

Research Article

Mitochondrial DNA Mutations and its Role in the Genesis of Renal Diseases an Update

Rodolfo J Gordillo de Anda*

Nephroimmunologist, Médica Sur Hospital, Ciudad de México, México

Abstract

The errors in the Mitochondrial DNA affects tissues that require highly dependent of energy to work properly like the Brain, the Heart, the Muscle and the Kidneys, the defects in the genesis of ATP affects this tissues sometimes involving more than one organ, therefore myopathies, encephalopathies, can be associated with renal diseases which rare in adults and more frequently in children in whom are frequently unsuspected and underestimated. Their prevalence in the general population is also underestimated and may be as high as 1-2:10,000 live births.

Keywords: Mitochondrial DNA mutations; Genesis of renal diseases

Introduction

The Mitochondrial DNA is localized in the cytosol within the mitochondria; it was completely sequenced in 1981 [1]. Mitochondria are divided in 4 principal components: the External Mitochondrial Membrane (EMM), the Internal Mitochondrial Membrane (IMM), the Intermediate Mitochondrial Space (IMS) and the matrix localized in the inside (organelle cytoplasm) [2]. The mitochondrial DNA is circular and constituted by two bands, one heavy and one light (Figure 1), contains about 16 569 nucleotides that codify for 37 genes, the most important codify 22 transfer RNA, 2 Ribosomal RNA and most important 13 polypeptides that are part of multiple subunits of enzymatic complexes that are involved in the Respiratory Chain, among them 7 subunits codify for Complex I, 1 sub-unit for Complex III, 3 subunits for complex IV and 2 subunits for Complex V all of them participate in the Oxidative Phosphorylation and in Tricarboxylic acid cycle: Krebs cycle [3] figure 2. As Mitochondrial DNA is more exposed to damage secondary to the oxygen radicals produced during the

*Corresponding author: Rodolfo J Gordillo de Anda, Nephroimmunologist, Médica Sur Hospital, Ciudad de México, México, Tel: +525 5568 6904; E-mail: rodolfgordillo2000@yahoo.com

Citation: Gordillo de Anda RJ (2019) Mitochondrial DNA Mutations and its Role in the Genesis of Renal Diseases an Update. J Nephrol Renal Ther 5: 021.

Received: February 08, 2019; **Accepted:** April 05, 2019; **Published:** April 19, 2019

Copyright: © 2019 Gordillo de Anda RJ. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

oxidative phosphorylation and because its mechanism for protection are more rudimentary and less effective than those pertinent to de nuclear DNA, the possibility of mitochondrial mutations is increased and it results in several troublesome diseases that involves mainly those organs with high energy requirements. In this paper, we focus on the known Mitochondrial DNA mutation that can be the origin of renal diseases.

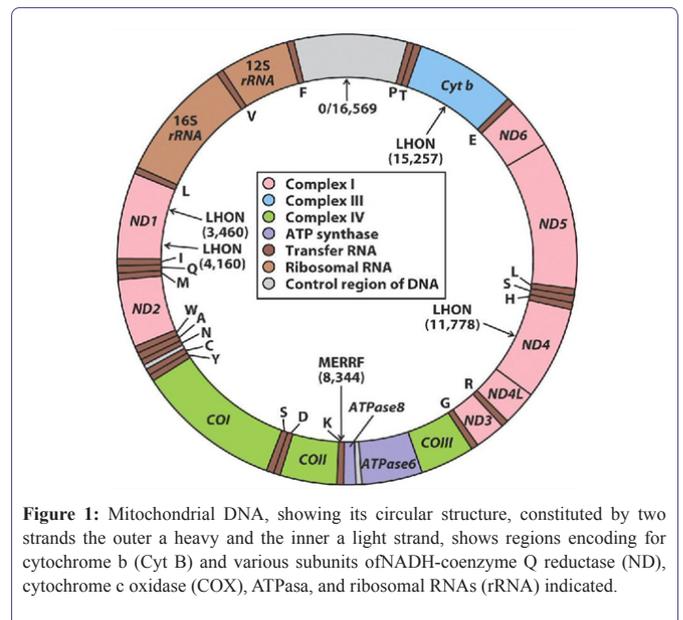


Figure 1: Mitochondrial DNA, showing its circular structure, constituted by two strands the outer a heavy and the inner a light strand, shows regions encoding for cytochrome b (Cyt B) and various subunits of NADH-coenzyme Q reductase (ND), cytochrome c oxidase (COX), ATPase, and ribosomal RNAs (rRNA) indicated.

