REVIEW ON HYPOXANTHINE GUANINE PHOSPHORIBOSYL TRANSFERASE (HGPRT)

Preeti Verma[1], [2]* Peeyush[1], [2] Yatendra Singh[1, 4] Anurita Rajpoot[3].

[1]Adarsh Vijendra Institute of Pharmaceutical Sciences, Shobhit University Gangoh, Saharanpur (U.P.), India 247341.

[2]Faculty of Pharmaceutical Sciences, Rama University, Mandhana, Kanpur (U.P.), India 209217.

[3]Advance Institute of biotech and paramedical Sciences, Naramau, Kanpur, (U.P), India 209217.

[4]Maharana Pratap College of Pharmacy, Mandhana, Kanpur (U.P.) 209217.

Abstract

Hypoxanthine-guanine phosphoribosyl transferase (HGPRT) is a purine salvage enzyme that shows significant role in regulation of purine metabolism in human. HGPRT has been produced to give a creature model to the infection of Lesch-Nyhan disorder. The commonness of Lesch–Nyhan ailment is unsurprising to be roughly 1/380 000 live births, making it quite rare. Ordinarily, influenced patients have a typical pre-birth and perinatal course followed by advancement of signs for the most part inside 3–6 months. The hereditary condition Lesch-Nyhan disorder, which is brought about by a protein hypoxanthine phosphoribosyl transferase (HPRT) deficiency is characterized by behavioural changes, including self-injurious behavior and intellectual retention [1].The current-considers were led to portray the results of the transformation on the declaration of HPRT and to describe potential changes in cerebrum purine content in these freaks. These outcomes demonstrate that the freak creatures have no noticeable HPRT-immunoreactivity material on western marks and no perceptible HPRT chemical movement in cerebrum tissue homogenates, Several various changes have been distinguished all through the coding area, however without exact data on the HPRT protein'3D dimensional structure, it remains difficult to determine any consistent correlation between the Structure and function of the enzyme. Selective inhibition of the enzymes HGPRT of parasite vs human are likely to be required as one of novel approach for treatment of malaria. In the present study, designing and virtual screening of PFHGPRT inhibitors could help in guiding medicinal chemists to improve target specificity for antimalarial chemotherapy.

Keywords- Hypoxanthine-guanine phosphoribosyl transferase, Lesch-Nyhan disease, Purine metabolism, antimalarial, 3D structure of HGPRT.

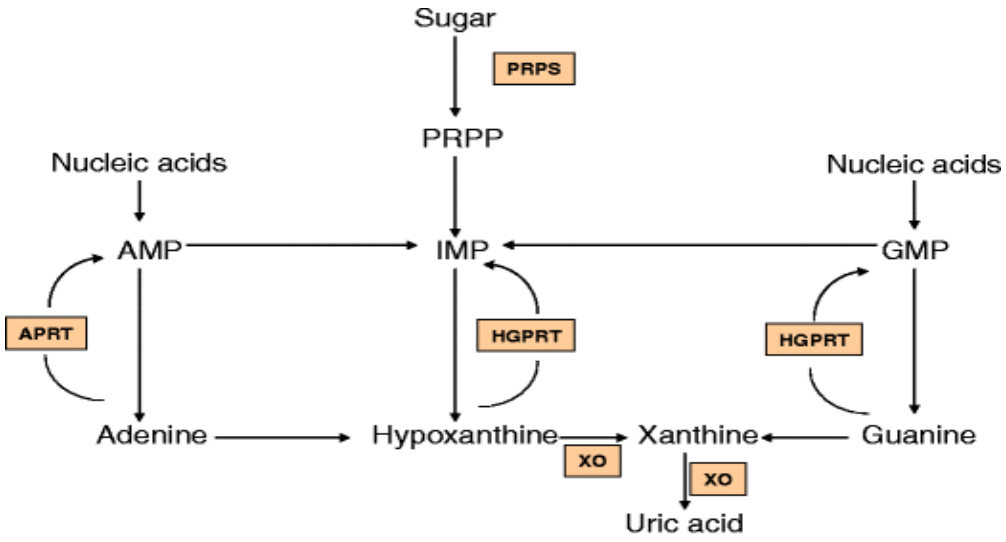
1 Introduction

Purines are fundamental particles for every single living life form. Hypoxanthine guanine phosphoribosyl transferase (HGPRT) is vital for purine nucleotide as it catalyse the transformation of 6-oxopurine bases to their individual nucleotides [hypoxanthine to inosine monophosphate (IMP) and guanine to guanosine monophosphate (GMP) from the purine bases hypoxanthine and guanine separately, using 5'- phosphoribosyl-1-pyrophosphate (PRPP) as a Co-substrate], and henceforth basic in Plasmodium falciparum just as in human for nucleic corrosive blend [2], [3].Purine containing nucleotides are the building blocks of nucleic acids (DNA

