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Case Report

UP and DOWN Expression of Genes Affects Ion Channels, Oxygen Transport and Mitochondrial Functions in a Case Report Study of Leigh Syndrome

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Abstract

Leigh syndrome is a neurodegenerative disease has an incidence of 1:40,000 live births and is the most frequent mitochondrial disease in the first year of life. The clinical presentation is variable and includes psychomotor retardation or regression, acute or acidotic neurological episodes, hypotonic, ataxia, spasticity, movement disorders, and multifocal spongiform degeneration throughout the brain, including the basal ganglia, thalamus, cerebellum, trunk brain, spinal cord and optic nerves which can be seen on MRI, occurs due to mitochondrial dysfunction caused by an inherited genetic defect, associated with bilateral lesions of the central nervous system. Herein we report a case of a child with clinical signs of pneumonia, acidosis, and a psychomotor and neurological disorder. A mutation in the mitochondrial Cytochrome C, encoded by the SURF1 gene as found by DNA sequencing. Interestingly, the pattern of genes up and down regulated affected different pathways and reactions (p-values <<<). From the metabolism of proteins, digestion and absorption to ion channel and oxygen transport, mitochondrial functions, and neuronal system. Altogether the results point, and strengthen the paramount importance of an integrated clinic, genetic and molecular diagnostic to carefully monitor any adverse reaction that can worst the state of health of the individuals.

Keywords: Mitochondrial Diseases; Leigh; Molecular Techniques; Microarrays; Cytokines

Introduction

Leigh syndrome is a rare neurodegenerative disease that usually manifests in infancy or early childhood. It is a rare, heterogeneous, progressive neurodegenerative disorder caused by mutations in the Mitochondrial DNA or in nuclear genes. It has an incidence of 1:40,000 live births and is the most frequent mitochondrial disease in the first year of life. The clinical presentation is variable and includes psychomotor retardation or regression, acute or acidotic neurological episodes, hypotonic, ataxia, spasticity, movement disorders, and multifocal spongiform degeneration throughout the brain, including the basal ganglia, thalamus, cerebellum, trunk brain, spinal cord and optic nerves which can be seen on MRI, occurs due to mitochondrial dysfunction caused by an inherited genetic defect, associated with bilateral lesions of the central nervous system [5,6,11-13].

The prognosis is usually poor, with a rapid decline in cognitive and motor function leading to death within months or years. Since the identification of the first pathogenic mutation in a patient with LS in 1991, more than 75 disease genes have been identified, most of them thanks to the introduction of next generation sequencing [NGS] technology. Dysfunction is found in LS in a restricted but vital area of mitochondrial metabolism, oxidative phosphorylation, where most cellular ATP is produced. There is no specific treatment, and the prognosis is guarded [11,14]. The genetic etiology is confirmed in about 50% of cases, with more than 60 mutations identified in nuclear or mitochondrial DNA, the latter being responsible for about 10 to 30% of cases. Nuclear DNA mutations are inherited in a Mendelian fashion, with X-linked and autosomal recessive inheritance thought to be the etiology of Leigh Syndrome. Maternal inheritance imparts the disease mutation to all children of an affected woman [13,15]. The onset can begin in utero with oligohydramnios and intrauterine growth restriction, and its variable onset has made the diagnosis present in more age groups. The classic form usually begins before 2 years of age, even in the neonatal period, and presents with hypotonic, epilepsy, respiratory distress, neurodevelopmental delay, ataxia, lactic acidosis, neurodevelopmental failure, ataxia, and lactic acidosis. Most parental complaints are related to loss of head control and other motor milestones and limpness prompt initial medical investigation. [13] Typical neuroimaging reveals symmetric T2-weighted magnetic resonance (MR) imaging hyper intensity in the basal ganglia and/or brain stem with a lactate spike in affected areas, using spectroscopy [16]. These lesions are attributed to ATP depletion, with consequent lacto acidosis, vascular congestion, hypoxia, and finally, necrosis [12]. During disease progression, muscle tissue is altered as aberrant brain function fails to control muscle contraction, leading to hypotonic, dystonia, and ataxia. This makes us think that muscle biopsy can also help to assess the severity of the disease, it is observed that irregular red fibers are found in 51% of muscle biopsies from patients. Therefore, early disease may not show abnormalities in muscle biopsies using light microscopy [17]. Conventional biomarkers used to support the diagnosis of mitochondrial disease in clinical practice are mostly metabolic intermediates, specific enzymes, or end products of anaerobic glucose metabolism, which are the result of impaired oxidative phosphorylation. Identification of molecular signals or metabolic fingerprints of a deficiency in oxidative phosphorylation have the potential to be more useful biomarkers for mitochondrial diseases [18]. The biochemical markers that are considered suggestive of Leigh syndrome are elevated plasma lactate levels, which are usually caused by glucose overload, and in turn, an increase in the lactate/pyruvate ratio; however, its absence does not exclude the diagnosis [12]. While postmortem diagnosis, strictly defined by histopathological observations, to a clinical entity with indicative laboratory, genetic, nuclear and radiological findings [5].

How to approach the treatment of LS patients with any for example periodontal disease? The anesthetic management of pediatric patients with congenital pathologies is notoriously difficult, since it is necessary to know in depth the characteristics of each anomaly in order to achieve effective and safe anesthesia. Patients with advanced sequelae of mitochondrial diseases may experience respiratory failure, cardiac depression, conduction defects, or dysphagia. Several reports suggest that such conditions may be at increased risk of complications during medical procedures using local anesthetics, such as respiratory depression, impaired cardiac function and arrhythmias, metabolic disorders, or severe neurological damage. It should be noted that other amide local anesthetics (ropivacaine and lidocaine) inhibit carnitine-acyl carnitine translocase to a lesser extent and therefore have a smaller detrimental effect than bupivacaine on carnitine-stimulated pyruvate oxidation [24]. Bupivacaine prevents oxidative phosphorylation and inhibits the respiratory

chain by reducing mitochondrial ATP synthesis. The high lipophilicity of bupivacaine can lead to high concentrations in the mitochondria and inhibit the respiratory chain [23]. Unfortunately, almost all general anesthetics studied have been shown to inhibit mitochondrial function. Most notable are volatile anesthetics and propofol (an alkyl phenol, $C_{12}H_{18}O$). There are studies in which it is shown that even at the doses commonly used in the operating room, anesthetics cause significant inhibition of mitochondria in normal patients [25]. Several mechanisms of action have been proposed to explain the cytotoxic effects of local anesthetics, such as: induction of mitochondrial membrane collapse, resulting in prolonged blockade of potassium channels and impaired calcium homeostasis. Local anesthetic molecules interact with phospholipids in cell membranes, causing imbalances in the activity of enzymes such as protein kinase C and phospholipase A2, and affecting mitochondrial energy metabolism, as well as interfering with other cellular communication pathways [26]. Which in turn has shown that highly lipid-soluble local anesthetics can reach the mitochondria and modify the membrane potential of 3T3 fibroblasts [27]. Mitochondrial patients generally require lower doses of general anesthetics, local anesthetics, sedatives, analgesics, and neuromuscular blocking agents (paralyzing agents) to achieve the desired endpoints. In addition, avoiding the increased metabolic load in patients with DM by not requiring prolonged fasting and preventing hypoglycemia, postoperative nausea and vomiting, hypothermia (with consequent chills), chronic application of orthopedic tourniquets, acidosis, and hypovolemia. Regional anesthetic techniques and local anesthetic infiltration provide analgesia without the depressant effects of parenteral opioids on respiratory drive and upper airway tone [30]. There is evidence that long-acting local anesthetics interfere with mitochondrial metabolism, a hypothesis that helps explain the cardiac depression associated with bupivacaine toxicity. Bupivacaine prevents oxidative phosphorylation and inhibits the respiratory chain by reducing mitochondrial ATP synthesis. The high lipophilicity of bupivacaine can lead to high concentrations in the mitochondria and inhibit the respiratory chain [31,32]. Nonsteroidal anti-inflammatory drugs, such as salicylates and ibuprofen commonly prescribed, have side effects that appear to be mediated by a process that includes mitochondrial damage and cyclooxygenase inhibition. These anti-inflammatory drugs modify oxidative phosphorylation, inhibiting ATP production and altering the permeability of the inner membrane. Ibuprofen directly induces the opening of the PPTM [31].

Molecular techniques

DNA sequencing. Whole exome sequencing is used to find mutations (changes) in genes that sometimes cause diseases such as cancer. The exome is the part of the genome (set of DNA molecules) made up of exons, the DNA fragments that are transcribed to give rise to proteins. The study of the exome is one of the most complete and complex ways of studying our DNA. Before explaining what the exome is, we will review some necessary concepts. A gene is the unit of genetic material that provides the necessary information for the synthesis of a protein. A gene is made up of a long chain of nucleotides, in which exons and introns are distinguished. The exons are the coding regions that are going to provide the information for the synthesis of a protein, while the introns are non-coding regions, which are interspersed in the gene and have other functions. The human exome consists of approximately 180,000 exons that constitute about 1% of the total genome (about 30 megabases of DNA).

Microarrays for biomarkers determination leads to a better understanding of the components that determine the disease spectrum of the Syndrome de Leigh. Therefore, this tool represents a powerful and potential alternative to predict or define prognostic or diagnostic tests. Microarrays technologies have enabled biomarkers candidates determination could potentiate the sensibility and specificity of diagnostic and prognostic tests. However, microarrays still need to be scaled and developed for clinical purposes.

Characteristics of the case report

An individual, a 6-year-old male (weight, height, and height) presented several clinical signs, **r**egression in the psychomotor development of the patient, such as neurodevelopmental regression, characteristic of Leigh Syndrome. The parents decided to consult different doctors, including pediatricians, neurologists, ophthalmologists, geneticists. In 2019, they were ordered to carry out an Exome analysis (Massive analysis of point mutations with analysis of the mitochondrial genome) which was carried out successfully, resulting in a pathogenic variant in a homozygous state in the SURF1 gene. The result obtained confirms the genetic

diagnosis of Leigh syndrome due to COX4 deficiency, of autosomal recessive inheritance (OMIM®: 185620).

Background of the case report

Neurological problems

- **THICK:** Head support at four months, sitting without support at five months, rolling over at four months, start of standing with support at twelve months, at the time of assessment with regression of developmental milestones, no path.-FINE: At five months able to take objects with a thick pool and pass it from one hand to another. At nine months I take the spoon and try to put the food in my mouth.
- **LANGUAGE:** He began to babble at six months of life, at eight months he spoke monosyllables and at twenty-four months two-syllables, he currently does not speak.
- **SOCIAL:** Social smile at three months. At six months he clapped and at eight months he waved. Currently attached to parents and sister.

General physiological problems.

- At 11 months of life, the individual presented an infection in the upper airways which triggered high fevers of up to 39* for which antibiotics (amoxicillin) were prescribed, the patient presented secondary reactions to the treatment.
- At 18 months after a bilateral cryptorchidism in which general anesthesia with Propofol was performed, there was a reduction in bicarbonate, which resulted in acidosis.
- At 24 months, psychomotor regression begins, the first regression being head control, the patient after a long episode of constipation was when he lost total control of his head, he began to lose speech and standing.

Clinical finding

Medical consultation, the individual first attended by a private pediatrician, who referred them to a nephrologist, who requested an arterial blood gas in which bicarbonate was found to be altered, for which a differential diagnosis of Renal Tubular Acidosis was given. However, in different renal studies, there were no alterations that gave rise to the patient's symptoms. Therefore, the patient was referred to a specialist in inborn errors of metabolism.

Molecular genetic diagnosis

Mitochondrial DNA sequencing, identification of a variant of the SURF1 gene that codes for Cytochrome c oxidase (COX4; CytC), homozygous recessive mutation, and that causes Leigh Syndrome. - Treatment with Levocarnitine, Biotin, Coenzyme Q10, Riboflavin, Vitamin C, Vitamin E, Citrates and Creatinine.

Physical exploration before periodontal checking.

- 11 November 2020. History of aspiration pneumonia.
- 11 November 2020. History of an infection associated to health care.
- 11 November 2020. Endoscopic gastrostomy and tracheostomy placement in the same intervention in the operating room, extraction of upper central and lateral incisors was performed due to a history of caries. (General anesthesia with Sevorane and local anesthesia with lidocaine)
- December 2020. Orchidopexy at two years, tracheostomy and gastrostomy in December 2020. Molar extraction was performed due to a history of caries. History of hospitalizations due to metabolic decontrol (metabolic acidosis and respiratory distress). Blood transfusion. No drug allergies. (Maternal and child hospital in the city of Saltillo, Coahuila. Mexico).
- 01 June 2021. Home visit, at that time, without dependence on supplemental oxygen with a ventilator, a diagnosis of bruxism was made.
- 08 July 2021. The technique of the parents for gastrostomy feeding was assessed, which was adequate and did not present leaks.
- 19 November 2021. Obstruction of the tracheostomy cannula was reported and a family member reported difficulty aspirating secretions, a replacement was performed without eventualities.
- 20 December 2021. It was reassessed at home due to mismanagement of secretions, nebulization with hypersaline 3% were indicated.
- 16 February 2022. Gastrostomy Mickey Button was replaced
- 24 February 2022. Home consultation was carried out. Limitation for hip abduction was found. The Traumatology service reported that a surgical approach was necessary (both for the hip and for the release of the Achilles heel).

