Sys Rev Pharm 2019; 10(1):173-178 *Original Research*
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

Ratio of *JAG1* and *NOTCH2* gene mutation characteristics in children with alagille syndrome at Children's hospital 1 in Ho Chi Minh city, Vietnam

Tram Van Ta [1,*], Tuan Anh Nguyen[2], Truong Viet Nguyen[3]
[1]Tien Giang General Hospital, Tien Giang province, Vietnam.
[2] University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam.
[3] Children Hospital 1 in Ho Chi Minh City, Ho Chi Minh city, Vietnam.

Article History: *Submitted: 12.03.2019* *Revised: 28.07.2019* *Accepted: 19.10.2019*

ABSTRACT
Background: The early diagnosis of ALGS is crucial because the disease is often a variable expression, and the symptoms are similar to other pathologies, especially biliary tract atrophy. The primary objective of this study was determined of the ratio of JAG1 and NOTCH2 gene mutation characteristics in children with Alagille syndrome (ALGS).
Methods: Batch description of the cases was performed on 32 pediatric patients with ALGS treated at Childrend's Hospital 1 from February 2015 to December 2018.
Results: Based on the study of 32 children with ALGS, the following results were obtained: The JAG1 gene mutation detection rate is 75%; No instances of NOTCH2 gene mutation were detected. The meaningless mutation rate was 33%, the false means was 29%, the split frame was 21%, the cutting connector was 13%, and the loss of the small segment was 4%. Mutations were distributed on most exons, and the surge screening ratio of JAG1 patient's relatives with mutations was 23.5%.
Conclusion: Results indicated that early diagnosis of ALGS based on JAG1 or NOTCH2 mutations is possible.

Keywords: ALGS, Alagille syndrome, gene mutation, JAG1, NOTCH2, Vietnam.

Correspondence:
Tram Van Ta (PhD., MD.)
Tien Giang General Hospital, Vietnam.
Address: 02 Hung Vuong Street, Ward 1, My Tho City, Tien Giang province, Vietnam.
Phone: (+84) 2733872363
Fax: (+84) 2733876702
Mobile: (+84) 913771779
Email: tavantram@gmail.com
DOI: 10.5530/srp.2019.1.32

INTRODUCTION

Alagille Syndrome (ALGS) is a rare disorder that occurs on the autosomal dominant, affecting many different organ systems, including the liver, heart, eyes, spine, and face [1, 2]. The disease was best described by Daniel Alagille in 1975[3]and was reported with an incidence of 1:70,000 for newborns [4]. Therefore, a diagnostic criteria for hepatic biliary dysplasia in combination with at least three major clinical symptoms was established. In 1997, a mutation of the *JAGGED1* gene (*JAG1*) of chromosome 20 was identified asthe main cause of ALGS[5, 6],and in 2006, a small percentage of *NOTCH2* gene mutations (<1%) was also identifiedas the second largest cause of the disease [7].Hence,ALGS diagnostic criteria were changed to includescreening for the mutant gene that causes*JAG1* or *NOTCH2* and a major clinical manifestation.

The early diagnosis of ALGS is crucial because the disease often manifests with a variety of symptoms that are similar to other conditions, especially biliary atrophy and especially in newborns. As a result, children are often misdiagnosed and subjected to unnecessary interventions that can severely affect the prognosis of diseases such as Kasai surgery[8-10]. Supportive treatment, specifically symptomatic treatment with appropriate nutrition, has been shown to significantlyimprove patients' quality of life. The prognosis is mainly based on liver and heart pathologies[11]. While heart damage usually results in premature death, liver diseases contribute to the decision to make a late death[12].

In the Gastroenterology Department atChildren's Hospital 1, the diagnosis of ALGS is typicallybased on clinical practice, andmisdiagnosis with biliary atrophy is common, which affects the patient's quality of life. Patient is fully monitored, so the prognosis for liver disease is not predicted. Due tothese challenges, this study was conducted to determine the rate of JAG1 and NOTCH2 gene mutation traits of children with ALGS, which contributesto the diagnosis and early diagnosis of ALGS to plan care and conduct earlier follow-up evaluates and treatmentto improve the quality of life for ALGS children.