and RNA), and purine bases are constituents of enzyme cofactors (e.g. NAD+, FAD), sources of chemical energy (e.g. ATP, GTP) or signalling molecules (e.g. cAMP). Defects in the human HPRT can result in gouty arthritis or Lesch-Nyhan syndrome. Thus, for FDA approval, drugs targeted to the HPRT of a human parasite are likely to be required to be selective inhibitors of the enzymes from the parasite [4]. The inherited disease Lesch-Nyhan syndrome, which is caused by a deficiency of the enzyme hypoxanthine phosphoribosyl transferase (HPRT), is characterized by behavioural alterations, including self-injurious behaviour and mental retardation. Although HPRT-deficient mice have been generated using the embryonic stem cell system, no spontaneous behavioural abnormalities had been reported. We examined whether mice were more tolerant of HPRT deficiency because they were more reliant on adenine phosphoribosyl transferase (APRT) than HPRT for their purine salvage. The administration of an APRT inhibitor to HPRT-deficient mice induced persistent self-injurious behaviour. This combined genetic and biochemical model will facilitate the study of Lesch-Nyhan syndrome and the evaluation of novel therapies [5]. New single nucleotide change of the hypoxanthine-guanine phosphoribosyl transferase (HPRT) gene on coding region has been identified from a Taiwanese aboriginal family with gout [6].

In people, transformations in the quality encoding the purine rescue catalyst hypoxanthine-guanine phosphoribosyl transferase (HPRT) are related with a range of sickness that ranges from hyperuricemia alone to hyperuricemia with significant neurological and conduct brokenness. Past endeavours to associate various sorts or areas of changes with various components of the malady phenotype have been constrained by the moderately little quantities of accessible cases. The present article portrays the sub-atomic hereditary reason for 75 new instances of HPRT lack, surveys 196 recently announced cases, and abridges four principle ends that might be gotten from the whole database of 271 transformations. Initially, the changes related with human ailment seem scattered all through the HPRT quality, with certain locales seeming to speak to relative mutational problem areas. Second, genotype–phenotype connections give no sign that particular infection highlights partner with explicit transformation areas. Third, cases with less serious clinical appearances commonly have transformations that are anticipated to allow some level of leftover catalyst work. Fourth, the nature of the transformation gives just a harsh manual for foreseeing phenotypic seriousness. In spite of the fact that transformation investigation doesn't give exact data to anticipating illness seriousness, it keeps on giving a significant apparatus to hereditary guiding as far as affirmation of conclusions, for recognizing potential bearers, and for pre-birth finding. Hypoxanthine-guanine phosphoribosyl transferase (HPRT) is a purine rescue compound that catalyses the transformation of hypoxanthine and guanine to their individual mononucleotides. Halfway inadequacy of this catalyst can bring about the overproduction of uric corrosive prompting an extreme type of gout, while a virtual nonappearance of HPRT action causes the Lesch-Nyhan disorder which is portrayed by hyperuricemia, mental hindrance, choreoathetosis and enthusiastic self-mutilation [7].

Hypoxanthine guanine phosphoribosyl transferase (HGPRT) is fundamental for purine nucleotide as it catalyse the transformation of 6-oxopurine bases to their individual nucleotides [hypoxanthine to inosine monophosphate (IMP) and guanine to guanosine monophosphate (GMP) from the purine bases hypoxanthine and guanine separately, using 5'- phosphoribosyl-1-pyrophosphate (PRPP) as a Co-substrate] and henceforth nucleic corrosive amalgamation in Plasmodium falciparum just as in human.