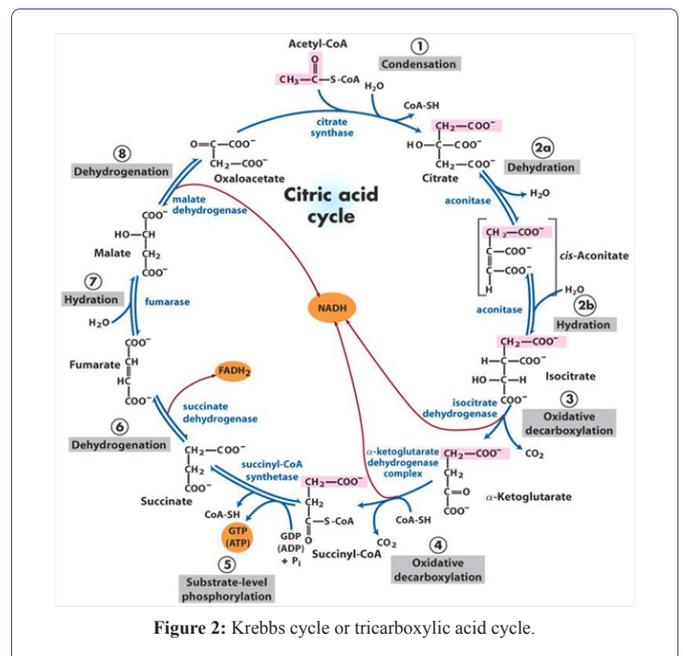


Figure 2: Krebs cycle or tricarboxylic acid cycle.

Human DNA was initially identified at the end of the 1860s by the swiss Chemistry Friederich-Miescher [4] and later two outstanding scientists, the rusian biochemistry PhiebusLevene and Erwin Chargaff conducted a series of reserch that revealed additional details of the DNA molecule, Levene was the first to describe the order of the three components of a simple nucleotide (fosfate, sugar and base) and also was the first one to discover that the sugar in RNA was Ribosa and in DNA was Desoxiribosa [5], later the studies of Linus Pauling and Maurice Wilkins contributed but the later researcher due to a personal dispute with Professor Rosalind Franklin and without her permission in 1953 took the photography of the DNA molecule taken with X-Ray diffraction by her, and gave them to Watson, the photography of the DNA showed with clarity the helicoidal structure of the molecule, wich allowed Watson and Crick to deduce the structure of DNA in 1954 [6] without the help of theX-Ray diffraction photographs it would have been very difficult for Watson and Crick to have attained their discovery [6]. DNA has been totally sequenced recently by Vant-er y cols [7] it is localized in the nucleous and orginized in structures denominated chromosoms; there are 46 chromosoms organized in 23 pairs, 22 of them are called autosoms and one pair are de sexual chromosoms: XX in the case of females and XY in the case of males [8] this is in reallity the real Human DNA (HDNA) wich contains our complete genetic code and contains 3.3 billions of bases pairs, the letters that encode the message for the synthesis of specific proteins and, codifies aproximately 100,000 genes [9].

About 1,500 millions of years ago a pro-eukarioteamitochondrial cell [10] engulfed an anaerobic alfa-proto-bacteria member of the sub-division of Rickettsias, a group of intracellular bacteria probably an Archezoaprimtiva, this interaction resulted in a symbiotic relation for both; the remanents of this bacterial endosymbiosis are known as the Mitochondrion, they are of monophylicorigen [10] and appeared both in aerobic and in anaerobic bacterias [11]. In the eukariotic organisms the Mithochondrion evolve into different organelas like the mitochondrias, the hidrogenosoms and the mitososms [12] that diverge among them in a very important ways, because one of the out-standig function of the mitochondria is the ATP synthesis dependent on the oxidative phosphorylation that has not been observed in the rest of the organeles derived from the mitochondrion. Therefore the hidrogenosoms uptakes ADP from the sourounding medium and excrete equimolar quantities of ATP. ATP synthesis in this organelas is done by the phosphorylation at the sustrate level through the catalytic conversion of Succinil-Coenzyme A to Succinate by the enzyme succinate-thiokinase [13]. In the mitosoms ATP is synthesized trough the phosphorylation at the sustrate level but inside the cytosol without a direct involvement of the mitososms [14], because of these differences it can be concluded that the energetic metabolism is not the unifying fact among the mitochondria and the rest of organeles derived from the mitochondrion. Theseorganeles do share among them ATP dependant chaperon molecules (Cpn60) and/or mitochondrial heat shock proteins like mtSP70, as well as ATP/ADP transporters, but what it seems to be in reality the unifying line among them are the iron sulphataded proteins (FES). This FES [15] have important function in the electron transference during the enzymatic catalysis and in the metabolic regulation, moreover this proteins have an universal distribution in proeukariote and eukariote organisms and the current evidences suggest that these proteins have a central role for the establishment and maintenance of the original mitochondrial endosymbiosis. Among these proteins one that is highlighth is nominated Rli-1 [16] with universal distribution in eukariote organisms an in the organeles

derived from the mitochondrion and it is involve in the maturation of both the ribosomal RNA and transference RNA and therefore it is of outstandig importance.