In the light of these clinical features of the disease, parents assessed the risk benefit, deciding to postpone the procedure and seek conservative treatment.

In Abril 2022, blood puncture was made in the clinic lab to evaluate potential genes involved in these clinical signs of LS. The genes UP regulated (n = 423 genes) and DOWN regulated (n = 593 genes). Among those most Up regulated genes (HBA1, α1, β, γ1, mu and θ1) (Z higher than 5.0) involved in s oxygen binding; oxygen carrier activity; binding of alpha Hb, forming part of the part of haptoglobin-hemoglobin complex; of hemoglobin complex. Participate in carbon dioxide transport; in cellular oxidant detoxification, and oxygen transport (Figure 1A Up and Down,

left panel; and Table 1A.1). Furthermore, and of note is that the genes involved in the mitochondria function such as LETM1 (Z = 4.43); TIMM44 (Z = 2.22). The first one related to the Leucine zipper and EF-hand containing transmembrane protein 1, located at in mitochondrial inner membrane located in mitochondrion and involved in calcium export from the mitochondrion, in cristae formation; mitochondrial calcium transmembrane transport. In addition, TIM44, a translocase of inner mitochondrial membrane 44, part of TIM23 mitochondrial import inner membrane translocase complex; mitochondrion; mitochondrial inner membrane, enables ATP binding chaperone, protein binding. And involved in intracellular protein transport, protein import into mitochondrial matrix, protein targeting to mitochondrion. Other genes involved in the mitochondria function are, CKM (Z = 3.04), creatine kinase, mitochondrial 2; the CYP2A7 (Z = 2.1176), cytochrome P450 family 2 subfamily A member 7 and the CYP3A4 (Z = 2.0977), cytochrome P450 family 3 subfamily A member 4, Located respectively in located in mitochondrial inner membrane; in mitochondrion, is active in cytoplasm; in intracellular membrane bounded organelle, and enables ATP binding; creatine kinase activity, protein binding, enables iron ion binding: oxygen binding: oxirreductase activity, enables testosterone 6-beta-hydroxylase activity, CKM participate in muscle contraction; phosphocreatine biosynthetic process, in phosphorylation, while CYP2A7 is involved in coumarin metabolic process; epooxygenase P450 pathway in xenobiotic metabolic process, and CYP3A4 in involved in cholesterol, lipid metabolic process; long chain fatty acid biosynthetic process, androgen metabolic process; Vitamin D, Xenobiotic catabolism, Oxidative demethylation. In addition other genes that are also Up regulated and are involved in immune responses (IFR2, Z = 3.25), BCL11 (BCL11 transcription factor B; Z = 2.317), KIR2DL1 (killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1; Z = 4.6680) and ATG3 (autophagy related 3; Z = 3.87). Located in nucleus, plasma membrane, cytoplasm, in cytosol, part of cytoplasmic ubiquitin ligase complex, part of SWI/SNF complex ; in neuron projection, active in nucleus), and involved in innate immune response, in antiviral response, in natural killer cell inhibitory signaling pathway, in auto phagosome assembly involved, in autophagy of mitochondrion, i protein ubiquitination, and in involved in T cell differentiation in thymus in epithelial cell morphogenesis; in hematopoietic stem cell migration; in keratinocyte development. Moreover, the gene TMEM119 (Z = 4.087), a transmembrane protein 119, located in endoplasmic reticulum membrane; active in plasma membrane, involved_in biomineral tissue development; endochondral ossification; osteoblast differentiation; bone mineralization (Table 1.I).

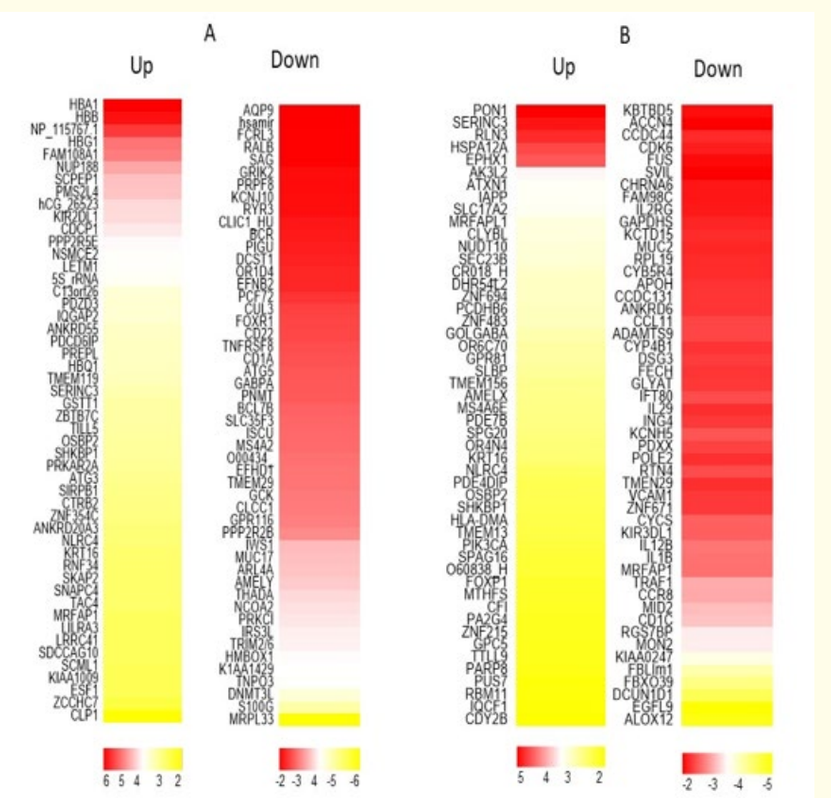

Figure 1: Heat map of the Up and Down regulated genes at systemic level of an individual with Syndrome of Leigh. Total RNA was obtained from whole blood (Mat and Methods) from a child that presented clinic manifestations that resemble Leigh syndrome. Microarray determinations were determined. A.1 Analysis of the Up and Down regulated genes at SD > 2 Up regulated genes with Z values from 3.6 to 5.91, encoding molecular components of the oxygen transport, mitochondrial functions, cellular response to stimuli. A.2. Down regulated genes with Z -2.00 through -6.33 encoding to the Aquaporin's, and other ion channel transporter of small molecules, BCR activator of RhoGEF and GTPase, hsa mir325 (affecting mostly the stability of the mRNAs), and involved in multicellular organism. In B. are represented the Up (Z from 3.2 to 4.95) (B.1) and Down (Z from -2.00 to -3.0) (B.2.) regulated genes from an individual with another non related disease.

A.1

Up regulated		Down regulated	
HBA1	5.90823	AQP9	-2.00126
HBB	5.81085	hsamir	-2.00144
NP1157671	5.57671	FCRL3	-2.01138
HBG1	5.24648	RALB	-2.013312
FAM108A1	5.19641	SAG	-2.01752
NUP188	4.96167	GRIK2	-2.11487
SCPEP1	4.81996	PRPF8	-2.10046
PMS2L4	4.80555	KCNJ10	-2.11372
hCG_26523	4.68145	RYR3	-2.1268
KIR2DL1	4.66887	CLIC1	-2.19959
CDCP1	4.58664	BCR	-2.21985
PPP2R5E	4.49633	PIGU	-2.25566
NSMCE2	4.44222	DCST1	-2.29887
LETM1	4.43137	OR1D4	-2.32553
5S_rRNA	4.40937	EFNB2	-2.3273
C13orf26	4.23447	PCF72	-2.4549
PDZD3	4.21105	CUL3	-2.56032
IQGAP2	4.20767	FOXR1	-2.60034
ANKRD55	4.13943	CD22	-2.6066
PDCD6IP	4.12436	TNFRSF8	-2.66631
PREPL	4.12248	CD1A	-2.6926
HBQ1	4.10387	ATG5	-2.74539
TMEM119	4.08731	GABPA	-2.75271
SERINC3	4.01404	PNMT	-2.76169
GSTT1	3.95624	BCL7B	-2.8385
ZBTB7C	3.95157	SLC35F3	-2.8725
TILL5	3.93887	ISCU	-2.8981
OSBP2	3.91718	MS4A2	-2.9193
SHKBP1	3.90622	O00434_	-2.964
PRKAR2A	3.8729	EFHD1	-2.9898
ATG3	3.82944	TMEM29	-3.0001
SIRPB1	3.7985	GCK	-3.0492
CTRB2	3.77421	CLCC1	-3.0575
ZNF354C	3.76248	GPR116	-3.09022
ANKRD20A3	3.70677	PPP2R2B	-3.1887
NLRC4	3.69354	IWS1	-3.59923
KRT16	3.64777	MUC17	-3.64137
RNF34	3.63119	ARL4A	-3.6722
SKAP2	3.62913	AMELY	-3.73694
SNAPC4	3.62615	THADA	-3.85748
TAC4	3.62067	NCO2	-3.91883
MRFAP1	3.55986	PRKCL	-3.97452
LILRA3	3.55568	IRS3L	-4.0467
LRRC41	3.54678	TRIM2/6	-4.0611
SDCCAG10	3.54653	HMBOX1	-4.15217
SCML1	3.51871	K1AA1429	-4.18804
KIAA1009	3.50955	TNPO3	-4.22044
ESF1	3.50955	DNMT3L	-4.53549
ZCCHC7	3.40922	S100G	-4.94273
CLP1	3.03973	MRPL33	-6.33996

B.1

Up regulated		Down regulated	
PON1	4.95394	K8TBD5	-2.031024
SERINC3	4.88559	ACCN4	-2.002726
RLN3	4.80521	CCDC44	-2.089914
HSPA12A	4.70117	CDK6	-2.065726
EPHX1	4.65124	FUS	-2.023353
AK3L2	4.10273	SVIL	-2.00115
ATXN1	4.04598	CHRNA6	-2.048567
APP	4.04491	FAM98C	-2.046617
SLC17A2	4.03411	IL2RG	-2.054572
MRFAPL1	3.96394	GAPDHS	-2.079756
CLYBL	3.96355	KCTD15	-2.095092
NUDT10	3.93471	MUC2	-2.082601
SEC23B	3.93457	RPL19	-2.092524
CR018_H	3.88747	CYB5R4	-2.095815
OHR54L2	3.87691	APOH	-2.109185
ZNF694	3.87237	CCDC131	-2.11295
PCDHB6	3.85546	ANKRD6	-2.110973
ZNF483	3.85536	CCL11	-2.149558
GOLGABA	3.80031	ADAMTS9	-2.148061
OR6C70	3.75977	CYP4B1	-2.111513
GPR81	3.75845	DSG3	-2.129957
SLBP	3.72549	FECH	-2.114005
TMEM156	3.69225	GLYAT	-2.121047
AMELX	3.68105	IFT80	-2.165338
MS4A6E	3.66477	IL29	-2.100346
PDE7B	3.65406	ING4	-2.122454
SPG20	3.62705	KCNH5	-2.182223
OR4N4	3.60604	PDXX	-2.141643
KRT16	3.59491	POLE2	-2.102102
NLRC4	3.52806	RTN4	-2.160291
PDE4DIP	3.48634	TMEN29	-2.101424
OSBP2	3.48072	VCAM1	-2.119515
SHKBP1	3.47168	ZNF671	-2.12223
HLA-DMA	3.45859	CYCS	-2.205695
TMEM13	3.44029	KIR3DL1	-2.201407
PIK3CA	3.41615	IL12B	-2.251091
SPAG16	3.38651	IL1B	-2.241355
O60838_H	3.37841	MRFAP1	-2.240607
FOXP1	3.34685	TRAF1	-2.363956
MTHFS	3.34366	CCR8	-2.360207
CFI	3.32556	MID2	-2.402419
PA2G4	3.30826	CD1C	-2.418225
ZNF215	3.30451	RGS7BP	-2.5021
GPC5	3.29082	MON2	-2.504488
TTLL9	3.28922	KIAA0247	-2.599387
PARP8	3.28498	FBLIm1	-2.712894
PUS7	3.24102	FBXO39	-2.801435
RBM11	3.23729	DCUN1D1	-2.900176
QCF1	3.22816	EGFL9	-3.075595
CDY2B	3.21029	ALOX12	-3.03517