AMP	Adenosine monophosphate
APRT	Adenine phosphoribosyl transferase
GMP	Guanosine monophosphate
HGPRT	Hypoxanthine-guanine phosphoribosyl transferase
IMP	Inosine monophosphate
PRPP	5-phosphoribosyl 1-pyrophosphate
PRPS	PRPP synthetase
XO	Xanthine-oxidase

Figure: 1. The mechanism of HGPRT **[8]**

1.1 HPRT

Hypoxanthine-guanine phosphoribosyl transferase (HPRT) is a universal catalyst found in the cytoplasm. Its most elevated action is in the mind and testicles. HPRT catalyses the exchange of the phosphoribosyl gathering of phosphoribosyl pyrophosphate to hypoxanthine and guanine, this structures inosine monophosphate and guanosine monophosphate. In circumstances in which hypoxanthine and guanine can't be reused, there is an absence of input control of union, bringing about fast catabolism of these bases to uric corrosive.

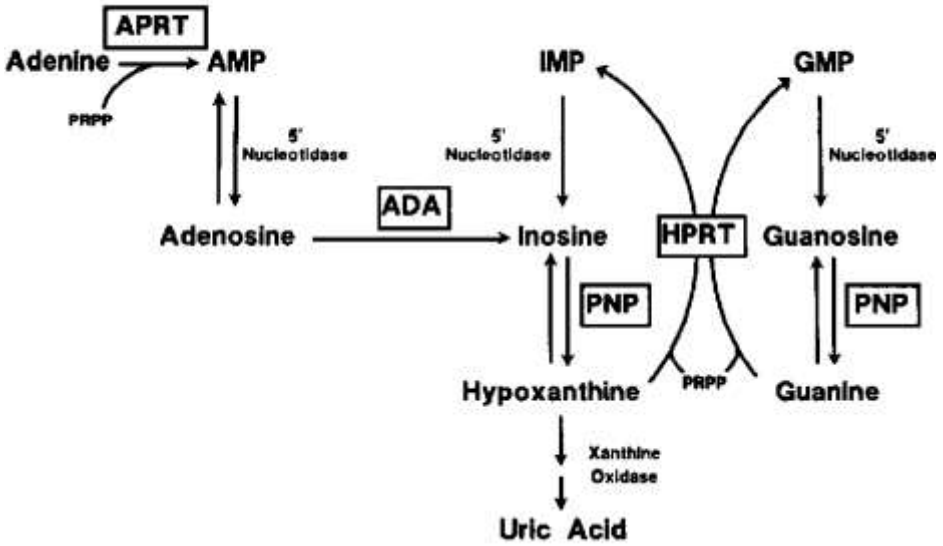


Figure: 2. Mechanism of IMP to Uric acid **[9]**

1.2 Purine Salvage

The word often refers to nucleotide salvage in specific, in which nucleotides (like purine and pyrimidine) are synthesized from intermediates in their degradative pathway. Nucleotide salvage pathways are used to improve bases and nucleosides that are formed during degradation of RNA and DNA**.** This is important in some organs because some tissues cannot undergo de novo synthesis .The chemical hypoxanthine-guanine phosphoribosyl transferase (HGPRT) is one of the focal catalysts that reuse the structure squares of RNA and DNA. It connects a purine base (either guanine or hypoxanthine, an adjusted type of adenine) to a sugar, making a nucleotide. The structure appeared here is the human compound, which is made out of four indistinguishable subunits, each with its own dynamic site. This structure incorporates the nucleotide item, guanine monophosphate, not long before it is fit to be discharged for use by the cell [10].

1.3 Perils of Purines

Similarly as with every metabolic pathway, significant issues happen if steps in the pathway are blocked. A few people acquire an uncommon damaged form of HGPRT, which prompts a genuine sickness named Lesch-Nyhan disorder. Since the catalyst isn't dynamic, purine bases develop causing serious neurological issues, including a perilous impulse for self-injury. In different cases, individuals with somewhat dynamic HGPRT have issues with gout, as the pathways for disposing of overabundance purines are over-burden and the waste items develop in the joints.

2 Classifications

HPRT deficiency can be classified according to the severity of the neurological manifestations and the enzyme defect. The first classification includes HPRT-deficient patients as complete or Lesch-Nyhan syndrome, and as partial or Kelly-Seegmiller syndrome [11]. Other classifications include three groups: classical Lesch-Nyhan or complete deficiency (LN); HPRT deficiency with neurological manifestations or HPRT related hyperuricemia with neurological disability (HRND), and HPRT-related hyperuricemia (HRH) for partial patients with no evident neurological manifestations.