METHODS

Study design

In this study, a series of cases at Children's Hospital 1 from February 2015 to December 2018 was evaluated, which included all patients with ALGS, to determine the rate of *JAG1* and *NOTCH2* gene mutations in childrenwith ALGS.

Sampling

The study applied the whole sampling method,whereby all the selected eligible samples were saved in the hospital database during the examination of the study sample selection criteria.

Inclusion and Exclusion Criteria

Inclusion criteria

- Children under 16 years oldwith at least three of the five main clinical symptoms of ALGS, including (1) liver abnormalities, (2) heart abnormalities, (3) spinal abnormalities, (4) eye abnormalities and/or (5) abnormal facial; or
- Children with a mutation associated with the *JAG1* or *NOTCH2* gene plus at least one of the main clinical symptoms; and
- Children with relatives (i.e., father, mother, sibling) who had the mutated gene causing *JAG1* or *NOTCH2* and agreed to genetic screening.

Exclusion criteria

- Children or parents who did not agree to participate in the research;
- Cases where not enough data had been collected for the study;
- Patients who had been previously diagnosed with ALGS.

Statistiacal analysis

Genetic analytical data collected from children and their relatives, including mutation location, mutation genes, mutation types, and clinical manifestations, were entered using Epidata 3.0 software and then analyzed using Stata 13.0 software.

Ethical cosiderations

The research protocol was reviewed and approved by the ethics committee at Children's Hospital 1 before the study was conducted. When respect to sampling, parents or guardians of each child first agreed to participate in the study and were assured that the information obtained would only be used for scientific research. Children with parents or guardians who did not agreeto participate in the study were omitted from consideration.

RESULTS

From February 2015 to December 2018, 32 patients were clinically diagnosed with ALGS in accordance with inclusionand exclusion criteria. All 32 cases were analyzed for the presence of JAG1 and NOTCH2 gene mutations. Results revealed mutations causing *JAG1*were present in 24 cases (75%), whileno cases of gene *NOTCH2* mutation were found.

Table 1. Genetic mutation characteristics in ALGS children (N=24)

No. of patient	Mutant gene	Exon location	Mutation (*)	Protein	Domain of influence (**)	Source	Type of mutation
1.	*JAG1*	Ex2	c.110T>C	p.L37S	NL	UK	MM
2.	*JAG1*	Ex2	c.247C>T	p.Q83X	NL	New	NM
3.	*JAG1*	Ex4	c.550C>T	p.R184C	DSL	UK	MM
4.	*JAG1*	Ex4	c.550C>T	p.R184C	DSL	New	MM
5.	*JAG1*	Ex4	c.550C>T	p.R184C	DSL	UK	MM
6.	*JAG1*	Ex4	c.590delA	p.197fs	DSL	New	FM
7.	*JAG1*	Ex4	c.551G>A	p.R184H	DSL	New	MM
8.	*JAG1*	Ex4	c.551G>A	p.R184H	DSL	UK	MM
9.	*JAG1*	Ex6	c.839G>A	p.W280X	UK	New	NM
10.	*JAG1*	Ex8	IVS8-12C>T	r. spl?	EGF	New	SFM
11.	*JAG1*	Ex8	c.1022-1023delTC	p.L342X	EGF	New	NM
12.	*JAG1*	Ex9	c.1156G>A	p.G386R	EGF	New	MM
13.	*JAG1*	Ex10	c.1326G>A	p.W442X	EGF	UK	NM
14.	*JAG1*	Ex10	c.1349-1G>T	r. spl?	EGF	Father	SFM
15.	*JAG1*	Ex12	c.1456-1457insA	p.R486fsX490	EGF	Father	FM
16.	*JAG1*	Ex15	c.1914T>A	p.C638X	EGF	New	NM
17.	*JAG1*	Ex16	c.2074-2079del	p.D692-C693del	EGF	Father	DM
18.	*JAG1*	Ex18	c.2271-2272insGG	p.T758fsX820	EGF	New	FM
19.	*JAG1*	Ex18	c.2274-2275delAT	p.759fs	EGF	UK	FM
20.	*JAG1*	Ex20	c.2419G>T	p.E807X	EGF	New	NM
21.	*JAG1*	Ex20	c.2422-2423insG	p.C808fsX8	EGF	New	FM
22.	*JAG1*	Ex21	c.2473C>T	p.Q825X	EGF	UK	NM
23.	*JAG1*	Ex23	c.2916+1G>A	r. spl?	UK	New	SFM
24.	*JAG1*	Ex24	c3031G>T	p.E1011X	UK	Mother	NM