Table 1

Table 1.I

Gene	Nombre	Function
HBA1	Hemoglobin subunit alpha 1 [Homo sapiens (human)]	The human alpha globin gene cluster located on chromosome 16 spans about 30 kb and includes seven loci: 5'- zeta - pseudozeta - mu - pseudoalpha-1 - alpha-2 - alpha-1 - theta - 3'. The alpha-2 (HBA2) and alpha-1 (HBA1) coding sequences are identical. These genes differ slightly over the 5' untranslated regions and the introns, but they differ significantly over the 3' untranslated regions. Two alpha chains plus two beta chains constitute HbA, which in normal adult life comprises about 97% of the total hemoglobin; alpha chains combine with delta chains to constitute HbA-2, which with HbF (fetal hemoglobin) makes up the remaining 3% of adult hemoglobin. Alpha thalassemias result from deletions of each of the alpha genes as well as deletions of both HBA2 and HBA1; some nondeletion alpha thalassemias have also been reported. [provided by RefSeq, Jul 2008]
HBB	Hemoglobin subunit beta	The alpha (HBA) and beta (HBB) loci determine the structure of the 2 types of polypeptide chains in adult hemoglobin, Hb A. The normal adult hemoglobin tetramer consists of two alpha chains and two beta chains. Mutant beta globin causes sickle cell anemia. Absence of beta chain causes beta-zero-thalassemia. Reduced amounts of detectable beta globin causes beta-plus-thalassemia. The order of the genes in the beta-globin cluster is 5'-epsilon -- gamma-G -- gamma-A -- delta -- beta--3'. [provided by RefSeq, Jul 2008]
NP_115767.1	PRAC1 small nuclear protein	This gene is reported to be specifically expressed in prostate, rectum and distal colon. Sequence analysis suggests that it may play a regulatory role in the nucleus. [provided by RefSeq, Jul 2008]
HBG1	Hemoglobin subunit gamma 1	The gamma globin genes (HBG1 and HBG2) are normally expressed in the fetal liver, spleen and bone marrow. Two gamma chains together with two alpha chains constitute fetal hemoglobin (HbF) which is normally replaced by adult hemoglobin (HbA) at birth. In some beta-thalassemias and related conditions, gamma chain production continues into adulthood. The two types of gamma chains differ at residue 136 where glycine is found in the G-gamma product (HBG2) and alanine is found in the A-gamma product (HBG1). The former is predominant at birth. The order of the genes in the beta-globin cluster is: 5'-epsilon -- gamma-G -- gamma-A -- delta -- beta--3'. [provided by RefSeq, Jul 2008]
FAM108A1	hydrolase domain containing 17A, depalmitoylase	Enables palmitoyl-[protein] hydrolase activity. Involved in protein depalmitoylation and protein localization to membrane. Located in endosome membrane; nuclear speck; and plasma membrane. [provided by Alliance of Genome Resources, Apr 2022]
NUP188	nucleoporin 188	The nuclear pore complex (NPC) is found on the nuclear envelope and forms a gateway that regulates the flow of proteins and RNAs between the cytoplasm and nucleoplasm. The NPC is comprised of approximately 30 distinct proteins collectively known as nucleoporins. Nucleoporins are pore-complex-specific glycoproteins which often have cytoplasmically oriented O-linked N-acetylglucosamine residues and numerous repeats of the pentapeptide sequence XFXFG. However, the nucleoporin protein encoded by this gene does not contain the typical FG repeat sequences found in most vertebrate nucleoporins. This nucleoporin is thought to form part of the scaffold for the central channel of the nuclear pore. [provided by RefSeq, Jan 2013]
SCPEP1	serine carboxypeptidase 1	Predicted to enable serine-type carboxypeptidase activity. Predicted to be involved in negative regulation of blood pressure and retinoic acid metabolic process. Predicted to act upstream of or within blood vessel diameter maintenance. Located in extracellular exosome. [provided by Alliance of Genome Resources, Apr 2022]
PMS2L4	PMS1 homolog 2, mismatch repair system component pseudogene 4	Ubiquitous expression in kidney (RPKM 5.0), thyroid (RPKM 4.0) and 24 other tissues
KIR2DL1	killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1	Killer cell immunoglobulin-like receptors (KIRs) are transmembrane glycoproteins expressed by natural killer cells and subsets of T cells. The KIR genes are polymorphic and highly homologous and they are found in a cluster on chromosome 19q13.4 within the 1 Mb leukocyte receptor complex (LRC). The gene content of the KIR gene cluster varies among haplotypes, although several "framework" genes are found in all haplotypes (KIR3DL3, KIR3DP1, KIR3DL4, KIR3DL2). The KIR proteins are classified by the number of extracellular immunoglobulin domains (2D or 3D) and by whether they have a long (L) or short (S) cytoplasmic domain. KIR proteins with the long cytoplasmic domain transduce inhibitory signals upon ligand binding via an immune tyrosine-based inhibitory motif (ITIM), while KIR proteins with the short cytoplasmic domain lack the ITIM motif and instead associate with the TYRO protein tyrosine kinase binding protein to transduce activating signals. The ligands for several KIR proteins are subsets of HLA class I molecules; thus, KIR proteins are thought to play an important role in regulation of the immune response. [provided by RefSeq, Jul 2008]

Gene	Nombre	Function
CDCP1	CUB domain containing protein 1	This gene encodes a transmembrane protein which contains three extracellular CUB domains and acts as a substrate for Src family kinases. The protein plays a role in the tyrosine phosphorylation-dependent regulation of cellular events that are involved in tumor invasion and metastasis. Alternative splicing results in multiple transcript variants of this gene. [provided by RefSeq, May 2013]
PPP2R5E	protein phosphatase 2 regulatory subunit B'epsilon	The protein encoded by this gene belongs to the phosphatase 2A regulatory subunit B family. Protein phosphatase 2A is one of the four major Ser/Thr phosphatases, and it is implicated in the negative control of cell growth and division. It consists of a common heteromeric core enzyme, which is composed of a catalytic subunit and a constant regulatory subunit, that associates with a variety of regulatory subunits. The B regulatory subunit might modulate substrate selectivity and catalytic activity. This gene encodes an epsilon isoform of the regulatory subunit B56 subfamily. Multiple transcript variants encoding several different isoforms have been found for this gene. [provided by RefSeq, Aug 2013]
NSMCE2	NSE2 (MMS21) homolog, SMC5-SMC6 complex SUMO ligase	This gene encodes a member of a family of E3 small ubiquitin-related modifier (SUMO) ligases that mediates the attachment of a SUMO protein to proteins involved in nuclear transport, transcription, chromosome segregation and DNA repair. The encoded protein is part of the structural maintenance of chromosomes (SMC) 5/6 complex which plays a key role genome maintenance, facilitating chromosome segregation and suppressing mitotic recombination. A knockout of the orthologous mouse gene is lethal prior to embryonic day 10.5. Naturally occurring mutations in this gene, that abolish the SUMO ligase activity, are associated with primordial dwarfism and extreme insulin resistance. [provided by RefSeq, Mar 2017]
LETM1	leucine zipper and EF-hand containing transmembrane protein 1	This gene encodes a protein that is localized to the inner mitochondrial membrane. The protein functions to maintain the mitochondrial tubular shapes and is required for normal mitochondrial morphology and cellular viability. Mutations in this gene cause Wolf-Hirschhorn syndrome, a complex malformation syndrome caused by the deletion of parts of the distal short arm of chromosome 4. Related pseudogenes have been identified on chromosomes 8, 15 and 19. [provided by RefSeq, Oct 2009]
C13orf26	testis expressed 26	Predicted to be active in cytoplasm. [provided by Alliance of Genome Resources, Apr 2022]
IQGAP2	IQ motif containing GTPase activating protein 2	This gene encodes a member of the IQGAP family. The encoded protein contains three IQ domains, one calponin homology domain, one Ras-GAP domain and one WW domain. This protein interacts with components of the cytoskeleton, with cell adhesion molecules, and with several signaling molecules to regulate cell morphology and motility. It also acts as a tumor suppressor and has been found to play a role in regulating innate antiviral responses. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Apr 2017]
ANKRD55	ankyrin repeat domain 55	Biased expression in testis (RPKM 1.8), lymph node (RPKM 0.8) and 10 other tissues
PDCD6IP	programmed cell death 6 interacting protein	This gene encodes a protein that functions within the ESCRT pathway in the abscission stage of cytokinesis, in intralumenal endosomal vesicle formation, and in enveloped virus budding. Studies using mouse cells have shown that overexpression of this protein can block apoptosis. In addition, the product of this gene binds to the product of the PDCD6 gene, a protein required for apoptosis, in a calcium-dependent manner. This gene product also binds to endophilins, proteins that regulate membrane shape during endocytosis. Overexpression of this gene product and endophilins results in cytoplasmic vacuolization, which may be partly responsible for the protection against cell death. Several alternatively spliced transcript variants encoding different isoforms have been found for this gene. Related pseudogenes have been identified on chromosome 15. [provided by RefSeq, Jan 2012]
PREPL	prolyl endopeptidase like	The protein encoded by this gene belongs to the prolyl oligopeptidase subfamily of serine peptidases. Mutations in this gene have been associated with hypotonia-cystinuria syndrome, also known as the 2p21 deletion syndrome. Several alternatively spliced transcript variants encoding either the same or different isoforms have been described for this gene. [provided by RefSeq, Jan 2010]
HBQ1	hemoglobin subunit theta 1	Theta-globin mRNA is found in human fetal erythroid tissue but not in adult erythroid or other nonerythroid tissue. The theta-1 gene may be expressed very early in embryonic life, perhaps sometime before 5 weeks. Theta-1 is a member of the human alpha-globin gene cluster that involves five functional genes and two pseudogenes. The order of genes is: 5' - zeta - pseudozeta - mu - pseudoalpha-2 -pseudoalpha-1 - alpha-2 - alpha-1 - theta-1 - 3'. Research supports a transcriptionally active role for the gene and a functional role for the peptide in specific cells, possibly those of early erythroid tissue. [provided by RefSeq, Jul 2008]