2.1.1. Normal development without neurological symptoms

Hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency is a hereditary disorder of purine metabolism associated with uric acid overproduction and a continuum spectrum of neurological manifestations depending on the degree of the enzyme deficiency. HPRT insufficiency in these patients could be showed as asymptomatic hyperuricemia with raised uric corrosive discharge rates, or as renal lithiasis as well as gout. These patients are absolutely free regarding day by day exercises and have ordinary existences. Just when deliberately analysed, they may introduce some minor dystonia, for example, work out prompt dystonia, consideration deficiency or over the top habitual conduct.

2.1.2. Mild neurological symptoms

These patients have mellow neurological side effects, for example, dystonic step, dysarthria, faltering, and some level of mental impediment. They are hampered by their neurological manifestations, in spite of the fact that they are free in many exercises, and can walk and live all alone.

2.1.3. Severe neurological symptoms

Patients are intellectually ordinary, can take care of them and deal with a portion of their own needs; however their extreme dystonia limits them to a wheelchair. These patients don't present self-damaging conduct.

2.2.4 Classic Lesch-Nyhan syndrome

These patients display average qualities of Lesch-Nyhan disorder, including self-damaging conduct, choreoathetosis and ballismus, powerlessness to stand or walk, some level of spasticity, and are completely reliant on others for day by day exercises and individual needs. A portion of these patients may not show auto-ruinous conduct or mental hindrance [11].

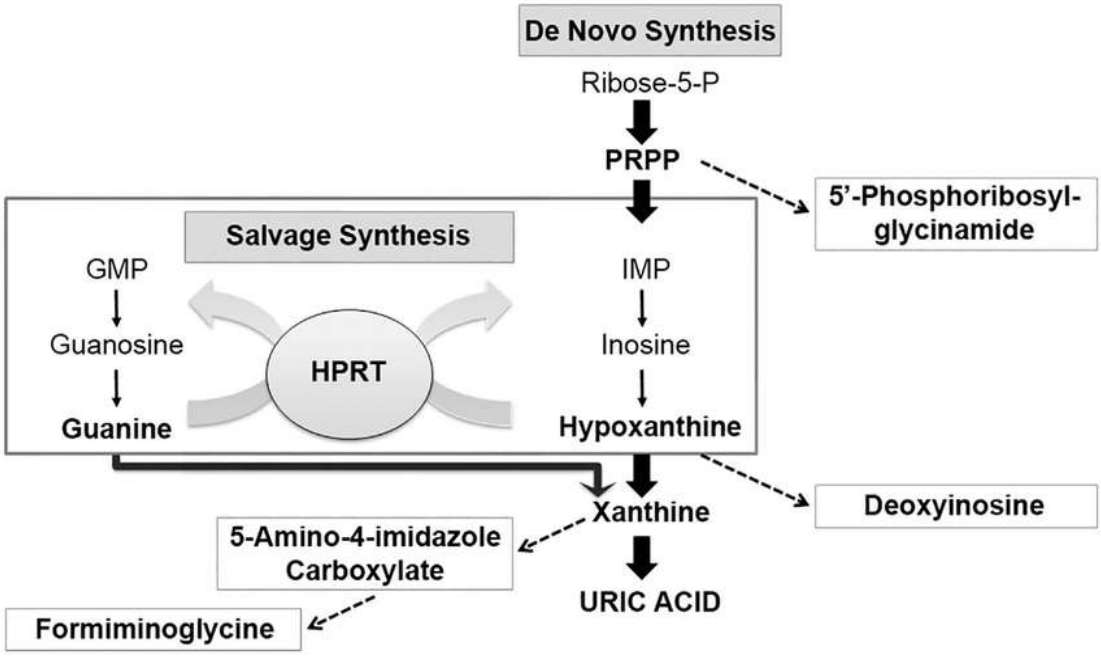


Figure: 3. De novo synthesis of HGPRT **[12]**

3. Role in Diseases

A few men have fractional (up to 20% less action of the catalyst) HGPRT lack that causes elevated levels of uricacid in the blood, which prompts the advancement of gouty joint pain and the arrangement of uric corrosive stones in the urinary tract. This condition has been named the [13].