The nuclear DNA controls the transcription activity of the mitochondrial DNA trough regulator proteins like the Mitochondrial Transcriptional Factor (MTFA) dependant of nuclear DNA. It is clear that the mitochondria is a so complex organele that it requires more than 37 genetic products for its function; in fact 850 polipetides codify by hDNA are required for its function, aproximately 75 are structural components of the respiratory complex and at least another 20 are required to maintain their structure and function. Mitochondria are divided in 4 principal components: the External Mitochondrial Membrane (EMM), the Internal Mitochondrial Membrane (IMM), the Intermediate Mitochondrial Space (IMS) and the matrix localized in the inside (organelecytoplasm) [2].

The five complexes of the respiratory chain/system OXPHOS are: complex I (NADH ubiquinonaoxidoreductase), complex II (Succinate-ubiquinonaoxidoreductase), complex III (Ubiquinol-cytochrome c oxidoreductase), complex IV (cytochrome c oxidase) and complex V (ATP synthase) are localized in the IMM, there are also two electron transporters: the ubiquinona localized in the IMM and the cytochrome C in the EMM [17]. Beside that the Mitochondrial DNA works sujet under a double genetic control (nuclear and mitochondrial) there are another unique four findings for the behavior of this organele that are important to know and comprehend to understand the mitochondrial functions.

Instead of the nuclear DNA where there exists only one pair of chromosoms in each cell, there are thousands copies of mitochondrial DNA and aproximately 5 copies per mitochondria. The division of the mitochondria and the replication of mitochondrial DNA take place independently of the cell cycle. After the cell division the mitochondrias and its DNAm are randomly distributed among the daughter's cells (mitotic segregation).

The number of organelas among the different cells is variable and depends primarily on the energetic requirements of that lineage cells; that is why the fibroblasts contain a few hundreds of mitochondrias while the neurons can contain thousands and the cardiomyocytes ten thousands of mtochondrias, this shows that mitochondrias do not follow a genetic mendelian pattern but in fact they obey laws according with the genetic-energetic requirements of the specific cell lineage [18]. The mitochondrial DNA is inherited to the human offspring exclusively by the maternal line [19] due to the fact that the Father's mitochondrias are present in the flagelous of the spermatozoids and once the spermatozoid penetrates the ovule it loses its flagelous and with it their mitochondrias (Figure 3). This fact allows establishing with great precision the genetic line to whom we belong for hundreds or thousands of generations prior to us and by this way give us information about or must remotorigens. In the mayority of cases, the mitochondrial DNA copies are identical among each other condition called homoplasmia. During the celular division, the mitochondrias are inherited randomly to the daughter cells (19).

The Kidney is a highly vascularized organ because it recives 25% of the cardiac output per minute, aproximately 125 ml/min wich equals to a volume of filtered blood of 180 liters per day. Taking into account that the adult bloodvolume is about 6 liters, it filters that amount about 30 times a day. With this high flow you can understand

that the kidney filtrates a great variety of substances, some toxic to the body but others not that require to be recovered from the urine by different mechanisms; an example is the sodium, we know that its normal serum concentration is around 140 mmol/l, so during a day an amount of 25 200 mmol/day are filtered, but the kidney reabsorbs 99% in their different segments and primarily in the proximal tubule and excrete less than 1%, lets say if the kidney reabsorbs 99.4% (24,948 mmol of sodium) the losses will equal 0.6% or 151.2 mmol, that amount excreted is called the Fractional Excretion of Sodium (FENA), if FENA is greater than 1 % (252 mmol) it would indicate acute renal failure. To accomplish the reabsorption of this valuable filtered elements the kidney counts with different methods for reabsorption among them; there is the paracellular transport that takes place in the adjacent portions of the cells in the tight junctions; and there is also the transcellular transport, although some of these mechanisms involve a facilitated transport through a concentration gradient and an advantageous pH gradient, the majority requires an active transporter with ATP consumption, for these reasons the epithelium of the renal tubules in its luminal side include a great number of mitochondrias to provide the required energy (Figure 4). Therefore the reduction or dysfunction of this organelles produces severe hydro-electrolytic alterations.