Gene	Nombre	Function
TMEM119	Transmembrane protein 119	Involved in positive regulation of bone mineralization; positive regulation of osteoblast differentiation; and positive regulation of osteoblast proliferation. Located in plasma membrane. [provided by Alliance of Genome Resources, Apr 2022]
NP_066012.1	Methyltransferase 14, N6-adenosine-methyltransferase subunit	Enables mRNA binding activity. Contributes to mRNA (2'-O-methyladenosine-N6-)-methyltransferase activity. Involved in mRNA metabolic process; negative regulation of hematopoietic progenitor cell differentiation; and positive regulation of translation. Located in nucleoplasm. Part of RNA N6-methyladenosine methyltransferase complex. [provided by Alliance of Genome Resources, Apr 2022]
SERINC3	Serine incorporator 3	Predicted to enable L-serine transmembrane transporter activity. Involved in defense response to virus; detection of virus; and innate immune response. Predicted to be located in Golgi apparatus. Predicted to be active in membrane. [provided by Alliance of Genome Resources, Apr 2022]
GSTT1	Glutathione S-transferase theta 1	The protein encoded by this gene, glutathione S-transferase (GST) theta 1 (GSTT1), is a member of a superfamily of proteins that catalyze the conjugation of reduced glutathione to a variety of electrophilic and hydrophobic compounds. Human GSTs can be divided into five main classes: alpha, mu, pi, theta, and zeta. The theta class includes GSTT1, GSTT2, and GSTT2B. GSTT1 and GSTT2/GSTT2B share 55% amino acid sequence identity and may play a role in human carcinogenesis. The GSTT1 gene is haplotype-specific and is absent from 38% of the population. Alternative splicing of this gene results in multiple transcript variants. [provided by RefSeq, Sep 2015]
ZBTB7C	Zinc finger and BTB domain containing 7C	Predicted to enable DNA-binding transcription factor activity, RNA polymerase II-specific and RNA polymerase II cis-regulatory region sequence-specific DNA binding activity. Involved in negative regulation of cell population proliferation. Predicted to be located in nucleus. [provided by Alliance of Genome Resources, Apr 2022]
TTLL5_HUMAN	tubulin tyrosine ligase like 5	This gene encodes a member of the tubulin tyrosine ligase like protein family. This protein interacts with two glucocorticoid receptor coactivators, transcriptional intermediary factor 2 and steroid receptor coactivator 1. This protein may function as a coregulator of glucocorticoid receptor mediated gene induction and repression. This protein may also function as an alpha tubulin polyglutamylase. [provided by RefSeq, Feb 2010]
OSBP2	Oxysterol binding protein 2	The protein encoded by this gene contains a pleckstrin homology (PH) domain and an oxysterol-binding region. It binds oxysterols such as 7-ketocholesterol and may inhibit their cytotoxicity. Alternatively spliced transcript variants encoding multiple isoforms have been observed for this gene. [provided by RefSeq, Sep 2013]
SHKBP1	SH3KBP1 binding protein 1	Enables identical protein binding activity. Predicted to be involved in positive regulation of epidermal growth factor receptor signaling pathway. Predicted to be located in lysosome. [provided by Alliance of Genome Resources, Apr 2022]
PRKAR2A	Protein kinase cAMP-dependent type II regulatory subunit alpha	cAMP is a signaling molecule important for a variety of cellular functions. cAMP exerts its effects by activating the cAMP-dependent protein kinase, which transduces the signal through phosphorylation of different target proteins. The inactive kinase holoenzyme is a tetramer composed of two regulatory and two catalytic subunits. cAMP causes the dissociation of the inactive holoenzyme into a dimer of regulatory subunits bound to four cAMP and two free monomeric catalytic subunits. Four different regulatory subunits and three catalytic subunits have been identified in humans. The protein encoded by this gene is one of the regulatory subunits. This subunit can be phosphorylated by the activated catalytic subunit. It may interact with various A-kinase anchoring proteins and determine the subcellular localization of cAMP-dependent protein kinase. This subunit has been shown to regulate protein transport from endosomes to the Golgi apparatus and further to the endoplasmic reticulum (ER). [provided by RefSeq, Jul 2008]
ATG3	Autophagy related 3	This gene encodes a ubiquitin-like-conjugating enzyme and is a component of ubiquitination-like systems involved in autophagy, the process of degradation, turnover and recycling of cytoplasmic constituents in eukaryotic cells. This protein is known to play a role in regulation of autophagy during cell death. A pseudogene of this gene is located on chromosome 20. Alternative splicing results in multiple transcript variants encoding different isoforms. [provided by RefSeq, Jul 2013]
SIRPB1	Signal regulatory protein beta 1	The protein encoded by this gene is a member of the signal-regulatory-protein (SIRP) family, and also belongs to the immunoglobulin superfamily. SIRP family members are receptor-type transmembrane glycoproteins known to be involved in the negative regulation of receptor tyrosine kinase-coupled signaling processes. This protein was found to interact with TYROBP/DAP12, a protein bearing immunoreceptor tyrosine-based activation motifs. This protein was also reported to participate in the recruitment of tyrosine kinase SYK. Multiple transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Feb 2009]

Gene	Nombre	Function
CTRB2	Chymotrypsinogen B2	This gene encodes a member of the serine protease family of enzymes and forms a principal precursor of the pancreatic proteolytic enzymes. The encoded preproprotein is synthesized in the acinar cells of the pancreas and secreted into the small intestine where it undergoes proteolytic activation to generate a functional enzyme. This CTRB2 gene is located head-to-head with the related CTRB1 gene. Some human populations have an alternate haplotype which inverts a 16.6 Kb region containing portions of intron 1, exon 1, and the upstream sequence of the CTRB1 and CTRB2 genes. In this inversion haplotype exon 1 and flanking sequence is swapped in CTRB1 and CTRB2. This inversion is associated with differential gene expression and increased risk for chronic pancreatitis. The GRCh38 assembly represents the minor allele for SNP rs8048956 of the CTRB1 gene. SNP rs8048956 is diagnostic for this inversion. [provided by RefSeq, Jan 2021]
ZNF354C	Zinc finger protein 354C	Predicted to enable DNA-binding transcription factor activity, RNA polymerase II-specific and RNA polymerase II cis-regulatory region sequence-specific DNA binding activity. Predicted to be involved in regulation of transcription by RNA polymerase II. Located in nucleoplasm. [provided by Alliance of Genome Resources, Apr 2022]
ANKRD20A3	Ankyrin repeat domain 20 family member A3, pseudogene	Biased expression in testis (RPKM 4.5), lung (RPKM 0.8) and 11 other tissues
NLRC4	NLR family CARD domain containing 4	This gene encodes a member of the caspase recruitment domain-containing NLR family. Family members play essential roles in innate immune response to a wide range of pathogenic organisms, tissue damage and other cellular stresses. Mutations in this gene result in autoinflammation with infantile enterocolitis. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Oct 2014]
KRT16	keratin 16	The protein encoded by this gene is a member of the keratin gene family. The keratins are intermediate filament proteins responsible for the structural integrity of epithelial cells and are subdivided into cytokeratins and hair keratins. Most of the type I cytokeratins consist of acidic proteins which are arranged in pairs of heterotypic keratin chains and are clustered in a region of chromosome 17q12-q21. This keratin has been coexpressed with keratin 14 in a number of epithelial tissues, including esophagus, tongue, and hair follicles. Mutations in this gene are associated with type 1 pachyonychia congenita, non-epidermolytic palmoplantar keratoderma and unilateral palmoplantar verrucous nevus. [provided by RefSeq, Jul 2008]
RNF34	Ring finger protein 34	The protein encoded by this gene contains a RINF finger, a motif known to be involved in protein-protein and protein-DNA interactions. This protein interacts with DNAJA3/hTid-1, which is a DnaJ protein reported to function as a modulator of apoptosis. Overexpression of this gene in Hela cells was shown to confer the resistance to TNF-alpha induced apoptosis, suggesting an anti-apoptotic function of this protein. This protein can be cleaved by caspase-3 during the induction of apoptosis. This protein also targets p53 and phospho-p53 for degradation. Alternatively splicing results in multiple transcript variants encoding distinct isoforms. [provided by RefSeq, Feb 2012]
SKAP2	Src kinase associated phosphoprotein 2	The protein encoded by this gene shares homology with Src kinase-associated phosphoprotein 1, and is a substrate of Src family kinases. It is an adaptor protein that is thought to play an essential role in the Src signaling pathway, and in regulating proper activation of the immune system. This protein contains an amino terminal coiled-coil domain for self-dimerization, a plecskstrin homology (PH) domain required for interactions with lipids at the membrane, and a Src homology (SH3) domain at the carboxy terminus. Some reports indicate that this protein inhibits actin polymerization through interactions with actin assembly factors, and might negatively regulate the invasiveness of tumors by modulating actin assembly. Alternative splicing results in multiple transcript variants encoding different isoforms. [provided by RefSeq, Jan 2015]
SNAPC4	Small nuclear RNA activating complex polypeptide 4	This gene encodes the largest subunit of the small nuclear RNA-activating protein (SNAP) complex. The encoded protein contains a Myb DNA-binding domain, and is essential for RNA polymerase II and III polymerase transcription from small nuclear RNA promoters. A mutation in this gene is associated with ankylosing spondylitis. [provided by RefSeq, Jul 2016]
NP_690878.2	N-acetyltransferase domain containing 1	Ubiquitous expression in fat (RPKM 12.3), bone marrow (RPKM 8.0) and 24 other tissues
TAC4	Tachykinin precursor 4	This gene is a member of the tachykinin family of neurotransmitter-encoding genes. Tachykinin proteins are cleaved into small, secreted peptides that activate members of a family of receptor proteins. The products of this gene preferentially activate tachykinin receptor 1, and are thought to regulate peripheral endocrine and paracrine functions including blood pressure, the immune system, and endocrine gland secretion. The products of this gene lack a dibasic cleavage site found in other tachykinin proteins. Consequently, the nature of the cleavage products generated in vivo remains to be determined. Multiple transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Jul 2008]
MRFAP1	Morf4 family associated protein 1	This gene encodes an intracellular protein that interacts with members of the MORF4/MRG (mortality factor on chromosome 4/MORF4 related gene) family and the tumor suppressor Rb (retinoblastoma protein.) The protein may play a role in senescence, cell growth and immortalization. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Jan 2013]

Table 1.II

Gene	Nombre	Function
AQP9	aquaporin 9 [Homo sapiens (human)]	The aquaporins are a family of water-selective membrane channels. This gene encodes a member of a subset of aquaporins called the aquaglyceroporins. This protein allows passage of a broad range of noncharged solutes and also stimulates urea transport and osmotic water permeability. This protein may also facilitate the uptake of glycerol in hepatic tissue . The encoded protein may also play a role in specialized leukocyte functions such as immunological response and bactericidal activity. Alternate splicing results in multiple transcript variants
bSamir	basic helix-loop-helix family member e40	This gene encodes a basic helix-loop-helix protein expressed in various tissues. The encoded protein can interact with ARNTL or compete for E-box binding sites in the promoter of PER1 and repress CLOCK/ARNTL's transactivation of PER1. This gene is believed to be involved in the control of circadian rhythm and cell differentiation. [provided by RefSeq, Feb 2014]
FCRL3	Fc receptor like 3	This gene encodes a member of the immunoglobulin receptor superfamily and is one of several Fc receptor-like glycoproteins clustered on the long arm of chromosome 1. The encoded protein contains immunoreceptor-tyrosine activation motifs and immunoreceptor-tyrosine inhibitory motifs in its cytoplasmic domain and may play a role in regulation of the immune system. Mutations in this gene have been associated with rheumatoid arthritis, autoimmune thyroid disease, and systemic lupus erythematosus. Alternative splicing results in multiple transcript variants
RALB	RAS like proto-oncogene B	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo This gene encodes a GTP-binding protein that belongs to the small GTPase superfamily and Ras family of proteins. GTP-binding proteins mediate the transmembrane signaling initiated by the occupancy of certain cell surface receptors.
SAG	S-antigen visual arretin	Members of arrestin/beta-arrestin protein family are thought to participate in agonist-mediated desensitization of G-protein-coupled receptors and cause specific dampening of cellular responses to stimuli such as hormones, neurotransmitters, or sensory signals. S-arrestin, also known as S-antigen, is a major soluble photoreceptor protein that is involved in desensitization of the photoactivated transduction cascade. It is expressed in the retina and the pineal gland and inhibits coupling of rhodopsin to transducin in vitro. Additionally, S-arrestin is highly antigenic, and is capable of inducing experimental autoimmune uveoretinitis. Mutations in this gene have been associated with Oguchi disease, a rare autosomal recessive form of night blindness
GRIK2	glutamate ionotropic receptor kainate type subunit 2	Glutamate receptors are the predominant excitatory neurotransmitter receptors in the mammalian brain and are activated in a variety of normal neurophysiologic processes. This gene product belongs to the kainate family of glutamate receptors, which are composed of four subunits and function as ligand-activated ion channels. The subunit encoded by this gene is subject to RNA editing at multiple sites within the first and second transmembrane domains, which is thought to alter the structure and function of the receptor complex. Alternatively spliced transcript variants encoding different isoforms have also been described for this gene. Mutations in this gene have been associated
PRPF8	pre-mRNA processing factor 8	Pre-mRNA splicing occurs in 2 sequential transesterification steps. The protein encoded by this gene is a component of both U2- and U12-dependent spliceosomes, and found to be essential for the catalytic step II in pre-mRNA splicing process. It contains several WD repeats, which function in protein-protein interactions. This protein has a sequence similarity to yeast Prp8 protein. This gene is a candidate gene for autosomal dominant retinitis pigmentosa. [provided by RefSeq, Jul 2008] Ubiquitous expression in ovary (RPKM 48.3), testis (RPKM 47.0) and 25 other tissues See more
KCNJ10	Potassium inwardly rectifying channel subfamily J member 10	This gene encodes a member of the inward rectifier-type potassium channel family, characterized by having a greater tendency to allow potassium to flow into, rather than out of a cell. The encoded protein may form a heterodimer with another potassium channel protein and may be responsible for the potassium buffering action of glial cells in the brain. Mutations in this gene have been associated with seizure susceptibility of common idiopathic generalized epilepsy syndromes. [provided by RefSeq, Jul 2008] Biased expression in brain (RPKM 52.7), kidney (RPKM 14.4) and 2 other tissues See more
RYR3	ryanodine receptor 3	The protein encoded by this gene is a ryanodine receptor, which functions to release calcium from intracellular storage for use in many cellular processes. For example, the encoded protein is involved in skeletal muscle contraction by releasing calcium from the sarcoplasmic reticulum followed by depolarization of T-tubules. Two transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Sep 2011]
CLICL1	chloride intracellular channel 1	Chloride channels are a diverse group of proteins that regulate fundamental cellular processes including stabilization of cell membrane potential, transepithelial transport, maintenance of intracellular pH, and regulation of cell volume. Chloride intracellular channel 1 is a member of the p64 family; the protein localizes principally to the cell nucleus and exhibits both nuclear and plasma membrane chloride ion channel activity. [provided by RefSeq, Jul 2008]
BCR	BCR activator of RhoGEF and GTPase	A reciprocal translocation between chromosomes 22 and 9 produces the Philadelphia chromosome, which is often found in patients with chronic myelogenous leukemia. The chromosome 22 breakpoint for this translocation is located within the BCR gene. The translocation produces a fusion protein which is encoded by sequence from both BCR and ABL, the gene at the chromosome 9 breakpoint. Although the BCR-ABL fusion protein has been extensively studied, the function of the normal BCR gene product is not clear. The unregulated tyrosine kinase activity of BCR-ABL1 contributes to the immortality of leukaemic cells. The BCR protein has serine/threonine kinase activity and is a GTPase-activating protein for p21rac and other kinases. Two transcript variants encoding different isoforms have been found for this gene.[provided by RefSeq, Jan 2020] Ubiquitous expression in testis (RPKM 14.9), brain (RPKM 14.5) and 25 other tissues See more
PIGU	phosphatidylinositol glycan anchor biosynthesis class U	The protein encoded by this gene shares similarity with Saccharomyces cerevisiae Cdc91, a predicted integral membrane protein that may function in cell division control. The protein encoded by this gene is the fifth subunit of GPI transamidase that attaches GPI-anchors to proteins. [provided by RefSeq, Jul 2008]