Lesch-Nyhan syndrome is due to deficiency of HGPRT caused by HPRT1 mutation. Some mutations have been linked to gout, the risk of which is increased in hypoxanthine-guanine phosphoribosyl transferase deficiency [14].

HPRT expression on the mRNA and protein level is induced by hypoxia inducible factor 1 (HIF1A). HIF-1 is a transcription factor that directs an array of cellular responses that are used for adaptation during oxygen deprivation. This finding implies that HPRT is a critical pathway that helps preserve the cell's purine nucleotide resources under hypoxic conditions as found in pathology such as myocardial ischemia [15].

This halfway lack was named Kelly-Seegmiller disorder or HPRT-related gout. These days it is viewed as that between the two disorders, a ceaseless range of neurological inclusion is available in HPRT-insufficient patients. The term Lesch-Nyhan a variation has been acquainted with incorporate patients with HPRT-related gout and some level of neurological inclusion, however without the total Lesch-Nyhan disorder. In 1959, preceding the Lesch and Nyhan depiction, Catel and Schmidt portrayed a 18-month old new-born child with hyperuricemia, hyperuricosuria and encephalopathy [16].

The association of a psychomotor delay in the first year of life with hyperuricemia and/or elevated uric acid to creatinine ratio suggest the possibility of HPRT-deficiency. On the other side of the spectrum, a patient with juvenile gout and elevated urinary uric acid excretion may also suffer HPRT deficiency.

4 Diagnostic criteria

4.1. Uric acid overproduction

HPRT inadequacy is portrayed by hyperuricemia with hyperuricosuria and a continuum range of neurological signs, which relies upon the seriousness of the imperfection. These appearances incorporate serious activity dystonia, choreoathetosis, mellow to direct mental hindrance, and self-mutilation in the total structure or Lesch-Nyhan disorder that can go unnoticed in the mildest forms [17].

The relationship of a psychomotor deferral in the primary year of existence with hyperuricemia as well as raised uric corrosive to creatinine proportion propose the chance of HPRT-insufficiency. On the opposite side of the range, a patient with adolescent gout and raised urinary uric corrosive discharge may likewise endure HPRT lack.

Uric corrosive overproduction can be controlled with the xanthine oxidase inhibitor allopurinol that hinders the change of xanthine and hypoxanthine into uric corrosive (Rundles RW 1985). Allopurinol treatment decreases serum urate and pee uric corrosive levels and consequently forestalls uric corrosive crystalluria, nephrolithiasis, gouty joint inflammation and tophi [18].

4.2 Clinical and biochemical diagnosis

HPRT lack ought to be suspected in patients with hyperuricemia and uric corrosive overproduction with or without neurological impedance. During the primary year of life, serum and pee uric corrosive judgments ought to be remembered for the differential determination of psychomotor deferral. Tragically, in earlier years Lesch-Nyhan disorder determination has been deferred until self-mutilation was obvious. Nephrolithiasis and obstructive nephropathy are basic early signs in patients with incomplete HPRT inadequacy [7], [19] Electroencephalograms are not symptomatic.

A high serum urate focus is generally the biochemical finding that prompts exceptional testing for the particular conclusion, albeit a few patients, especially youthful new-born children, may have marginal serum uric corrosive levels because of expanded renal leeway of uric corrosive [19]. Typical qualities for serum urate levels rely upon age and sex. Thus, the urinary uric corrosive/creatinine proportion can be utilized as a screening test for acquired clutters of purine digestion (Kaufman 1958) however the qualities ought to be assessed dependent on the age of the patient. Typical qualities for the urinary uric corrosive/creatinine proportion are underneath 1.0 after age 3-years. Mean plasma groupings of urate, hypoxanthine, and xanthine, and their urinary discharge rates, are particularly raised in HPRT-inadequate patients. Be that as it may, there is a non-measurably critical contrast in these biochemical factors among halfway and Lesch-Nyhan patients, with the exception of xanthine urinary discharge that seems, by all accounts, to be expanded in Lesch-Nyhan patients when contrasted with incomplete HPRT lacking patients [20].

