

## The role of ATP-binding cassette transporter A2 in childhood acute lymphoblastic leukemia multidrug resistance

Aberuyi N MSc<sup>1</sup>, Rahgozar S PhD<sup>1,\*</sup>, Moafi A PhD<sup>2</sup>

1. Division of Cell and Molecular Biology, Department of Biology, Faculty of Science, University of Isfahan, Iran

2. Department of Paediatric-Oncology, SayedolShohada Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

Received: 6 May 2014

Accepted: 7 August 2014

### Abstract

Acute lymphoblastic leukemia (ALL) is one of the most prevalent hematologic malignancies in children. Although the cure rate of ALL has improved over the past decades, the most important reason for ALL treatment failure is multidrug resistance (MDR) phenomenon. The current study aims to explain the mechanisms involved in multidrug resistance of childhood ALL, and introduces ATP-binding cassette transporter A2 (ABCA2) as an ABC transporter gene which may have a high impact on MDR.

Benefiting from articles published in reputable journals from 1994 to date and experiments newly performed by our group, a comprehensive review is written about ABCA2 and its role in MDR regarding childhood ALL.

ABCA2 transports drugs from the cytoplasm into the lysosomal compartment, where they may become degraded and exported from the cell. The aforementioned mechanism may contribute to MDR. It has been reported that ABCA2 may induce

resistance to mitoxantrone, estrogen derivatives and estramustine. It is resistant to the aforementioned compounds. Furthermore, the overexpression of ABCA2 in methotrexate, vinblastine and/or doxorubicin treated Jurkat cells are observed in several publications. The recent study of our group shows that the overexpression of ABCA2 gene in children with ALL increases the risk of MDR by 15 times.

ABCA2 is the second identified member of the ABCA; ABC transporters' subfamily. ABCA2 gene expression profile is suggested to be an unfavorable prognostic factor in ALL treatment. Better understanding of the MDR mechanisms and the factors involved may improve the therapeutic outcome of ALL by modifying the treatment protocols.

### Keywords

Leukemia, drug resistance, ATP-binding cassette transporter

### Corresponding Author:

Rahgozar S PhD, Division of Cell and Molecular Biology, Department of Biology, Faculty of Science, University of Isfahan, Iran. Email: rahgozar@sci.ui.ac.ir.

### Introduction

Cancer is the second most important factor causing death in developing countries (1) and a main health concern worldwide (2). Leukemia is one of the commonly reported cancers (9%) (3) including 34% of all cases among the children under 15-year-olds (4) and 28 to 30% of cases below 18-year-olds (5). Acute lymphoblastic leukemia (ALL) is one of the four types of hematologic malignancies among children with the highest frequency (6). Despite enhancing the efficiency of treatment for childhood ALL, multidrug resistance (MDR) is remained a serious impediment in this regard (7-11). MDR is a multifactorial phenomenon (12, 13) which mostly attributed to ABC transporters (10, 12, 13). ABCA2 is the second member of the A subfamily of ABC transporters which may have a role in MDR (14,

15). Our group has recently suggested that ABCA2 is related to poor prognosis in childhood ALL (7, 16, 17). The present study is a literature based review article which explains the aforementioned topics, especially the impact of ABCA2 in multidrug resistance of childhood ALL.

### Acute lymphoblastic leukemia (ALL)

Acute lymphoblastic leukemia is one of the most important blood cancers in human kind (6) and it is a malignant illness of white blood cells (18). This kind of leukemia includes 32 percent of cancers in children under 15 years old (19) and it includes 80 percent of cases of blood cancers in children (5, 7, 8). The vast majority of the cases are between 2 to 5 years old (20). In a research that is conducted in Iran,

it is revealed that this prevalent cancer contains 36 percent of the cases (21). The World Health Organization (WHO) divides ALL into 3 groups (22):