Gene	Nombre	Function
DCSTI	DC-STAMP domain containing 1 [	This gene encodes a protein with a domain similar to one found in dendritic cells (PMID:11169400) which play a key role in antigen processing and display for immune responses. Multiple transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Sep 2011] Biased expression in testis (RPKM 2.9), skin (RPKM 1.8) and 8 other tissues See more
OR11D4	olfactory receptor family 1 subfamily D member 4	Ifactory receptors interact with odorant molecules in the nose, to initiate a neuronal response that triggers the perception of a smell. The olfactory receptor proteins are members of a large family of G-protein-coupled receptors (GPCR) arising from single coding-exon genes. Olfactory receptors share a 7-transmembrane domain structure with many neurotransmitter and hormone receptors and are responsible for the recognition and G protein-mediated transduction of odorant signals. The olfactory receptor gene family is the largest in the genome. The nomenclature assigned to the olfactory receptor genes and proteins for this organism is independent of other organisms. This olfactory receptor gene is a segregating pseudogene, where some individuals have an allele that encodes a functional olfactory receptor, while other individuals have an allele encoding a protein that is predicted to be non-functional. [provided by RefSeq, Jan 2017]
EFNB2	ephrin B2	This gene encodes a member of the ephrin (EPH) family. The ephrins and EPH-related receptors comprise the largest subfamily of receptor protein-tyrosine kinases and have been implicated in mediating developmental events, especially in the nervous system and in erythropoiesis. Based on their structures and sequence relationships, ephrins are divided into the ephrin-A (EFNA) class, which are anchored to the membrane by a glycosylphosphatidylinositol linkage, and the ephrin-B (EFNB) class, which are transmembrane proteins. This gene encodes an EFNB class ephrin which binds to the EPHB4 and EPHA3 receptors. [provided by RefSeq, Jul 2008]
FCF72	cullin 3	This gene encodes a member of the cullin protein family. The encoded protein plays a critical role in the polyubiquitination and subsequent degradation of specific protein substrates as the core component and scaffold protein of an E3 ubiquitin ligase complex. Complexes including the encoded protein may also play a role in late endosome maturation. Mutations in this gene are a cause of type 2E pseudohypoaldosteronism. Alternatively spliced transcript variants encoding multiple isoforms have been observed for this gene. [provided by RefSeq, Mar 2012]
Cul3	cullin 3	This gene encodes a member of the cullin protein family. The encoded protein plays a critical role in the polyubiquitination and subsequent degradation of specific protein substrates as the core component and scaffold protein of an E3 ubiquitin ligase complex. Complexes including the encoded protein may also play a role in late endosome maturation. Mutations in this gene are a cause of type 2E pseudohypoaldosteronism. Alternatively spliced transcript variants encoding multiple isoforms have been observed for this gene. [provided by RefSeq, Mar 2012]
FOXR2	forkhead box R1	his gene encodes a member of the forkhead box (FOX) family of transcription factors. FOX family members are monomeric, helix-turn-helix proteins with a core DNA-binding domain of approximately 110 aa. Many FOX transcription factors play roles in determining cell fates during early development. This forkhead box protein lacks the C-terminal basic region found in many other FOX family members. It is located within the 11q23.3 region which is commonly deleted in neuroblastomas. [provided by RefSeq, Jul 2008] Predicted to enable CD4 receptor binding activity; protein phosphatase binding activity; and sialic acid binding activity. Involved in B cell activation; negative regulation of B cell receptor signaling pathway; and regulation of endocytosis. Located in early endosome and recycling endosome. [provided by Alliance of Genome Resources, Apr 2022]
CD22	CD22 molecule	
TNFRSF8	TNF receptor superfamily member 8	The protein encoded by this gene is a member of the TNF-receptor superfamily. This receptor is expressed by activated, but not by resting, T and B cells. TRAF2 and TRAF5 can interact with this receptor, and mediate the signal transduction that leads to the activation of NF-kappaB. This receptor is a positive regulator of apoptosis, and also has been shown to limit the proliferative potential of autoreactive CD8 effector T cells and protect the body against autoimmunity. Two alternatively spliced transcript variants of this gene encoding distinct isoforms have been reported. [provided by RefSeq, Jul 2008]
CD1A	CD1a molecule	This gene encodes a member of the CD1 family of transmembrane glycoproteins, which are structurally related to the major histocompatibility complex (MHC) proteins and form heterodimers with beta-2-microglobulin. The CD1 proteins mediate the presentation of primarily lipid and glycolipid antigens of self or microbial origin to T cells. The human genome contains five CD1 family genes organized in a cluster on chromosome 1. The CD1 family members are thought to differ in their cellular localization and specificity for particular lipid ligands. The protein encoded by this gene localizes to the plasma membrane and to recycling vesicles of the early endocytic system. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Mar 2016]
ATG5	autophagy related 5	The protein encoded by this gene, in combination with autophagy protein 12, functions as an E1-like activating enzyme in a ubiquitin-like conjugating system. The encoded protein is involved in several cellular processes, including autophagic vesicle formation, mitochondrial quality control after oxidative damage, negative regulation of the innate antiviral immune response, lymphocyte development and proliferation, MHC II antigen presentation, adipocyte differentiation, and apoptosis. Several transcript variants encoding different protein isoforms have been found for this gene. [provided by RefSeq, Sep 2015]
GABPA	GA binding protein transcription factor subunit alpha	This gene encodes one of three GA-binding protein transcription factor subunits which functions as a DNA-binding subunit. Since this subunit shares identity with a subunit encoding the nuclear respiratory factor 2 gene, it is likely involved in activation of cytochrome oxidase expression and nuclear control of mitochondrial function. This subunit also shares identity with a subunit constituting the transcription factor E4TF1, responsible for expression of the adenovirus E4 gene. Because of its chromosomal localization and ability to form heterodimers with other polypeptides, this gene may play a role in the Down Syndrome phenotype. Two transcript variants encoding the same protein have been found for this gene. [provided by RefSeq, Oct 2010]
PNMT	phenylethanolamine N-methyltransferase	The product of this gene catalyzes the last step of the catecholamine biosynthesis pathway, which methylates norepinephrine to form epinephrine (adrenaline). The enzyme also has beta-carboline 2N-methyltransferase activity. This gene is thought to play a key step in regulating epinephrine production. Alternatively spliced transcript variants have been found for this gene. [provided by RefSeq, Nov 2012]

Gene	Nombre	Function
BCLAB	BAF chromatin remodeling complex subunit BCL7B	This gene encodes a member of the BCL7 family including BCL7A, BCL7B and BCL7C proteins. This member is BCL7B, which contains a region that is highly similar to the N-terminal segment of BCL7A or BCL7C proteins. The BCL7A protein is encoded by the gene known to be directly involved in a three-way gene translocation in a Burkitt lymphoma cell line. This gene is located at a chromosomal region commonly deleted in Williams syndrome. This gene is highly conserved from C. elegans to human. Multiple alternatively spliced transcript variants have been found for this gene. [provided by RefSeq, Oct 2010]
SLC35F3	solute carrier family 35 member F3	Involved in thiamine transport. Predicted to be integral component of membrane. [provided by Alliance of Genome Resources, Apr 2022]
ISCU	iron-sulfur cluster assembly enzyme	This gene encodes a component of the iron-sulfur (Fe-S) cluster scaffold. Fe-S clusters are cofactors that play a role in the function of a diverse set of enzymes, including those that regulate metabolism, iron homeostasis, and oxidative stress response. Alternative splicing results in transcript variants encoding different protein isoforms that localize either to the cytosol or to the mitochondrion. Mutations in this gene have been found in patients with hereditary myopathy with lactic acidosis. A disease-associated mutation in an intron may activate a cryptic splice site, resulting in the production of a splice variant encoding a putatively non-functional protein. A pseudogene of this gene is present on chromosome 1. [provided by RefSeq, Feb 2016]
MS4A2	membrane spanning 4-domains A2	The allergic response involves the binding of allergen to receptor-bound IgE followed by cell activation and the release of mediators responsible for the manifestations of allergy. The IgE-receptor, a tetramer composed of an alpha, beta, and 2 disulfide-linked gamma chains, is found on the surface of mast cells and basophils. This gene encodes the beta subunit of the high affinity IgE receptor which is a member of the membrane-spanning 4A gene family. Members of this nascent protein family are characterized by common structural features and similar intron/exon splice boundaries and display unique expression patterns among hematopoietic cells and nonlymphoid tissues. This family member is localized to 11q12, among a cluster of membrane-spanning 4A gene family members. Alternative splicing results in multiple transcript variants encoding distinct proteins. Additional transcript variants have been described but require experimental validation. [provided by RefSeq, Mar 2012]
DNAH3	Axonemal dynein heavy chain.	Axonemal dyneins form the inner and outer rows of arms associated with the doublet microtubules of motile cilia. These enzymes convert the chemical energy released from adenosine triphosphate (ATP). hydrolysis into mechanical work by causing the doublets to slide with respect to each other. Dyneins form two major groups based on the number of heavy-chain motors within of eah complex. In addition, these enzymes contain other components that are required for assembly of the complete that are required for assembly of the complete particles and/or for the regulation of motor function in response to phosphorylations status, ligands such as Ca2+
EFHD1	EF-hand domain family member D1	This gene encodes a member of the EF-hand super family of calcium binding proteins, which are involved in a variety of cellular processes including mitosis, synaptic transmission, and cytoskeletal rearrangement. The protein encoded by this gene is composed of an N-terminal disordered region, proline-rich elements, two EF-hands, and a C-terminal coiled-coil domain. This protein has been shown to associate with the mitochondrial inner membrane, and in HeLa cells, acts as a novel mitochondrial calcium ion sensor for mitochondrial flash activation. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Jul 2016]
TMEM29	family with sequence similarity 156 member A	Predicted to enable methylated histone binding activity. Located in nuclear envelope. [provided by Alliance of Genome Resources, Apr 2022]
GCK	glucokinase	This gene encodes a member of the hexokinase family of proteins. Hexokinases phosphorylate glucose to produce glucose-6-phosphate, the first step in most glucose metabolism pathways. In contrast to other forms of hexokinase, this enzyme is not inhibited by its product glucose-6-phosphate but remains active while glucose is abundant. The use of multiple promoters and alternative splicing of this gene result in distinct protein isoforms that exhibit tissue-specific expression in the pancreas and liver. In the pancreas, this enzyme plays a role in glucose-stimulated insulin secretion, while in the liver, this enzyme is important in glucose uptake and conversion to glycogen. Mutations in this gene that alter enzyme activity have been associated with multiple types of diabetes and hyperinsulinemic hypoglycemia. [provided by RefSeq, Aug 2017]
CLCC1	chloride channel CLIC like 1	Predicted to enable chloride channel activity. Predicted to be involved in chloride transport. Located in endoplasmic reticulum and mitochondria-associated endoplasmic reticulum membrane. Implicated in retinitis pigmentosa 32. [provided by Alliance of Genome Resources, Apr 2022] Ubiquitous expression in brain (RPKM 9.3), thyroid (RPKM 9.3) and 25 other tissues See more
GPR116	ADGRF5 adhesion G protein-coupled receptor F5	Predicted to enable G protein-coupled receptor activity. Predicted to be involved in G protein-coupled receptor signaling pathway and cell surface receptor signaling pathway Predicted to act upstream of or within several processes, including glomerular filtration; pharyngeal arch artery morphogenesis; and surfactant homeostasis. Located in cell surface and cytoplasmic vesicle. [provided by Alliance of Genome Resources, Apr 2022]
PPP2R2B	protein phosphatase 2 regulatory subunit Bbeta	The product of this gene belongs to the phosphatase 2 regulatory subunit B family. Protein phosphatase 2 is one of the four major Ser/Thr phosphatases, and it is implicated in the negative control of cell growth and division. It consists of a common heteromeric core enzyme, which is composed of a catalytic subunit and a constant regulatory subunit, that associates with a variety of regulatory subunits. The B regulatory subunit might modulate substrate selectivity and catalytic activity. This gene encodes a beta isoform of the regulatory subunit B55 subfamily. Defects in this gene cause autosomal dominant spinocerebellar ataxia 12 (SCA12), a disease caused by degeneration of the cerebellum, sometimes involving the brainstem and spinal cord, and in resulting in poor coordination of speech and body movements. Multiple alternatively spliced variants, which encode different isoforms, have been identified for this gene. The 5' UTR of some of these variants includes a CAG trinucleotide repeat sequence (7-28 copies) that can be expanded to 55-78 copies in cases of SCA12. [provided by RefSeq, Jul 2016]
IWS1	interacts with SUPT6H, CTD assembly factor 1	Involved in regulation of histone modification; regulation of mRNA export from nucleus; and regulation of mRNA processing. Located in nucleoplasm. [provided by Alliance of Genome Resources, Apr 2022]