Notes: (*): GenBank RefSeq: NM_000214.
(**): GenBank RefSeq: NP_000205.1
MM: Missense mutation, NM: Nonsense mutation, FM: Frameshift mutation, SFM: Splicing Factor Mutations, DM: Deletions mutation, NL: Notch ligand, DSL: Delta serrate ligand, UK: Unknown, EGF: epidermal growth factor, r.spl?: mutant cut off position, C: Cysteine, D: Aspartate, E: Glutamate, H: Histidine, L: Leucine, Q: Glutamine, R: Arginine, S: Serine, T: Threonine, W: Trytophan

The genetic mutation characteristics in those children with ALGS were further examined.All were JAG1 mutations, the majority were new mutations, and thtere were many different mutations in many different places, which affects the power and domain of influence of many functional proteins (Table 1).

Table 2. Type of mutatios in JAG1 gen with ALGS children(N=24)

Type of mutation	n	%
Missense mutation	7	29.0
Nonsense mutation	8	33.0
Frameshift mutation	5	21.0
Splicing Factor Mutations	3	14.0
Deletions mutation	1	4.0

The JAG1 gene mutations included nonsense mutations, parallax mutations, frame deflection mutations, splicing mutations, and one small fragment mutation. In particular, the most common type of meaningless mutations (33%) (Table 2).As shown in Table 3, most mutations were found in the JAG1 exon genes, and in particular, the location mutation exon 4 was the most common (6 cases).

Table 3. JAG1 mutation position (N = 24)

Location	Type of mutation					Total
	Missense mutation	Nonsense mutation	Frameshift mutation	Splicing Factor Mutations	Deletions mutation	
exon 2	1	1	0	0	0	2
exon 4	5	0	1	0	0	6
exon 6	0	1	0	0	0	1
exon 8	0	1	0	1	0	2
exon 9	1	0	0	0	0	1
exon 10	0	1	0	1	0	2
exon 12	0	0	1	0	0	1
exon 15	0	1	0	0	0	1
exon 16	0	0	0	0	1	1
exon 18	0	0	2	0	0	2
exon 20	0	1	1	0	0	2
exon 21	0	1	0	0	0	1
exon 23	0	0	0	1	0	1
exon 24	0	1	0	0	0	1

Table 4. Characteristics of single nucleotide polymorphism

Single nucleotide polymorphism	Location
IVS1-85C>T	Region connected toexon 1
IVS2 +85C>T	Region connected to exon 2
c.247C>T (p.Q83X) (rs1051415)	Exon 2
IVS3-15T>C	Region connected to exon 3
c.526G>A (p.V176I)	Exon 4
IVS11+11T>G	Region connected to exon 11
IVS12+68T>G	Region connected to exon 12
IVS12 -136T>A	Region connected to exon 12
IVS19+80T>A	Region connected to exon 19
g.32770-32771insA	Exon 22
c.2612C>G(p.P871R)(rs35761929)	Intron 23
p.P1174L	Exon 26

Single nucleotide polymorphisms are diverse and can occur in many different locations, such as exons, introns, or junctions (Table 4, Figure 1).