4.3 Enzymatic diagnosis

HPRT inadequacy must be affirmed by enzymatic judgments Patients present low or imperceptible HPRT movement in haemolysates, with expanded adenine phosphoribosyl transferase (APRT) action. Lesch-Nyhan patients (grade 4) present imperceptible HPRT action, however in incomplete HPRT-insufficient patients HPRT action in haemolysate ranges from 0 to 10% Evaluation 1 patients for the most part show recognizable haemolysate HPRT action, while grade 2 or 3 patients for the most part don't. To all the more likely describe the HPRT insufficiency, compound movement can be estimated in unblemished cells (erythrocytes or fibroblasts). A relationship was found between leftover HPRT action in unblemished erythrocytes and fibroblasts and neurological contribution, in spite of the fact that qualities may cover for patients with altogether different phenotypes [17], [21].

4.4 Molecular diagnosis

Human HPRT is encoded by a solitary basic quality spreading over around 45 Kb on the long arm of the X chromosome at Xq26, and comprises of nine exons with a coding arrangement of 654 bp [20] Most HPRT-inadequate patients present HPRT mRNA articulation and sub-atomic conclusion can be cultivated by cDNA sequencing In different cases, genomic DNA sequencing might be vital Recorded changes in HPRT insufficiency show a high level of heterogeneity in type and area inside the quality: cancellations, inclusions, duplications, and point transformations have been depicted as the reason for HPRT lack. Until this point in time, in excess of 300 ailment related transformations have been found. Single point transformations are the fundamental driver of incomplete lack of the compound, though Lesch-Nyhan disorder is caused mostly by changes that alter the size of the anticipated protein. HPRT insufficiency is acquired as a X-connected passive attribute. Be that as it may, about 30% of patients' moms are not substantial bearers, and these patients most likely convey again changes because of a germinal cell transformation. Atomic finding in HPRT-insufficient patients permits quicker and progressively precise bearer and pre-birth analysis [22].

Conclusion

HGPRT has been produced to give a creature model to the infection of Lesch-Nyhan disorder. Atomic docking is a protected and simple instrument that aides in researching, translating, clarifying, recognizable proof of sub-atomic properties utilizing 3D structure, sub-atomic docking is attempts to utilize foresee the structure of intermolecular complex shaped between at least two constituent particles. Plasmodium falciparum HGPRT (PFHGPRT) is an appealing objective site contender for hostile to malarial medication disclosure and the homology displaying method stands apart as a superb and ground-breaking choice to foresee a solid 3-D structure of the protein [18]. the Global specialized procedure of WHO for intestinal sickness 2016–2030 sets the most ambitious focuses for decreases in intestinal sickness cases. The Protein-Ligand cooperation assumes a huge job in basic based medication planning. In future research, toxicological profile of these mixes could be tried in wet lab and research could be continuing for preclinical/clinical preliminary. The structural information of HGPRT model will pave the way for further laboratory experiments to design potential anti-malarial drug in near future. PFHGPRT inhibitors could help to improve target specificity for antimalarial chemotherapy.

REFERENCES

1. Hatse, S. Clercq, E. De and Balzarini, J. 1999. Role of Antimetabolites of Purine and Pyrimidine Nucleotide Metabolism in Tumor Cell Differentiation. Biochemical pharmacology, 58(4): 539–55.

2. Raman, J. Ashok, CS. Subbayya, SI. Anand, RP. Selvi, ST. Balaram, H. 2005.Plasmodium falciparum hypoxanthine guanine phosphoribosyltransferase stability studies on the product-activated enzyme. FEBS J, 272(8):1900-11

3. Susan, A. Tarlé,B.L. Davidson Veda, C. Wu Frank Zidar. J. Edwin, J. Seegmiller, William, N. Kelley, Thomas, D. Palella.1991 Determination of the mutations responsible for the lesch-nyhan syndrome. science Direct,10 (2):499-50.

4. Freymann, DM. Wenck, MA. Engel, JC. Feng, J. Focia, P J. Eakin, A E. Craig, S P. 2000. Efficient identification of inhibitors targeting the closed active site conformation of the HPRT from Trypanosoma cruzi. Chem. Biol, (7):957-968.

5. Wu, CL. Melton, DW . 1993. Production of a model for Lesch-Nyhan syndrome in hypoxanthine phosphoribosyltransferase-deficient mice Institute of Cell and Molecular Biology, Edinburgh University, Scotland. Nature Genetics. 3(3):235-240.