Gene	Nombre	Function
MUC17	mucin 17, cell surface associated	The protein encoded by this gene is a membrane-bound mucin that provides protection to gut epithelial cells. The encoded protein contains about 60 tandem repeats, with each repeat being around 60 aa. N-glycosylation enables the encoded protein to localize on the cell surface, while the C-terminus interacts with the scaffold protein PDZ domain containing 1 (PDZK1). Two transcript variants, one protein-coding and the other non-protein coding, have been found for this gene. [provided by RefSeq, Nov 2015]
ARL4A	ADP ribosylation factor like GTPase 4A	ADP-ribosylation factor-like 4A is a member of the ADP-ribosylation factor family of GTP-binding proteins. ARL4A is similar to ARL4C and ARL4D and each has a nuclear localization signal and an unusually highly guanine nucleotide exchange rate. ARL4A is located in both the nuclear and extranuclear cell compartments. Multiple transcript variants encoding the same protein have been found for this gene.
AMELY	amelogenin Y-linked	This gene encodes a member of the amelogenin family of extracellular matrix proteins. Amelogenins are involved in biomineralization during tooth enamel development. Mtations in a related gene on chromosome X cause X-linked amelogenesis imperfecta. [provided by RefSeq, Jul 2008]
THADA	THADA armadillo repeat containing	type. This gene is the target of 2p21 choromosomal aberrations in benign thyroid adenomas. Single nucleotide polymorphisms (SNPs) in this gene may be associated with 2 diabetes and polycystic ovary syndrome. The encoded protein is likely involved in the death receptor pathway and apoptosis. [provided by RefSeq, Sep 2016]
NCOA2	NCOA2 nuclear receptor coactivator 2	The protein encoded by this gene functions as a transcriptional coactivator for nuclear hormone receptors, including steroid, thyroid, retinoid, and vitamin D receptors. the encoded protein acts as an intermediate factor for the ligand-dependent activity of these nuclear receptors, which regulate their target genes upon binding of cognate response elements this gene has been found to be involved in translocation that result in fusion with other genes in various cancers, including the lysine acetyl-ransferase 6A (KAT6A) gene in acute myeloid leukemia, the ETS variant 6 (ETV6) gene in acute lymphoblastic leukemia, and the hes related family bHLH. transcription factor with YRPW motif 1 (HEY1) gene in mesenchymal chondrosarcoma. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Mar 2016]
PRKC1	protein kinase C iota	This gene encodes a member of the protein kinase C (PKC) family of serine/threonine protein kinases. The PKC family comprises at least eight members which are differentially expressed and are involved in a wide variety of cellular processes. This protein kinase is calcium-independent and phospholipid-dependent. It is not acti-vated by phorbolesters or diacylglycerol. This kinase can be recruited to vesicle independent and phospholipid-dependent. It is not activated by phorbolesters or diacylglycerol tubular clusters (VTCs) by direct interaction with the small GTPase RAB2, where this kinase phosphorylates glyceraldehyde-3-phosphate dehydro-geanse (GAPD/GAPDH) and plays a role in microtubule dynamics in the earlysecretiry oathway. This kinase is found to be necessary for BCL-ABL-mediated resis-tance to drug-induced induced apoptosis and therefore protects leukemia cells against drug- and therefore protects leukemia cells against drug- apoptosis.
IRS3L	insulin receptor substrate 3, pseudogene	There is a single exon pseudogene mapped on chromosome X. [provided by RefSeq, Jul 2008] Predicted to enable phosphatidylinositol 3-kinase binding activity. Predicted to be located in plasma membrane. [provided by Alliance of Genome Resources, Apr 2022]
HMBOX1	homeobox containing 1	Enables double-stranded telomeric DNA binding activity; identical protein binding activity; and sequence-specific double-stranded DNA binding activity. involved in negative regulation of transcription by RNA polymerase II; positive regulation of telomerase activity; and positive regulation of telomere maintenance via telomerase.. Located in several cellular components, including centrosome; chromosome, telomeric region; and nuclear body. [provided by Alliance of Genome Resources, Apr 2022]
K1AA1429	sushi domain containing 6	Involved in cell death and cellular response to DNA damage stimulus. Predicted to be integral component of membrane. [provided by Alliance of Genome Resources, Apr 2022]
TNPO3	TNPO3 transportin 3	The protein encoded by this gene is a nuclear import receptor for serine/arginine-rich (SR) proteins such as the splicing factors SFRS1 and SFRS2. The encoded protein has also been shown to be involved in HIV-1 infection, apparently through interaction with the HIV-1 capsid protein. Several protein-coding and non-coding transcript variants have been found for this gene. [provided by RefSeq, Apr 2020]
DNMT3L	DNA methyltransferase 3 like	CpG methylation is an epigenetic modification that is important for embryonic development, imprinting, and X-chromosome inactivation. Studies in mice have demonstrated that DNA methylation is required for mammalian development. This gene encodes a nuclear protein with similarity to DNA methyltransferases, but is not thought to function as a DNA methyltransferase as it does not contain the amino acid residues necessary for methyltransferase activity. However, it does stimulate de novo methylation by DNA cytosine methyltransferase 3 alpha and is thought to be required for the establishment of maternal genomic imprints. This protein also mediates transcriptional repression through interaction with histone deacetylase 1. Alternatively spliced transcript variants encoding isoforms have been found for this gene. [provided by RefSeq, Jul 2012]
TRIM2/6	tripartite motif containing 6	The protein encoded by this gene is a member of the tripartite motif (TRIM) family. The TRIM motif includes three zinc-binding domains, a RING, B-box type 1 and B-box type 2 domain and a coiled-coil region. The protein localizes to the nucleus, but its specific function has not been identified. This gene is mapped to chromosome , 11p15, where it resides a TRIM cluster. Alternative splicing results in multiple transcripts variant. A read-through transcript from this gene into the downstream TRIM34 gene has also been observed, which results in a fusion product from these neighboring family members [provided by RefSeq, Oct 2010]

Gene	Nombre	Function
S100G	S100 calcium binding protein G	This gene encodes calbindin D9K, a vitamin D-dependent calcium-binding protein. This cytosolic protein belongs to a family of calcium-binding proteins that includes calmodulin,, parvalbumin, troponin C, and S100 protein. In the intestine, the protein is vitamin D-dependent and its expression correlates with calcium transport activity. The protein may increase Ca2+ absorption by buffering Ca2+ in the cytplasm and increase ATP-dependent Ca2+ transport in duodenal basolateral membrane vesicles. [provided by RefSeq, Jul 2008
MRPL33	mitochondrial ribosomal protein L33	Mammalian mitochondrial ribosomal proteins are encoded by nuclear genes and help in protein synthesis within the mitochondrion. Mitochondrial ribosomes (mitoribosomes) consist of a small 28S subunit and a large 39S subunit. They have an estimated 75% protein to rRNA composition compared to prokaryotic ribosomes, where this ratio is reversed. Another difference between mammalian mitoribosomes and prokaryotic ribosomes is that the latter contain a 5S rRNA. Among different species, the proteins comprising the mitorribosome differ greatly in sequence and sometimes in biochemical properties, which prevents easy recognitio by sequence homology .This gene encodes a 39S subunit protein. Alternatively spliced transcripts variants encoding different isoforms have been described [provided by RefSeq, Jul 2008]

By another hand, and insight Reactome data base analysis of the 25 most representative genes, to note is that these genes have the probability (p values, <<<) to react at pathways such as heme signaling, Hemostasis, β-catenin phosphorylation cascade, O2/ CO2 exchange in erythrocyte; factors involved in megakaryocyte development and platelet products, and intestinal infections disease (Table 2A).

In comparison with a gene expression Reactome profile of an unrelated disease (Allergy), the Up regulated genes (Figure 1B Up and Down;, Table 1B.1. right panel), and Table 2A.1 (right panel), Among them, regulation of gene expression genes, cotransporter's of different molecules, relaxin receptors, purine catabolism, G-alpha signaling.

The most DOWN regulated genes (Figure 1B.1) that are involved in the transport are the aquaporin's, AQP9 (Z =

-2.0), active in basolateral plasma membrane; in intracellular membrane-bounded organelle; in plasma membrane, enables water channel activity; glycerol channel activity; purine nucleobase transmembrane transporter act; urea channel activity; involved in amine transport; in water, urea, glycerol transport; in canalicular bile acid transport; in cellular response to cAMP; purine, pyrimidine transport. The gene CLCC1 (Z = -3.05) chloride channel CLIC like 1, located in membrane, nuclear, Golgi; part of chloride channel complex; in mitochondria-associated ER membrane, enables chloride channel activity; protein binding and it is involved in chloride transmembrane transport. CLIC1 (Z = -2.19), chloride intracellular channel 1; nuclear chloride ion channel 27; located in nuclear envelope; in nucleus; in perinuclear region of cytoplasm; in plasma membrane; in vesicle, in nuclear membrane; enables cadherin binding; chloride channel act; protein binding; voltage-gated monoatomic ion channel activity. It is involved in chloride transmembrane transport; in platelet aggregation; in positive regulation of osteoblast differentiation; in regulation of mitochondrial membrane potential; regulation of monoatomic ion transport; in signal transduction. hsa mir325 (Z = .2.0), microRNA 325, part of RISC complex; in extracellular exosome, in extracellular space, and involved in post-transcriptional regulation of gene expression in multicellular organisms by affecting both the stability and translation of mRNAs. BCR (Z = -2.219), BCR activator of RhoGEF and GTPase, located in axon, in cytosol, in plasma membrane, enables ATP binding, GTPase activator act, protein binding, kinase activity, nucleotide exchange factor activity; involved in intracellular protein transmembrane transport; in keratinocyte differentiation, in macrophage migration. ISCU (-2.99), iron-sulfur cluster assembly enzyme, located in mitochondrial matrix; in mitochondrion; cytoplasm, nucleus, enables iron ion binding; zinc ion binding, ferrous binding, protein binding, involved in iron-sulfur cluster assembly; in negative regulation of iron ion import across plasma membrane; in positive regulation of mitochondrial electron transport, NADH to ubiquinone, while the genes that are related also with the mitochondria function and are related to the mutation SURF1, FECH (Z = -3.298), a Ferro chelatase, located in mitochondrial inner membrane; in mitochondrial matrix; is active in mitochondrion, enables 2 iron, 2 sulfur cluster binding; ferrous iron binding; heme binding; iron responsive element binding, protein binding. It is involved in involved in cholesterol metabolic process; in heme biosynthetic process; in iron iron homeostasis; in generation of precursor metabolites and energy as well as in erythrocyte differentiation. TIM50 (Z = -3.33), translocase of inner mitochondrial membrane 50; part of TIM23 mitochondrial import inner membrane translocase complex; mitochondrial inner membrane; in mitochondrion, in nucleoplasm; in nuclear speck; enables protein tyrosine phosphatase activity; ribonucleoprotein complex binding: It is involved in intracellular protein transport ; in mitochondrial mem org; in protein phosphorylation; in protein import into mitochondrial matrix; act upstream of release of cytochrome c from mitochondria. ABCE10 (Z = -2.657), ATP binding cassette subfamily B member 10, located in mitochondrial inner membrane; mitochondrial membrane, in mitochondrion; enables ABC-type transporter activity; ATP binding; ATP hydrolysis act; protein binding. It is involved in erythrocyte development; in heme biosynthetic process; in mitochondrial transport; mitochondrial unfolded protein response. Furthermore, the lowest down regulated genes MRLP33 (Z = 6.33), a mitochondrial ribosomal protein L33. Mammalian mitochondrial ribosomal proteins are encoded by nuclear genes and help in protein synthesis within the mitochondrion. Mitochondrial ribosomes (mitoribosomes) consist of a small 28S subunit and a large 39S subunit. They have an estimated 75% protein to rRNA composition compared to prokaryotic ribosomes, where this ratio is reversed. Another difference between mammalian mitoribosomes and prokaryotic ribosomes is that the latter contain a 5S rRNA. Among different species, the proteins comprising the mitoribosome differ greatly in sequence, and sometimes in biochemical properties, which prevents easy recognition by sequence homology. This gene encodes a 39S subunit protein. Alternatively spliced transcript variants encoding different isoforms have been described. AMELY (Z = -3.7369), AMELY amylogenic Y-linked. This gene encodes a member of the amylogenic family of extracellular matrix proteins. Amelogenins are involved in bio mineralization during tooth enamel development. Mutations in a related gene on chromosome X cause. GRIK2 (Z = -2.11), glutamate ionotropic receptor kainate type subunit 2; excitatory amino acid receptor 4. located in glutamatergic synapse; in hippocampal mossy fiber to CA3 synapse; is active and located in plasma membrane; in presynaptic membrane; enables extracellularly glutamate-gated ion channel activity; kainite selective glutamate receptor act; ligand gated monoatomic channel act. Presynaptic membrane potential. It is involved in behavioral fear response; chemical synaptic transmission; in detection of cold stimulus, in Thermoception; in neuronal action potential; in