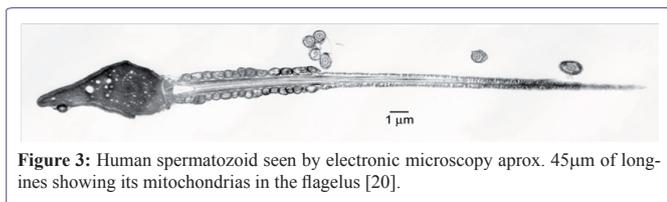


Figure 3: Human spermatozoid seen by electronic microscopy approx. 45µm of longines showing its mitochondrias in the flagelus [20].

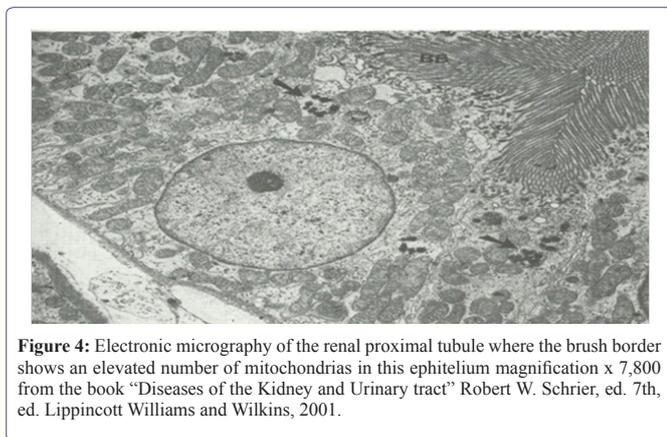


Figure 4: Electronic micrography of the renal proximal tubule where the brush border shows an elevated number of mitochondrias in this epithelium magnification x 7,800 from the book "Diseases of the Kidney and Urinary tract" Robert W. Schrier, ed. 7th, ed. Lippincott Williams and Wilkins, 2001.

Mutations on mitochondrial DNA with neuromuscular clinical presentation are well known and recognized among them is the MELAS syndrome with mitochondrial encephalopathy, lactic acidosis and cerebrovascular stroke; the MERRF syndrome with myoclonic epilepsy with red twisted fibers; the medula and pancreas Pearson syndrome and the Kearns-Sayre syndrome, the Leber hereditary optic neuritis and the Leber plus syndrome in which there is also degeneration of the basal ganglia and dystonia with a variety of parkinsonism that do respond with Levodopa treatment. The Leigh syndrome is a mortal neurodegenerative disease with subcortical brain lesions [21]. Renal diseases can occur in these four syndromes, they show up as nephrotic syndrome and, patients with a puntualmutation in

m3243A>G manifest as Fanconi syndrome in the mitochondrial Pearson and Kearns-Sayre syndromes.

The presence of multisystemic diseases in childhood should suggest the existence of mitochondrial defects especially if they are associated with metabolic acidosis and renal tubular defects. One has to recall that the renal tubulo-interstitial disease with polyuria and hyposthenuria are a very common manifestation of mitochondrial diseases affecting the proximal renal tubule. More than a hundred of mitochondrial diseases inherited with mendelian character have been reported, many of them are associated with nephropathies [22].

Clinical expression of mitochondrial renal cytopathies:

1. Tubulopathies: In the renal proximal tubule is where take place more than the 90% of reabsorption of the necessary elements for the body that are filtrated through the glomeruli and this activity requires most of the time to spend energy (ATP) what explains the elevated number of mitochondrias at this level.

Proximal Tubulopathies:

- a. Toni Debré Fanconi syndrome: With glucosuria, aminoaciduria, phosphaturia proteinuria, uricosuria and kaluresis.
 - b. Proximal Tubular Acidosis: With Bicarbonaturia and hypercalciuria.
 - c. Tubulointerstitialnephropaty: With hypostenuria, poliuria, hypernatriuresis and nicturia
 - d. Bartter syndrome: With metabolic alkalosis, hypokalemia, hyperreninemia, and hyperaldosteronism without arterial hypertension.
2. Glomerulopathies: Nephrotic syndrome with Focal Semental Sclerosis resistant to corticosteroids therapy.
 3. End Stage Renal disease, with elvation of serum creatinine over 1.3 mg/dl, BUN elevation, hyperphosphahemia, hypocalcemia, hyperkalemia, and anemia, hyponatremia of variable degree, hyperparathyroidism and anemia.