Table 5. Frequency of detection of the JAG1 mutation in relatives of ALGS patients (N = 17)

Relatives (n=26)	n	%
Father(n=9)	3	17.6
Mother(n=15)	1	5.9
Brotther/sister (n=2)	0	0
Total	4	23.5

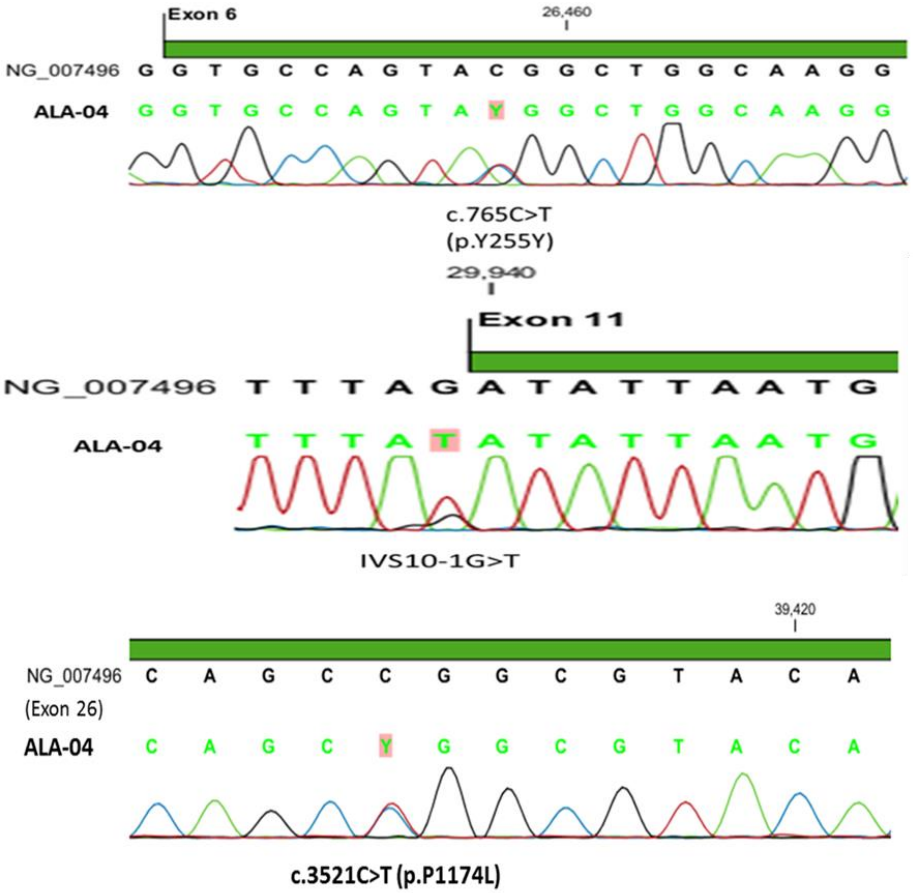

Figure 1.Single nucleotide polymorphisms in a patient with ALGS.

Twenty-six relatives from 17 ALGS patients with the *JAG1* mutation agreed to participate in the *JAG1* mutation screening. As a result, the detection rate for the *JAG1* mutation was very low, with only 4 cases of detection (3 cases from the fathers and 1 case from the mothers (Table 5).

DISCUSSION

JAG1 mutation percentage

A genetic analysis of 32 ALGS cases found a 75% *JAG1* mutation rate, while no mutations in the Notch receptor gene (*NOTCH2*) were found. In particular, the rate of detection of the *JAG1* mutation in patients displaying three main clinical symptoms, four main clinical symptoms, and five main clinical symptoms were 63%, 88.2%, and 57.2%, respectively. This indicated that the frequency of clinical symptom expression did not affect the rate of detection of the*JAG1* gene mutation. This result is consistent with the results reported in other studies that also concluded that there was no relationship between the mutant gene and its trait expression [12].

In addition, the mutation rate of the*JAG1* gene in this study wassimilar to the rates found byLi L.(76.9%)[5], Jurkiewicz D.(74.3%)[13], and Cho JM. (74%)[14], while it was higher than the rates found byCrosnier C. (63%)[15], Krantz ID. (69%)[16]and lower than the rate found by Lin HC. (86%)[17]. It is important to note that the actual rate of detection of the JAG1 mutation in the actual study was not as high as expected compared to the literature (> 90%)[5, 6].Although the new genome sequencing methods were applied foreight patients without the JAG1 mutation, the NOTCH2 gene mutation wasnot detected, which waslikelydue to the very low incidenceof NOTCH2 gene mutation (<1%)[7]and the relatively small sample size. In addition, a small percentage of patients met the criteria for diagnosing ALGS but did not have JAG1 or NOTCH2 mutations. This is an Alagille-like syndromecaused by an inherited autosomal dominant mutation, which is unrelated to the JAG1 or NOTCH2 gene and has been reported in an indigenous Canadian family [18].People with this disease

present with biliary dysplasia, cholestasis, and pulmonary stenosis[19]. Therefore, in addition to the small sample size in this study, the genetic analyticaltechniques were also limited (i.e. the large fragment and the entire JAG1 gene were not investigated). Other genetic factors that cause clinical symptoms of ALGS must be further investigated.