glutamate receptor signaling pathway. Other down regulated genes involved in the immune response and in autophagy, are FOXP1 (Z = -2.60), fork head box R, located in chromatin; active and located in nucleus; cytoplasm; enables DNA-binding transcription repressor activity, RNA polymerase II-specific sequence-specific double-stranded DNA binding. It is involved in brain development; in negative, positive regulation of transcription by RNA polymerase II. ATG5 (Z = -2.745), autophagy related 5; APG5 autophagy-5-like; ATG5 autophagy related 5 homolog; located in cytosol, in membrane; part of the Atg12-Atg16 complex of auto phagosome, in membrane; in axioneme; contributes to Atg8 ligase activity; protein binding. It is involved in autophagy; in auto phagosome assembly; in autophagy in mitochondrion; in autophagy in nucleus, in blood vessel remodeling; in heart contraction; in mucus secretion; in negative regulation of cardiac muscle, in cell apoptotic process. TNFRSF8 (Z = -2.60), TNF receptor superfamily member 8, located in cytoplasm; in extracellular exosome; in plasma membrane; enables transmembrane signaling receptor activity. It is involved in cellular response to mechanical stimulus; negative regulation of cell population proliferation, positive regulation of apoptotic process, in signal transduction, in TRAIL production; positive regulation. CD22 (Z = -2.69), B cellular receptor CD22; B-lymphocyte cell adhesion molecule; T cell surface antigen Leu-14; Sialic acid binding Ig-Like lectin 2; is active in plasma membrane; located in plasma membrane; is active in recycling endosome; enables protein phosphatase binding; sialic acid binding; signaling receptor binding. It is involved in B cell activation; in cell adhesion; in regulation of B cell proliferation; in regulation of endocytosis; in regulation of immune responses; in negative regulation of B cell receptor signaling pathway. FCRL3 (Z = -2.01), Fc receptor like 3; located in clathrin-coated endocytic vesicle membrane; in early endosome membrane active in plasma membrane; enables Ig receptor activity; IgG binding; enables transmembrane signaling receptor activity. It is involved in Fc receptor signaling pathway; adaptive immune response, in cell surface receptor signaling pathway, regulation of immune response (Table 1.II).

The Reactome base data analysis of the most 25 down regulated genes shows that he pathways in which there are a high probability that these genes are involved are several around 10 pathways, among them, in the transport of glycerol from the adipocytes into the liver by Aquaporin's (AQP9), passive transport by aquaporins, biogenesis of mitochondria, neurotransmitter receptors and postsynaptic signal transmission. Activation of Ca2+ permeable kainate receptor. Receptor mediated mitophagy (Table 2B). The down regulated genes in allergy individual are most directed to the stimulation of immune responses (STAT-3; IL-13 signaling; eicosanoids; synthesis of leukotriens, and Eoxins), fatty acids; disease of cellular response to stress (Table 2B.1).

Discussion

The Syndrome of Leigh is characterized by psychomotor retardation or regression, acute or acidotic neurological episodes, hypotonic, ataxia, spasticity, movement disorders, and multifocal spongiform degeneration throughout the brain, including the basal ganglia, thalamus, cerebellum, trunk brain, spinal cord and optic nerves which can be seen on MRI, occurs due to mitochondrial dysfunction caused by an inherited genetic defect, associated with bilateral lesions of the central nervous system.

The results of the case study report of an individual with clinical signs of pneumonia, acidosis, psychomotor and neurological problems, a mutation in the gene SURF1 encoding to the mitochondrial cytochrome C, and pattern of up and down regulated genes affecting ion transport and oxygen transport carriers, as well as the mitochondrial function, and neuronal system. The data reported herein point the importance of an early and integrated clinic, genetic and molecular diagnostic to assure that subjects with Leigh syndrome be carefully treated before any surgical intervention or under treatment with antibiotics for potential adverse reactions. The specificity of the Up and Down genes that affect different pathways are represented in Figures 1A (UP and DOWN regulated); Figure 1B (UP and DOWN regulated); Table 1A.1; 1B.1). The identity of the UP regulated genes (n = 50) (Table 1.I) and DOWN regulated genes (n = 50) (Table 1.II). Reactome base data of the 25 most representative gene reactions Table 2A, UP regulated genes (n = 25) in LS. The unrelated disease (Table 2A.1). DOWN regulated genes (Table 2B, UP LS genes), The unrelated disease (Table 2B.1).

Table 2A.1

Up regulated	
PON1	4.95394
SERINC3	4.88559
RLN3	4.80521
HSPA12A	4.70117
EPHX1	4.65124
AK3L2	4.10273
ATXN1	4.04598
IAPP	4.04491
SLC17A2	4.03411
MRFAPL1	3.96394
CLYBL	3.96355
NUDT10	3.93471
SEC23B	3.93457
CR018_H	3.88747
DHR54L2	3.87691
ZNF694	3.87237
PCDHB6	3.85546
ZNF483	3.85536
GOLGABA	3.80031
OR6C70	3.75977
GPR81	3.75845
SLBP	3.72549
TMEM156	3.69225
AMELX	3.68105
MS4A6E	3.66477

Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Regulation of gene expression in beta cells	2 / 35	0.002	0.002	0.119	1 / 12	8.06e-04
Defective SLC34A1 causes hypophosphatemic nephrolithiasis/osteoporosis 1 (NPHLOP1)	1 / 3	1.93e-04	0.005	0.125	1 / 1	6.72e-05
Regulation of beta-cell development	2 / 67	0.004	0.006	0.125	1 / 26	0.002
Type II Na+/Pi cotransporters	1 / 5	3.21e-04	0.009	0.125	1 / 2	1.34e-04
Hydroxycarboxylic acid-binding receptors	1 / 7	4.50e-04	0.013	0.125	1 / 3	2.02e-04
Sodium-coupled phosphate cotransporters	1 / 7	4.50e-04	0.013	0.125	1 / 3	2.02e-04
Relaxin receptors	1 / 8	5.14e-04	0.014	0.129	3 / 4	2.69e-04
SLBP Dependent Processing of Replication-Dependent Histone Pre-mRNAs	1 / 11	7.06e-04	0.02	0.137	3 / 3	2.02e-04
Calcitonin-like ligand receptors	1 / 11	7.06e-04	0.02	0.137	1 / 8	5.37e-04
Atorvastatin ADME	1 / 20	0.001	0.035	0.203	3 / 12	8.06e-04
Synthesis of 5-eicosatetraenoic acids	1 / 24	0.002	0.042	0.203	1 / 4	2.69e-04
Serine biosynthesis	1 / 25	0.002	0.044	0.203	1 / 7	4.70e-04
G alpha (s) signalling events	2 / 190	0.012	0.046	0.203	3 / 28	0.002
Synthesis of pyrophosphates in the cytosol	1 / 29	0.002	0.051	0.203	4 / 15	0.001
Processing of Capped Intronless Pre-mRNA	1 / 30	0.002	0.053	0.207	3 / 10	6.72e-04
Transport of the SLBP Dependant Mature mRNA	1 / 40	0.003	0.069	0.207	3 / 3	2.02e-04
Phosphate bond hydrolysis by NUDT proteins	1 / 41	0.003	0.071	0.207	1 / 17	0.001
Transport of Mature mRNAs Derived from Intronless Transcripts	1 / 47	0.003	0.081	0.207	3 / 9	6.05e-04
Surfactant metabolism	1 / 52	0.003	0.089	0.207	1 / 29	0.002
GPCR ligand binding	3 / 609	0.039	0.095	0.207	5 / 217	0.015
RNA Polymerase II Transcription Termination	1 / 69	0.004	0.117	0.207	1 / 4	2.69e-04
Purine catabolism	1 / 80	0.005	0.134	0.207	1 / 33	0.002
Amyloid fiber formation	1 / 89	0.006	0.148	0.207	2 / 33	0.002
Transport of Mature Transcript to Cytoplasm	1 / 90	0.006	0.15	0.207	3 / 13	8.73e-04
Inositol phosphate metabolism	1 / 90	0.006	0.15	0.207	4 / 71	0.005

Table 2A.1

Table 2A

Up regulated	
HBA1	5.90823
HBB	5.81085
NP1157671	5.57671
HBG1	5.24648
FAM108A1	5.19641
NUP188	4.96167
SCPEP1	4.81996
PMS2L4	4.80555
hCG_26523	4.68145
KIR2DL1	4.66887
CDCP1	4.58664
PPP2R5E	4.49633
NSMCE2	4.44222
LETM1	4.43137
5S_rRNA	4.40937
C13orf26	4.23447
PDZD3	4.21105
IQGAP2	4.20767
ANKRD55	4.13943
PDCD6IP	4.12436
PREPL	4.12248
HBQ1	4.10387
TMEM119	4.08731
SERINC3	4.01404
GSTT1	3.95624

Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Erythrocytes take up oxygen and release carbon dioxide	2 / 16	0.001	4.21e-04	0.038	1 / 6	4.03e-04
Factors involved in megakaryocyte development and platelet production	4 / 194	0.012	4.46e-04	0.038	1 / 43	0.003
Erythrocytes take up carbon dioxide and release oxygen	2 / 24	0.002	9.38e-04	0.039	2 / 8	5.37e-04
O2/CO2 exchange in erythrocytes	2 / 24	0.002	9.38e-04	0.039	3 / 14	9.40e-04
Intestinal infectious diseases	1 / 3	1.93e-04	0.006	0.125	1 / 1	6.72e-05
Uptake and actions of bacterial toxins	2 / 60	0.004	0.006	0.125	3 / 66	0.004
Heme signaling	2 / 70	0.004	0.008	0.125	2 / 25	0.002
RHOG GTPase cycle	2 / 78	0.005	0.009	0.125	2 / 6	4.03e-04
SUMOylation of DNA damage response and repair proteins	2 / 81	0.005	0.01	0.125	5 / 24	0.002
Cytoprotection by HMOX1	2 / 91	0.006	0.012	0.125	3 / 22	0.001
Hemostasis	5 / 804	0.052	0.015	0.125	2 / 342	0.023
Scavenging of heme from plasma	2 / 106	0.007	0.017	0.125	5 / 12	8.06e-04
Truncations of AMER1 destabilize the destruction complex	1 / 14	8.99e-04	0.026	0.125	1 / 1	6.72e-05
APC truncation mutants have impaired AXIN binding	1 / 14	8.99e-04	0.026	0.125	1 / 1	6.72e-05
AXIN missense mutants destabilize the destruction complex	1 / 14	8.99e-04	0.026	0.125	1 / 1	6.72e-05
Signaling by APC mutants	1 / 14	8.99e-04	0.026	0.125	1 / 2	1.34e-04
Signaling by GSK3beta mutants	1 / 15	9.63e-04	0.028	0.125	1 / 1	6.72e-05
Signaling by AMER1 mutants	1 / 15	9.63e-04	0.028	0.125	1 / 2	1.34e-04
Signaling by AXIN mutants	1 / 15	9.63e-04	0.028	0.125	1 / 2	1.34e-04
Signaling by CTNNB1 phospho-site mutants	1 / 16	0.001	0.029	0.125	4 / 4	2.69e-04
CTNNB1 S37 mutants aren't phosphorylated	1 / 16	0.001	0.029	0.125	1 / 1	6.72e-05
CTNNB1 S33 mutants aren't phosphorylated	1 / 16	0.001	0.029	0.125	1 / 1	6.72e-05
CTNNB1 T41 mutants aren't phosphorylated	1 / 16	0.001	0.029	0.125	1 / 1	6.72e-05
CTNNB1 S45 mutants aren't phosphorylated	1 / 16	0.001	0.029	0.125	1 / 1	6.72e-05
Beta-catenin phosphorylation cascade	1 / 19	0.001	0.035	0.125	4 / 4	2.69e-04

Table 2A

Table 2B.1.