The vast majority of patients with renal findings have extra-renal symptoms like muscular findings as myopathies, muscle pain, myoclonus; and also show ocular findings like diplopia, palpebral ptosis, restrictions of ocular movements, pigmentary retinopathy, also course with several neurological findings like psicomotor delay development, seizures, neurosensorial deafness, optic atrophy, myoclonus, pheripherneuropathy, dementia and also show cerebro-vascular events and cardiac findings as blokage of different degrees, disrritmias, hypertrophic concentric cardiomiopathy. Also the endocrine glands may be involved showing as diabetes mellitus, hypoparathyroidism and growth hormone deficiency [23].

The pediatricians and pediatric nephrologist have to be aware of these class of diseases, new discovered of seven defects in the biosynthesis of coenzyme Q10 in three of these COQ2, PDSS2 and COQ6 have an association with a prominent renal phenotype and show up as a corticosteroid resistant nephrotic syndrome with variable association with multisystemic findings as neurosensorial deafness, epilepsy, ataxia and syndromes alike cerebro vascular events. Many progress to End Stage Renal Diseases and require renal replacement function procedures like dialysis either Hemo or peritoneal or Kidney transplantation, nevertheless as it has been pointed out by several researchers that the presymptomatic therapy with Coenzima Q10 in high dosages

can prevent the progression of the renal disease and save of the neurological symptoms [24].

To establish the diagnosis of mitochondrial mutations it is very helpfull the familiar background, in the particular patient the presence of multisystemic disease affecting other organs highly aerobics: brain, liver, muscle, the presence of metabolic acidosis with elevation of lactate and piruvate help to establish the diagnosis but these alterations are not always present. In the kidney the presence of corticoresistant nephrotic syndrome, Fanconi syndrome, poliuria with incapacity to concentrate the urine and the presence of túbulo-intersticial findings in the renal biopsy and or focal segmental sclerosis and the finding in the epithelium of the renal proximal tubule eviudence of mitochondrial dismorphogenesis or its presence in the muscle biopsy help to establish the diagnosis. Up to date more than a 100 mitochondrial diseases heredited in a mendelian way are known, those who affect primarialy the kidney appear on table 1 [25].

Treatment

Unfortunaly currently there are not specific therapy for the mitochondrialscitopathies, in general the therapy is palliative and symptomatic, although there are starting to emerge new options to limit de damage and the progression of these diseases as well new general mesurements to prevent their exhacerbation. In a not far future we will see a change because it has been started the use of proteins and trasporters of biological active molecules to stimulate at the mitochondrial level the synthesis of antioxidants and blockers of mitochondrial apoptosis programs [26].

The Therapy consists of the following mesurament.

General Mesuraments

To prevent disturbances in the oxidative phosphorylation and prevent by this way mitochondrial citopathiesexhacerbations and the aperance of acute liver failure, these include:

- a. Prevention: Prevent the use of commonly use medication that interfiere with the respiratory chain and can cause acute liver failure like valproic acid and barbiturates, prevent the use of comon antibiotics that can alter mitochondrial protein synthesis like tetracyclines and cloranfenicol; also prevent the use of biguanides and steroids.

- b. Infections and extenuated exercercise should be avoid because they can excacerbate the lactic acidosis that has to be treated with a low infusión of sodium bicarbonate and good hydration.
- c. Supplementation: In cases of Complex III deficiency it can improve with Vitamin K3 suplementes (40-60 mg/day) and Coenzyme Q10(80-300mg/day) both show that is early use besides improving the neurological symptoms can have a beneficial effect in the prognostic of renal function. Proton acceptors, Carnitine and Vitamin C are partially effective though there effects are minimal. Use of Citrate solution, potasium, phosphorous, Vitamin-D and fluids may be required for patients with renal tubulopathies with poliuria, renal tubular-acidosis and Fanconi syndrome that produce those deficiencies [27].
- d. Dislipidemia when severe has to be controled because high blood concentrations of free fatty acids can enter the cell and the mitochondriastraspassing their internal membrane incresing their concentrations in this compartament and due to the absence of AcylCoAsynthethasa for large chain free fatty acids they can not be directed to the β oxidative pathway which results in and increased Lipid Peroxidation with lipotoxicity and damage to the mitochondrias, here the treatment besides diet with reduction in the content of mono and polyinsaturated fats has to include PPAR γ agonists using any of them in the appropriate dosages [28].
- e. Antioxidantes: Like omega-3 polyinsaturated fats, the N-acetilcisteine and alopurinol.
- f. Thiazolinedions: Is a PPAR γ useful in patients with adquired-mitochondrial dysfunction due to its anti-inflamatories properties and other immunological effects known currently, they inhibit the production of Tumor necrosis factor alfa, as well as the Nuclear Factor kappa Beta, they also inhibit the attraction and migration of macrophges through the inhibition of macrophge Migration Protein-1 (MP-1), with all thes effects they reduce inflammation and fibrosis and at the renal level they stimulate the Nephtrin gene expression a protein crucial in the renal filter that prevents proteinuria and consequentely the progression of renal disease [29].
- g. Sirtruius and Resveratrol:A new strategy that has demostrated to prolong life span in all the animal species is the caloric restriction [30] but is a complicated task to get to the target and can produce proteins and vitamins deficiencies; on the other hand the Sirtruius family in particular Sirtruin-1 act as desacetylation enzymes of