Type of mutationsin *JAG1* gene

Based on research from the NCBI gene bank, different types of mutations in different locations havea significant effect on proteins. As a result, the affected protein regions include NL (Notch ligand), DSL (Delta serrate ligand), EGF (Epidermal growth factor), and unspecified regions. These mutations are usually recent mutations, though some are inherited from one parent, whileothers are unknown due to a lack of screening of the parents of ALGS patients (i.e. relatives did not agree to participate in the screening).

Results of the genetic analysis in this study revealedfivecommon mutations that were similar to those reported inprior studies. Most prior studies indicatedthat the most common frame deflection mutation is the most common meaningless mutation, which is different than the results found in this study. This is important because the stop mutation usually affects the protein structure relative to the frameshift mutation.In addition, the study also found onecase of small segment loss (4%) and no cases of large segment loss (the study has not been surveyed). The frequency of small segment loss found in this study was lower than the frequencies reported byLi L. (7.1%), Jurkiewicz D. (30.7%), and Lin HC. (16.7%). Moreover, the author Cho JM.[14], Krantz ID.[16], Crosnier C.[15]The author did not detect any case of mutations disappear chromosomes.

Spiner (2001) reported on 233 ALGS patients from Europe, the United States, Australia, and Japan, and it was estimated that about 60-75% of patients with ALGS were clinically diagnosed (i.e., patients displaying at least three of the five main clinical symptoms of main clinical) with a *JAG1* mutation. Of these patients, 3-7% had genetic deletions,and the remainder hadintragenic mutations [20]. Of the 168 patients with mutations, many haddislocated frames, whichledto premature protein coding termination and 13% of the false mutations. The rate of meaningless mutations was no greater than 33%, while the other studies wereframe mutations. Mutations were wrong (29%) higher than other studies at 13%. Thus, in this study, there were no cases of total gene loss orlarge gene fragment (becauseanalysishad not yet been conducted), mainly mutations in the gene, in which the meaningless mutations accounted for the highest proportion. However, the limitation in this research study wasassociated with the relatively small sample size, andit is necessary to have studies with a larger sample size to properly reflect the mutationcharacteristicsof ALGS children in Vietnam.

Location distribution of mutants JAG1

Regarding the location of mutations, the resultsindicatedthat exon 4 (6 cases) wasmore affected than other exons, including exons 2, 6, 8, 9, 10, 12, 15, 16, 18, 20, 21, 23, and 24, though it is important to note that all exons can be affected. This result was consistent with the results reported byLi Ln.(2015)[5], Jurkiewicz D. (2014)[13], Cho JM.(2014)[14], Lin HC. (2012)[17], Crosnier C.(1999)[15], and Krantz ID.(1998)[16]. According to the literature, no specific location of the gene has been identified, thoughall regions of the coding position maybe related [20]. This suggests that mutations can occur anywhere on the JAG1 gene, without beingconcentrated in specific exons.

Characteristics of single nucleotide polymorphism

When peroformingdirect sequencing of the JAG1 gene, a number of structural changes in the gene were noted, thoughthese structures are considered to be normal because they occur in healthy people, and their synthetic protein products are not affected by the function. power. These structural changes are characterized by a single nucleotide polymorphism. The results if this study indicated there were12 polymorphic polymorphs among the children with ALGS, which mainly focused on exons 1,2, 3, 4, 11, 12, 19, 22, 26 and one case onintron 23. This contributes to the diversity of JAG1 genotype in Vietnamese ALGS children. Results of the mutation survey of patient ALGS-04 indicatedthat their JAG1 gene has 3 point mutations, of which 2 mutations are reportedly non-pathogenic (SNP: p.Y255Y (rs1131695) -Ex6 - heterozygous and p.P1174L (rs775363555) -Ex26-heterozygous). The IVS10-1G> T mutation has never been reported, which means that the newly discovered mutation is highly likely to cause disease because the mutation site is a conservative location for intron-exon splice identification. It is thus highly likely that it will affect the maturation of the mRNA of the JAG1 gene, leading to a change in this gene protein. However, because the technique used in thisstudy has not been effectively used to determined how the protein is affected, the consequences of this mutation have yet to be investigated.