Down regulated	
KBTBD5	-2.031024
ACCN4	-2.002726
CCDC44	-2.089914
CDK6	-2.065726
FUS	-2.023353
SVIL	-2.00119
CHRNA6	-2.048567
FAM98C	-2.046617
IL2RG	-2.054572
GAPDHS	-2.079756
KCTD15	-2.095092
MUC2	-2.082601
RPL19	-2.092524
CYB5R4	-2.095815
APOH	-2.109189
CCDC131	-2.11299
ANKRD6	-2.110973
CCL11	-2.149558
ADAMTS9	-2.148061
CYP4B1	-2.111513
DSG3	-2.129957
FECH	-2.114003
GLYAT	-2.121047
IFT80	-2.165338
IL29	-2.100346

Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
STAT3 nuclear events downstream of ALK signaling	2 / 19	0.001	6.33e-04	0.051	3 / 11	7.39e-04
Interleukin-4 and Interleukin-13 signaling	4 / 211	0.014	6.97e-04	0.051	16 / 47	0.003
Eicosanoids	2 / 27	0.002	0.001	0.051	2 / 6	4.03e-04
Miscellaneous substrates	2 / 27	0.002	0.001	0.051	1 / 5	3.36e-04
Fatty acids	2 / 29	0.002	0.001	0.051	2 / 4	2.69e-04
Signaling by ALK	2 / 46	0.003	0.004	0.081	3 / 42	0.003
Synthesis of Leukotrienes (LT) and Eoxins (EX)	2 / 52	0.003	0.005	0.081	3 / 20	0.001
Chemokine receptors bind chemokines	2 / 57	0.004	0.005	0.081	2 / 19	0.001
Evasion of Oxidative Stress Induced Senescence Due to Defective p16INK4A binding to CDK4 and CDK6	1 / 3	1.93e-04	0.006	0.081	1 / 1	6.72e-05
Evasion of Oncogene Induced Senescence Due to Defective p16INK4A binding to CDK4 and CDK6	1 / 3	1.93e-04	0.006	0.081	1 / 1	6.72e-05
Evasion of Oncogene Induced Senescence Due to p16INK4A Defects	1 / 3	1.93e-04	0.006	0.081	1 / 2	1.34e-04
Evasion of Oxidative Stress Induced Senescence Due to p16INK4A Defects	1 / 3	1.93e-04	0.006	0.081	1 / 2	1.34e-04
Diseases of cellular response to stress	1 / 4	2.57e-04	0.008	0.087	1 / 3	2.02e-04
Diseases of Cellular Senescence	1 / 4	2.57e-04	0.008	0.087	1 / 3	2.02e-04
Signaling by Interleukins	5 / 658	0.042	0.008	0.087	70 / 505	0.034
Diseases associated with O-glycosylation of proteins	2 / 78	0.005	0.01	0.109	4 / 9	6.05e-04
Drug-mediated inhibition of CDK4/CDK6 activity	1 / 6	3.85e-04	0.011	0.115	1 / 2	1.34e-04
Highly calcium permeable nicotinic acetylcholine receptors	1 / 11	7.06e-04	0.021	0.151	2 / 2	1.34e-04
Interleukin-9 signaling	1 / 11	7.06e-04	0.021	0.151	7 / 13	8.73e-04
Negative regulation of activity of TFAP2 (AP-2) family transcription factors	1 / 11	7.06e-04	0.021	0.151	1 / 6	4.03e-04
Apoptotic cleavage of cell adhesion proteins	1 / 11	7.06e-04	0.021	0.151	1 / 10	6.72e-04
Interleukin-21 signaling	1 / 12	7.71e-04	0.023	0.151	4 / 5	3.36e-04
Highly calcium permeable postsynaptic nicotinic acetylcholine receptors	1 / 13	8.35e-04	0.025	0.151	2 / 2	1.34e-04
Interleukin-2 signaling	1 / 14	8.99e-04	0.027	0.151	11 / 19	0.001
Conjugation of benzoate with glycine	1 / 14	8.99e-04	0.027	0.151	1 / 2	1.34e-04

Table 2B.1

Note. Pathways that are mostly affected (p-values low)(<< 0) by the up (Table 2A; 2A.1) and down (Table 2B; 2B.2) expression of the genes.

Table 2B.

Down regulated	
AQP9	-2.00126
hsamir	-2.00144
FCRL3	-2.01138
RALB	-2.013312
SAG	-2.01752
GRIK2	-2.11487
PRPF8	-2.10046
KCNJ10	-2.11372
RYR3	-2.1268
CLIC1	-2.19959
BCR	-2.21985
PIGU	-2.25566
DCST1	-2.29887
OR1D4	-2.32553
EFNB2	-2.3273
PCF72	-2.4549
CUL3	-2.56032
FOXR1	-2.60034
CD22	-2.6066
TNFRSF8	-2.66631
CD1A	-2.6926
ATG5	-2.74539
GABPA	-2.75271
PNMT	-2.76169
BCL7B	-2.8385

Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Transport of glycerol from adipocytes to the liver by Aquaporins	2 / 3	1.93e-04	1.72e-05	0.002	2 / 2	1.34e-04
Activation of Ca-permeable Kainate Receptor	2 / 13	8.35e-04	3.19e-04	0.016	2 / 2	1.34e-04
Ionotropic activity of kainate receptors	2 / 14	8.99e-04	3.69e-04	0.016	4 / 4	2.69e-04
Passive transport by Aquaporins	2 / 21	0.001	8.24e-04	0.026	6 / 8	5.37e-04
Activation of kainate receptors upon glutamate binding	2 / 34	0.002	0.002	0.053	4 / 6	4.03e-04
Potassium transport channels	1 / 4	2.57e-04	0.008	0.151	1 / 1	6.72e-05
Aquaporin-mediated transport	2 / 69	0.004	0.008	0.151	8 / 25	0.002
Activation of Na-permeable kainate receptors	1 / 5	3.21e-04	0.01	0.152	2 / 2	1.34e-04
Neurotransmitter receptors and postsynaptic signal transmission	3 / 232	0.015	0.011	0.152	6 / 110	0.007
Transcriptional activation of mitochondrial biogenesis	2 / 89	0.006	0.014	0.163	16 / 32	0.002
Attachment of GPI anchor to uPAR	1 / 10	6.42e-04	0.02	0.181	1 / 2	1.34e-04
Receptor Mediated Mitophagy	1 / 13	8.35e-04	0.026	0.181	1 / 7	4.70e-04
Mitochondrial biogenesis	2 / 129	0.008	0.027	0.181	16 / 36	0.002
RHOBTB3 ATPase cycle	1 / 14	8.99e-04	0.027	0.181	1 / 3	2.02e-04
Transmission across Chemical Synapses	3 / 344	0.022	0.031	0.181	6 / 167	0.011
p38MAPK events	1 / 19	0.001	0.037	0.181	2 / 5	3.36e-04
Activation of the phototransduction cascade	1 / 20	0.001	0.039	0.181	1 / 8	5.37e-04
Catecholamine biosynthesis	1 / 22	0.001	0.043	0.181	1 / 6	4.03e-04
PINK1-PRKN Mediated Mitophagy	1 / 22	0.001	0.043	0.181	1 / 8	5.37e-04
Ephrin signaling	1 / 23	0.001	0.045	0.181	11 / 11	7.39e-04
Signaling by cytosolic FGFR1 fusion mutants	1 / 23	0.001	0.045	0.181	13 / 14	9.40e-04
RHOBTB1 GTPase cycle	1 / 24	0.002	0.047	0.181	1 / 2	1.34e-04
RHOBTB2 GTPase cycle	1 / 24	0.002	0.047	0.181	1 / 2	1.34e-04
Signalling to RAS	1 / 26	0.002	0.05	0.181	2 / 10	6.72e-04
Inactivation of CSF3 (G-CSF)	1 / 27	0.002	0.052	0.181	2 / 9	6.05e-04

Table 2B

The clinic manifestation of the individual with Leigh Syndrome point to a strong effect in all the cellular functions, that includes among many, ion channel transport (Aquaporin), the neurological system, the intestinal (absorption/digestion), the cellular responses to stimuli and all the signal transduction where the grow factor and the second messengers are involved. Gene expression (transcription), The hemostasis or the fibre cloth cascade, the platelet activation, signaling and aggregation. Specifically it is observed that from the genes most up regulated are those genes encoding the different subunits of the hemoglobin (Hb) complex, that function in the erythrocyte oxygen take up and carbon dioxide release (Table 1A). Another set of genes up regulated and that have an impact in the mitochondrial functions are LETM, LRFN2, LRRCR1, Leucine zipper and EF-hand containing transmembrane protein located in mitochondrial inner membrane ;located in mitochondrion, enables calcium ion binding; calcium proton antiporter act; protein binding, involved in calcium export from the mitochondrion, in modulation of chemical synaptic transmission. While TIMM44, TMBiM1, TMEM119, translocase of inner mitochondrial membrane 44 part of TIM23 mitochondrial import inner membrane translocase complex; mitochondrial inner membrane enables ATP binding chaperone, protein binding involved in intracellular protein transport, protein import into mitochondrial matrix, protein targeting to mitochondrion transmembrane. As a molecular function, involved in bio mineral tissue development; endochondral ossification; osteoblast differentiation; bone mineralization.

Many other physiological pathways are affected by clinic manifestation of the gene SURF1 gene, at the level of nucleus, nucleoplasm, and cytoplasm such as. ZCCHC7, ZNF215, ZNF354C, located in nucleus, cytosol and in the nucleoplasm, enables RNA binding; besides the gene ISCU. Iron-sulfur cluster assembly enzyme. Located in mitochondrial matrix; in mitochondrion; cytoplasm, nucleus. Enables iron ion binding; zinc ion binding, ferrous binding, protein binding. Involved in iron-sulfur cluster assembly; in negative regulation of iron ion import across plasma membrane; in positive regulation of mitochondrial electron transport, NADH to ubiquinone. ABCE10. ATP binding cassette subfamily B member 10. Located in mitochondrial inner membrane; mitochondrial membrane, in mitochondrion. Enables ABC-type transporter activity; ATP binding; ATP hydrolysis act; protein binding. Involved in erythrocyte development; in home biosynthetic process; in mitochondrial transport; mitochondrial unfolded protein response. FOXP1. Fork head box R1. Located in chromatin; active and located in nucleus; cytoplasm; enables DNA-binding transcription repressor activity, RNA polymerase II-specific; sequence-specific double-stranded DNA binding. Involved in brain development; in negative, positive regulation of transcription by RNA polymerase II.

Conclusions and Perspectives

On refereeing specifically to a case study of an individual with Leigh syndrome under a odonatological intervention, there is no guide on how to perform dental management which guarantees the absence of complications during the procedures performed, that is, there are various studies which have shown that the use of the local anesthetic lidocaine causes apoptosis and mitochondrial dysfunction in chondrocytes. Individuals after exposure to it, giving similar results when exposed to bupivacaine and ropivacaine. Therefore the use of lidocaine as a local anesthetic can put the patient's condition at risk with mitochondrial diseases, such as LS. Surprisingly, local anesthetic of choice (lidocaine) during multiple dental extractions the individual does not present any negative reaction, however, the reaction is different between different individuals.

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Ethics Approval and Consent to Participate

The study and all the procedures for medical research involving human subjects, including research on identifiable human material and data were performed under the principles of the Declaration of Helsinki, and approved by the ethic committee in Research of the Zacatecas, General Hospital "Luz Gonzalez Cosio" CONBIOETICA-32-CEI-001-20180807.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review.

Competing Interests

The authors declare no competing of interests.

Availability of Data and Material

Data will be shared following institutional guidelines. The review of the literature was based on search and data from Pubmed database without limitation to 202.

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Author's Contributions

B.R.A. patient's contact, L.A.A.G: conceptualization, data analysis, discussion. G.G.G.M. methodology, analysis, discussion and writing. D.C.G. collaboration in patient's contact, discussion. G.A.M.L. methodology.

Discussion, Analysis

All authors have read and approved the manuscript.

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