Molecular defects	Gen(es)	Renal Afection	Other Clinical Findings
Maintainace of	RRM2B, DGUPK, TK2	Proximal Tubulopathy	s. of Mitochondrial DNA depletion
Mitochondrial DNA	SUCLA2, MPV17	3 principal phenotypes: hepato-cerebralmyopathic andcéfalomyopathic	
TranslationMitochondrial(aminoacylation)	SARS2	Tubulointerstiscial salt looser disease and with Hypomagneseemia	Pulmonary hypertension
Mitochondrial Ribosomas	MRPS22	Tubulopathy	HypertrophicCardiomiopathy and Encephalopathy
TranslationMitochondrial (elongation)	TFSM	Tubulopathy	Intrauterine growth delay, hepatic failure and Hipotonicity
Assembly of Complex I	NDUFAF2	Renal Tubular Acidosis	Leigh Syndrome
Assembly of Complex III	BCSIL	Proximal TubulopathyEncephalopathyand Hepatic failure	
Assambley of Complex IV	COX10, SURF 1	Renal Tubulopathy and distal tubular Acidosis(SURF 1)	Leigh Syndrome
Assambley of Complex V	TMEM70	Proximal Tubulopathy	HypertrophicCardiomiopathy
Co-Enzyme Q10	PDSS2, COQ2,COQ6, COQ9	RSNS, Tubulopathy	Seizures, Ataxia, neurosensorialdeafeness, multisystemic disease

Table 1: Molecular Mechanisms responsible of the appearance of Mitochondrial Renal Diseases codify in the celular nucleus [22].

Histones and other proteins regulators of the DNA transcription including HIF-2 α , COX2, PGC- α , Smad3, Smad7, the tumoral-supressor p53, FOXO3, FOXO4, NK- κ β and induce Nitric Oxide Synthesis (NOS), all of them are related with the biogénesis and the mitochondrial function, besides they reduce the oxidative stress, fibrosis and apoptosis [31]. The resveratrol founded in the red grapes and strawberries, cranberries, blueberries, raspberries and red wines (wich is an inductor of Sirtruin-1) improves the mitochondrial function and the lipid concentrations, keep and maintain the PGC-1 α , protecting at the renl level the integrity of the podocytes and therefore the renal filter. Other new Sirtruin-1 agnolist have been described like the mononuclide precursor of NAD⁺ or the riboside that incresase metabolism [32].

Genetic Therapy

- a. Genetic therapy focus to the mitochondrial DNA is directed to correct genetic defects by directly replazing the affected gene or for the reparation of a point mutation are still in a very early satge but they are a promissory research avenue.
- b. MicroRNAs (miRNAs) are small endogens RNAs non-codify but that can interfere with the translation or stability of specific translations that regulte the expression or repression of some genes [33], they have been localized in the mitochondria and for that reason are known as MitomiRs [34].

Conclusion

A great advance has taken place in recent years in the knowledge of mitochondrial citopathies, the mayority are due to nuclear DNA mutations and a minority to mitochondrial DNA mutations, is well known that these diseases affect organs with high energy demands like the brain, the heart, the muscleskeletal, the kidneyand the endocrine system, although must of them have multisystemic and catastrophic symptoms and start early in the first year of life other are not so severe and the early diagnosis and therapy can improve their clinical conditions and prevent the progression of the damage in the affected organs, moreover in the future the genic therapy and the epigenomic medicine using different deacetylation and metylation enzymes and using MitomiRs offer new hope for their therapy.