The frequency of detection of JAG1 mutation in relative of ALGS patients

This study included the screening of 26 patient's relatives (9 fathers, 15 mothers, and 2 siblings), and there were no abnormal clinical manifestations (no history of abnormal liver, heart, eye, spine, etc.), kidney, face) in17 ALGS infants who had a *JAG1* mutation. Among these relatives, fourof themwere found to have the JAG1 mutation gene (3 fathers, 1 mother), including the IVS10-1G> T mutations (cut mutations), c.1456-1457insA-Ex12 (bias mutation frame), c3031G> T (p.E1011X) - Ex24 (meaningless mutations), and p.del D692-C693 - Ex16 (small-segment mutation), while no sibling cases were detected. This result indicatedthat no cases of false mutations were detected in thegenetic screening of therelatives of patients with the *JAG1* gene mutation. Affordable, only nonsense mutations, splicing, dislocations and deletions are likely genetic and false mutations usually mutations occur. However, due to the relatively small sample size, the results were not conclusive with respect to this issue. It is important to note thatwhen conditional execution with larger sample sizes. The frequency of detection of JAG1 gene mutations in patient's relatives was23.5%.According to the literature, about 30-50% of individuals have a gene that causes a genetic disease and 50-70% have a new disease gene. Mosaic mutations can occur with a frequency of 8%[12, 15, 16].Mutation screening will help detect diseases in individuals without clinical manifestations. It will also contribute to tracking for hidden anomalies of ALGS as well as help improvegenetic consultations. For parents with children who have a disease caused by a new gene, the risk of it

developing in the next child is very low, but higher than the general population due to the ability to mosaicmutation[21]. Children of ALGS patients have a 50% risk of having ALGS. Oncethe pathogen gene in the family members has been identified, a prenatal test may be performed onpregnant women. However, prenatal testing does not predict the likelihood or the severity of clinical manifestations.This screening is entirely voluntary, and it isbased on the relative's wishes after the disease and the meaning of the screening resultshave been explained. Most patients do not agree to participate due to their fear of disease detection, andwithout their consent, the screening is not performed.

CONCLUSION

This study only revealed mutations in the JAG1 gene, with the most common being the meaningless mutation, which occurred on many different exons and affected many different protein regions. In addition, the clinical characteristics of ALGS diagnosis were not found to be associated with the rate of gene mutation. The characteristics of JAG1 single-nucleotide polymorphism are very diverse, and the vast majority of gene mutations are relatively recent, with only a few inheriting from one parent. For those who intend to conduct further research on this subject, it is important to note that most relatives of patients do not agree to participate in genetic screening after they are fully informed, which can lead to having relatively small samples sizes.

