of research towards the involvement of G6PD in neurodegenerative disorders. It is essential to develop a diagnostic tool expression of G6PD and profiling of enzyme. Several research findings have demonstrated that the onset and progression of cerebral ischemia are associated with ROS generation, and hence the role of G6PD cannot be denied. The significance of G6PD is not only limited to an enzyme for energy harnessing via PPP, but also a key player for several organs physiology. Glucose 6-phosphatase plays a critical role in glucose homeostasis, and an abnormal enzyme activity triggers tissues to opt alternate mechanism for energy harnessing. In a recent finding, it has been demonstrated that the phenylpyruvic acid decreases G6PD activity in rat brains. Further, G6PD deficiency in red-green color blindness has been established. Such findings further direct an involvement of G6PD in many metabolic disorders, and explorations at the molecular level are needed.

Conflicts of interest

The author declares no conflict of interest.

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