References

1. Balk J, Pierik AJ, Netz DJ, Mühlenhoff U, Lill R (2004) The hydrogenase-like Nar1p is essential for maturation of cytosolic and nuclear iron-sulphur proteins. *EMBO* 23: 2105-2115.
2. Chial H, Craig J(2008) mtDNA and Mitochondrial Diseases. *Nature Education* 1:217.
3. Ingman M, Kaessmann H, Pääbo S, Gyllensten U (2000) Mitochondrial genome variation and the origin of modern humans. *Nature* 408: 708-713.
4. Francesco Emma, Enrico Bertini (2012) Leonardo Salvati and Giovanni Montini: Renal Involvement in mitochondrial cytopathies, *PediatrNephrol* 27: 539-550.
5. McFarlandR, Taylor RW, Turbull DM (2007) Mitochondrial diseases- its impact, etiology and pathology. *Curr Top Dev Biol* 77: 113-155.
6. Chargaff E (1950) Chemical specificity of nucleic acids and mechanisms of their enzymatic degradation. *experientia* 6: 201-209.
7. <http://www.biography.com/people/rosalind-franklin-9301344>.

8. Wilkins MH, Strokes AR, Wilson HR (1953) Molecular structure of deoxyntose nucleic acid. *Nature*.421: 398-400.
9. Venter JC, Mark D Adams, Eugene W Myers, Peter W Li, Richard J Mural, et al.,(2001) The sequence of the human genoma. *Science* 291: 1304-1351.
10. Michael W Gray, Gertraud Burger, Franz Lang B (1999) *Science* 283: 1476-1481.
11. International Human Genome Sequencing Consortium(2001) *Nature* 409, 860Mark van der Giezen and Jorge Tovar(2005);Degenerate Mitochondria, *EMBO* 6: 525-530.
12. Maechler P, Wolheim CB (2011) Mitochondrial function in normal and diabetic cells. *Nature* 13: 807-812.
13. Allen JF (2003) The function of genomes in bioenergetic organelles. *Philos Trans R Soc B Biol Sci* 358:19-38.
14. Ho Joong Sung, Wenzhe Ma, Ping-yuan Wang, James Hynes, Tomas C. O’Riordan, Christian A. Combs, J. Phillip McCoy Jr, Fred Bunz, Ju-Gyenong Kang Paul, M. Hwang. (2010). *Nature: Communications* 1:1-8
15. Abrahamsen MS, Templeton TJ, Enomoto S, Abrahante JE, Zhu G, et al. (2004) Complete genome sequence of the apicomplexan, *Cryptosporidium parvum*. (2004), Complete genoma sequence of the apicomplexan, *Cryptosporidium parvum*. *Science* 304: 441-445.
16. Wallance DC, Fan W, Procaccio V (2010) Mitochondrial Energetics and Therapeutics. *Annu Rev Pathol* 5: 297-348.
17. Takasi T, Thomas L (2008) Quality control of mitochondria: protection against neurodegeneration and ageing. *EMBO*; 27: 306-314.
18. McBride HM, Neuspiel M, Wasiak S (2006) Mitochondria: more than just a powerhouse.. *Curr Biol* 16: 551-560.
19. Ema F, Enrico B, Leonardo S, Giovanni M (2012) Renal involvement in mitochondrial cytopathies. *Pediatr Nephrol* 27: 539-550.
20. Barratt CLR, Kay V, Oxenham SK (2009) The human spermatozoon - a stripped down but refined machine. *J Biol* 8: 63-66.
21. Schon EA, Manfredi G (2003) Neuronal Degeneration and mitochondrial dysfunction. *J Clin Inves* 111: 303-312.
22. Russell JF, Fu YH, Ptáček LJ (2013) Episodic neurologic disorders: syndromes, genes, and mechanisms. *Annu. Annu Rev Neurosci* 36: 25-50.
23. Che R, Yuan Y, Huang S, Zhang A (2014) Mitochondrial dysfunction in the pathophysiology of renal diseases. *Am J Physiol Renal Physiol* 306: 367-378.
24. Armstrong JS (2007) Mitochondrial Medicine: Pharmacological targeting of mitochondria in disease. *British J Pharmacol* 151: 1154-1165.
25. Emma F, Bertini E, Salvati L, Montini G (2012): Renal involvement in mitochondrial cytopathies. *Pediatr Nephrol* 27: 539-550.
26. Rahman S, Hall AM (2013) Mitochondrial diease-an important cause of end-stage renal failure. *Pediatr Nephrol* 28: 357-361.
27. Kao MP, Ang DS, Gandy SJ, Nadir MA, Houston JG, et al. (2011) Allopurinol benefits left ventricular mass and endotelial dysfunction inchronic kidney disease. *J Am Soc Nephrol* 22: 1382-1389.
28. Ambros V (2004) The Function of animal microRNAs. *Nature* 431: 350-355.
29. Hesselink MKC, Mensink M, Schrauwen P (2007) Lipotoxicity and Mitochondrial Dysfunction in Type 2 Diabetes. *Inmun, Endoc. & Metab. Agents in Med. Chem* 7: 3-17.
30. Sarafidis PA, Stafylas PC, Georgianos PI, Saratzis AN, Lasaridis AN (2010) Effect of Thiazolidinedions on albuminuria and proteinuria in diabetes: a meta-analysis. *Am J Kidney Dis* 55: 835-847.