1. Precursor B acute lymphoblastic leukemia/lymphoma

2. Burkitt leukemia/lymphoma/mature B

3. Precursor T acute lymphoblastic leukemia/lymphoma

Genetic and environmental factors engage in accession of ALL. The examples of these genetic factors are wrong expression of protooncogenes, more than 50 chromosome hyperdiploidy and chromosome translocations that create fusion genes that code active kinases and changed transcription factors (23, 24). These disorders maybe influenced by changed DNA repair and the control processes of cell cycle(25). The instances of influential environmental factors are the impact of electromagnetic waves, some viral pollutions and smoking of parents. These factors help the progress of leukemia by making secondary genetic changes. Some rare genetic syndromes exposed under radio therapy, and heavyweight born children are instances of some other factors which may improve the risk of ALL. The rate of survival in childhood ALL had a significant increase in some countries, during more than four decades (26). Five-year survival rates, since 1990 to 1994 raised to 83.7% (27). Some countries have achieved the rate of long-term survival, in more than 80% of children suffering from ALL from 1 to 10 years old (28, 29). Including them, Iran has revealed a survival rate of 56.6% in a study performed in Shiraz (30). However, despite the successes in treatment of childhood ALL, the difficult challenge in the treatment of these children is resistance to chemotherapy (7-11). Due to the increased outflow of a wide range of chemotherapeutic drugs from inside of the cell to the outside, this resistance was named multidrug resistance (10). In ALL, the biological features of leukemia cells (number and translocations of chromosomes) and clinical properties (including: age, leukocyte counting at the time of diagnosis) are efficient prognostic factors for treatment selection including the number and dosage of drugs chosen in chemotherapy.

### **Multidrug resistance (MDR)**

MDR is a phenomenon through which cancer cells become resistant to variety of anti-cancer drugs which are functionally and structurally unrelated and discrete (10, 12, 13, 31, 32). MDR mechanisms in cancers were studied extensively and identified as multifactorial and complex phenomenon (12, 13). MDR induction is related to the changes of some molecular pathways (33). The loss of drug transporter proteins on the surface of the cell, change or mutation in drug specific targets (12), decrease in absorption of

water soluble drugs, DNA damage repair, decrease in apoptosis and increase in energy dependent efflux of hydrophobic drugs affect these molecular pathways (33, 34)(figure 1).

There are 2 groups of "resistance to anti-cancer drugs":

1. Those that disturb drug delivery to cancer cells.  
2. Those that emerge in cancer cells through genetic and epigenetic changes and affect drug sensitivity.

Dysfunction in drug delivery can be the result of weak absorption of prescribed oral medicines or increase in medicinal metabolism and excretion, which may contribute to tumor growth (35). A proved and important recently proposed reason of MDR (10, 12, 13, 33, 36, 37) (figure 2) is the increased expression of ATP-binding cassette (ABC) transporters, that extract a variety of chemotherapeutic drugs from the cell and prevent an appropriate response to cure (10, 38, 39).

### **ABCA2 transporter**

ABC transporters are transmembrane proteins[40] acting as uniporter carrier (to inside or outside of the cell) of a variety of substrates (36, 41-44) across the intracellular (organelles) and cytoplasmic membrane (33, 40, 45). This uniporter is against the concentration gradient and depends on ATP hydrolysis (33, 34, 44, 46). This large group of protein family which has 49 members (33, 40, 42, 47-49) is divided into 7 subfamilies from A to G (12, 36, 40, 44, 46-48, 50-52). These transporters are engaged in energy dependent transporting of xenobiotic and other toxic compounds, as well as, anti-cancer natural materials (12), and consequently they develop resistance to chemotherapy in various cancers including lymphoblastic and myeloid leukemia (53). The second member of ABCA subfamily is an endolysosomal protein which is related to lipid transport and drug resistance and is named ABCA2 (54, 55). It is a large and symmetric protein with a channel-like functional structure. This functional structure is placed in the membrane (56). ABCA2 protein, like other members of this family, contains two symmetric halves containing a long cytoplasmic regulator domain in between. Cytoplasmic regulator domain contains a high hydrophobic sequence that dips into the membrane (figure 3) (14). This protein contains 2436 amino acids (43, 57) and its molecular weight is almost 250 kDa (14, 57). ABCA2 protein has the highest homology with ABCA1 (14, 57-59) and it is cleared that this high amount of same homology is due to the duplication of ancestral gene during the evolution [14]. This gene is located on the q arm of chromosome 9, near the ABCA1 gene (13, 14, 42, 43, 47, 56, 57, 59-61). ABCA2 gene contains 48 exons (54) and in comparison with other transporters that have 32 to 250 kbp gene length, but