REFERENCES

1. Guandalini, S., A. Dhawan, and D. Branski, Textbook of pediatric gastroenterology, hepatology and nutrition. A Comprehensive Guide to practice, 2016. 2015939902. https://doi.org/10.1007/978-3-319-17169-2
2. Turnpenny, P.D. and S. Ellard, Alagille syndrome: pathogenesis, diagnosis and management. European Journal of Human Genetics, 2012. 20(3): p. 251. https://doi.org/10.1038/ejhg.2011.181
3. Alagille, D., et al., Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac murmur. The Journal of pediatrics, 1975. 86(1): p. 63-71. https://doi.org/10.1016/s0022-3476(75)80706-2
4. Danks, D., et al., Studies of the aetiology of neonatal hepatitis and biliary atresia. Archives of disease in childhood, 1977. 52(5): p. 360-367. https://doi.org/10.1136/adc.52.5.360
5. Li, L., et al., JAG1 mutation spectrum and origin in Chinese children with clinical features of Alagille syndrome. PloS one, 2015. 10(6): p. e0130355. https://doi.org/10.1371/journal.pone.0130355
6. Oda, T., et al., Mutations in the human Jagged1 gene are responsible for Alagille syndrome. Nature genetics, 1997. 16(3): p. 235. https://doi.org/10.1038/ng0797-235
7. Mattei, P., et al., Relief of intractable pruritis in Alagille syndrome by partial external biliary diversion. Journal of pediatric surgery, 2006. 41(1): p. 104-107. https://doi.org/10.1016/j.jpedsurg.2005.10.014
8. Rajnish Gupta (2019) Cadmium Nanoparticles And Its Toxicity. Journal of Critical Reviews, 6 (5), 1-7. http://dx.doi.org/10.22159/jcr.2019v6i5.34073
9. De Melo P N. "Polycystic Ovary Syndrome (PCOS)." International Journal of Pharmacy Research & Technology 8.2 (2018), 48-50. Print. http://dx.doi.org/10.31838/ijprt/08.02.06
10. Abdul Qader, O.A.J., Sukmasari, S., Doolaanea, A.A., Abdul Rahman, M.N., Ismail, A.F. "The effect of incorporating Baccaurea Angulata extract on rheological properties of various gelling polymers(2018)", International Journal of Pharmaceutical Research, 10 (2), pp. 246-250. https://doi.org/10.1155/2018/8406193
11. Dhorne-Pollet, S., et al., Segregation analysis of Alagille syndrome. Journal of medical genetics, 1994. 31(6): p. 453-457. https://doi.org/10.1136/jmg.31.6.453
12. Kamath, B.M., et al., Systematic review: the epidemiology, natural history, and burden of Alagille syndrome. Journal of pediatric gastroenterology and nutrition, 2018. 67(2): p. 148. https://doi.org/10.1097/mpg.0000000000001958
13. Jurkiewicz, D., et al., Spectrum of JAG1 gene mutations in Polish patients with Alagille syndrome. Journal of applied genetics, 2014. 55(3): p. 329-336. https://doi.org/10.1007/s13353-014-0212-2
14. Han, S., et al., Imaging findings of Alagille syndrome in young infants: differentiation from biliary atresia. The British Journal of Radiology, 2017. 90(1077): p. 20170406. https://doi.org/10.1259/bjr.20170406
15. Gilbert, M.A. and N.B. Spinner, Alagille syndrome: genetics and functional models. Current pathobiology reports, 2017. 5(3): p. 233-241. https://doi.org/10.1007/s40139-017-0144-8
16. Krantz, I.D., et al., Spectrum and frequency of jagged1 (JAG1) mutations in Alagille syndrome patients and their families. The American Journal of Human Genetics, 1998. 62(6): p. 1361-1369. https://doi.org/10.1086/301875
17. Lin, H.C., et al., Alagille syndrome in a Vietnamese cohort: mutation analysis and assessment of facial features. American Journal of Medical Genetics Part A, 2012. 158(5): p. 1005-1013. https://doi.org/10.1002/ajmg.a.35255
18. Dyack, S., et al., An autosomal recessive form of Alagille-like syndrome that is not linked to JAG1. Genetics in Medicine, 2007. 9(8): p. 544. https://doi.org/10.1097/gim.0b013e318133a802
19. Dyack, S., et al., An autosomal recessive form of Alagille-like syndrome that is not linked to JAG1. Genetics in Medicine, 2007. 9(1): p. 544-550. https://doi.org/10.1097/gim.0b013e318133a802
20. Spinner, N.B., et al., Jagged1 mutations in Alagille syndrome. Human mutation, 2001. 17(1): p. 18-33. https://doi.org/10.1002/1098-1004(2001)17:1<18::aid-humu3>3.0.co;2-t
21. Laufer-Cahana, A., et al., Alagille syndrome inherited from a phenotypically normal mother with a mosaic 20p microdeletion. American journal of medical genetics, 2002. 112(2): p. 190-193. https://doi.org/10.1002/ajmg.10616