31. Timmers S, Konings E, Bilet L, Houtkooper RH, van de Weijer T, et. al (2011) Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell Metab* 14: 612-622.
32. Kitada M, Kume S, Takeda-Watanabe A, Kanasaki K, Koya D (2013) Sirtuins and renal diseases: relationship with ageing and diabetic nephropathy *Clin Sci (Lond)* 124: 153-164.
33. Mai A, Valente S, Meade S, Carafa V, Tardugno M, et al. (2009) Study of 1,4-dihydropyridine structural scaffold: discovery of novel sirtuin activators and inhibitors. *J Med Chem* 52: 5496-5504.
34. Bandiera S, Ruberg S, girard M, Cagnard N, Hanein S, et al. (2011) Nuclear outsourcing of RNA interference components to mitochondria. *Plos One* 6: 20746.



Journal of Anesthesia & Clinical Care
Journal of Addiction & Addictive Disorders
Advances in Microbiology Research
Advances in Industrial Biotechnology
Journal of Agronomy & Agricultural Science
Journal of AIDS Clinical Research & STDs
Journal of Alcoholism, Drug Abuse & Substance Dependence
Journal of Allergy Disorders & Therapy
Journal of Alternative, Complementary & Integrative Medicine
Journal of Alzheimer's & Neurodegenerative Diseases
Journal of Angiology & Vascular Surgery
Journal of Animal Research & Veterinary Science
Archives of Zoological Studies
Archives of Urology
Journal of Atmospheric & Earth-Sciences
Journal of Aquaculture & Fisheries
Journal of Biotech Research & Biochemistry
Journal of Brain & Neuroscience Research
Journal of Cancer Biology & Treatment
Journal of Cardiology & Neurocardiovascular Diseases
Journal of Cell Biology & Cell Metabolism
Journal of Clinical Dermatology & Therapy
Journal of Clinical Immunology & Immunotherapy
Journal of Clinical Studies & Medical Case Reports
Journal of Community Medicine & Public Health Care
Current Trends: Medical & Biological Engineering
Journal of Cytology & Tissue Biology
Journal of Dentistry: Oral Health & Cosmesis
Journal of Diabetes & Metabolic Disorders
Journal of Dairy Research & Technology
Journal of Emergency Medicine Trauma & Surgical Care
Journal of Environmental Science: Current Research
Journal of Food Science & Nutrition
Journal of Forensic, Legal & Investigative Sciences
Journal of Gastroenterology & Hepatology Research
Journal of Gerontology & Geriatric Medicine
Journal of Genetics & Genomic Sciences
Journal of Hematology, Blood Transfusion & Disorders
Journal of Human Endocrinology
Journal of Hospice & Palliative Medical Care
Journal of Internal Medicine & Primary Healthcare
Journal of Infectious & Non Infectious Diseases
Journal of Light & Laser: Current Trends
Journal of Modern Chemical Sciences
Journal of Medicine: Study & Research
Journal of Nanotechnology: Nanomedicine & Nanobiotechnology
Journal of Neonatology & Clinical Pediatrics
Journal of Nephrology & Renal Therapy
Journal of Non Invasive Vascular Investigation
Journal of Nuclear Medicine, Radiology & Radiation Therapy
Journal of Obesity & Weight Loss
Journal of Orthopedic Research & Physiotherapy
Journal of Otolaryngology, Head & Neck Surgery
Journal of Protein Research & Bioinformatics
Journal of Pathology Clinical & Medical Research
Journal of Pharmacology, Pharmaceutics & Pharmacovigilance
Journal of Physical Medicine, Rehabilitation & Disabilities
Journal of Plant Science: Current Research
Journal of Psychiatry, Depression & Anxiety
Journal of Pulmonary Medicine & Respiratory Research
Journal of Practical & Professional Nursing
Journal of Reproductive Medicine, Gynaecology & Obstetrics
Journal of Stem Cells Research, Development & Therapy
Journal of Surgery: Current Trends & Innovations
Journal of Toxicology: Current Research
Journal of Translational Science and Research
Trends in Anatomy & Physiology
Journal of Vaccines Research & Vaccination
Journal of Virology & Antivirals

Submit Your Manuscript: <http://www.heraldopenaccess.us/Online-Submission.php>