6. Chang, SJ . Chang, JG . Chen, CJ .Wang, JC. Ou, TT. Chang, KL. Ko, YC.1999. Identification of a new single nucleotide substitution on the hypoxanthine-guanine phosphoribosyltransferase gene (HPRT) (Tsou) from a Taiwanese aboriginal family with severe gout, The Journal of Rheumatology, 26(8):1802-1807.

7. Jinnah, HA. Visser, JE. Harris, JC. Verdu, A. Larovere L, Ceballos-Picot I, Gonzalez-Alegre P, Neychev V, Torres RJ, Dulac O, Desguerre I, Schretlen DJ, Robey KL, Barabas G, Bloem BR, Nyhan W, De Kremer R, Eddey GE, Puig, JG. Reich, SG.2006. Lesch-Nyhan Disease International Study Group Delineation of the motor disorder of Lesch-Nyhan disease. Brain. 129: 1201–1217.

8. Timothy Stout, J. 1985.HPRT: gene structure, expression, and mutation, Howard Hughes Medical Institute, and Departments of Medicine, Biochemistry, and Cell Biology, Baylor College of Medicine, Houston, Texas. 19, 127-48.

9. Pierre Cochat, Valérie Pichault, Justine Bacchetta, Laurence Dubourg, Jean-François Sabot, Christine Saban, Michel Daudon & Aurélia Liutkus.2010. Nephrolithiasis related to inborn metabolic diseases, Pediatric Nephrology. 25, 415–424.

10. Kompis,IM. Islam. K. Then, RL. 2005. DNA and RNA synthesis: antifolates, *Chemical Reviews*, 105 (2):593–620.

11. Kelley, WN. Jinnah, HA. Page,T and Friedmann, T. 1993.Journal of Neurochemistry,60 (6): 2036-2045.

12. Torres, RJ. Prior, C. Puig, JG. 2007. Hypoxanthine-guanine phosphoribosyltransferase deficiency(HGPRT), Lesch-Nyhan Syndrome, Orphanet Journal of rare disease,48 (2):1750-1172.

13. Khattak, FH. Morris, IM. Harris, K.1998. Kelley-Seegmiller syndrome, A case report and review of the literature". British Journal of Rheumatology, 37(5), 580–592.

14. Hladnik, U. Nyhan, WL. Bertelli, M. 2008. Variable expression of HPRT deficiency in 5 members of a family with the same mutation, Archives of Neurology, 65 (9): 1240–1243.

15. Kelley, WN. Rosenbloom, FM. Miller, J. Seegmiller, JE. 1968. An enzymatic basis for variation in response to allopurinol. Hypoxathine-Guanine Phosphoribosyl transferase deficiency, N Eng J Med. 278, 287-293.

16. Catel, W. Schmidt, J. 1959. On familial gouty diathesis associated with cerebral and renal symptoms in a small child. Dtsch Med Wochenschr. 84, 2145–2147.

17. Kelley, WN. Jinnah, HA. Page,T and Friedmann, T. 1992.Journal of Neurochemistry,60 (6): 2030-2035.

18. Christie ,R. Bay, C. Kaufman, IA. Bakay, B. Borden, M. Nyhan, WL.1982. Lesch-Nyhan disease, clinical experience with nineteen patients, Develop Med Child Neurol. 24, 293-306.

19. Khattak, FH. Morris, IM. Harris, K.1998. Kelley-Seegmiller syndrome a case report and review of the literature. British Journal of Rheumatology, 37(5):580–58.

20. Torres, RJ. Prior, C. Puig, JG. 2007 Efficacy and safety of allopurinol in patients with hypoxanthine-guanine phosphoribosyltransferase deficiency. Metabolism, 56, 1179-1186.

21. Townsend, MH. Robison, RA. ONeill, KL. 2018. A review of HPRT and its emerging role in, cancer. Med Oncol. 35(6):89.

22. Gibbs, RA. Nguyen, PN. Edwards, A. Civitello, AB. Caskey, CT. 1990.Multiplex DNA, deletion detection and exon sequencing of the hypoxanthine phosphoribosyltransferase gene in Lesch-Nyhan families. Genomics.7(2): 235-44.