this gene, unexpectedly, has 21 kbp (14, 57). The coding region length of this gene is 7.3 kbp (57). Additionally, two transcriptions are recognized for this gene (62). ABCA2 protein, is located on inner vesicles (63) such as late endosomes, lysosomes (14, 64-66), trans Golgi (67) and endoplasmic reticulum (44, 45, 55, 62, 68, 69). For detoxification, ABCA2 transporter protein imports waste output of the cell and toxic compounds from cytoplasm to lysosomes (47, 69, 70).

ABCA2 transports a variety of substrates (10, 35, 51, 66, 67, 71, 72) that they have commonality with toxic compounds of ABCA3 substrates (38). ABCA2 is the third unknown member of ABC transporters subfamily and it has a role in occurrence of MDR phenotype in childhood ALL (16).

ABCA2, is naturally expressed in some tissues, such as, blood cells (15), including macrophages (73, 74), monocytes (35, 42) and blood stem cells (50, 51). Its important role in some of these cells including macrophages and neurons is lipid homeostasis and metabolism (figure 4) (14, 75). ABCA2 is also expressed in cancer cell lines (43). It is believed that during tumor growth, the gene expression increases in order to maintain tumor cell proliferation (15). ABCA2 gene promoter has a cholesterol-response element [76] and cholesterol has a role in regulating the survival and differentiation of normal and tumor cells. Therefore, it can be presumed that ABCA2 may also play a role in cancer development (15). Gene dysfunction causes latency in metastasis and chemotactic migration in prostate cancer (74). ABCA2 protein is related to diseases such as, early atherosclerosis (46, 67), Tangier's, small cell lung cancer, acute myeloid leukemia (71) and Alzheimer's disease early infection (46, 67, 71, 77). This transporter protein may cause drug resistance in response to cancer chemotherapy (13).

#### **ABCA2 and MDR in ALL**

MDR1 is one of the drug resistance genes that produces P-glycoprotein (p-gp). This gene is expressed in some cancers. However, in ALL, there is a controversy regarding the relationship between p-gp and MDR (7, 38). Although, some researchers reported that the high expression of this protein and its function is related to the failure of all chemotherapy and poor prognosis (78), some others did not observe such a relationship (38, 79). It is probable that these contradictory results are due to different experimental methods used in these studies. The role of ABCA2 protein in drug transport and its role in MDR are under investigation. It is suggested that this transporter has a role in MDR by saving drugs in the lysosome and probably their efflux from the cell (figure 4) (14, 15, 80). Although, there are

few reports that show the in vivo impact of ABCA2 in MDR, considerable number of experimental studies have revealed this relationship (73). For instance, drug resistance to metoxantrone (14, 59, 70, 81), Estrogen derivatives (42) and Stramostin (14, 42, 43, 59, 70, 74) are observed in cell lines with high expression of ABCA2 (35). Stramostin is an anti-microtubule drug which is used for chemotherapy of ovarian and prostate cancers. In comparison with parental cell line, prostate and ovarian cancer cell lines, resistant to Stramostin, demonstrate more expression of ABCA2 in mRNA (41, 42, 55) and protein (74) levels. High protein expression levels of ABCA2 are reported in human malignant mesothelioma (MM) cell lines resistant to doxorubicin. This overexpression may decrease drug centralization through activating "extra cellular signal regulated kinases", named ERK1 and ERK2 which may contribute to tumor growth (82). Some of the studies showed that the level of ABCA2 protein in patients having chronic myeloid leukemia has no relationship with response to imatinib drug (51), while, some other studies have shown that ABCA2 protein leads to drug resistance in T-ALL and AML (83). In 2006, Steinbach and his colleagues studied the mRNA expression profiles of 38 ABC transporter genes in patients with AML in 25, 50 and 75 age levels divided into two groups with good and poor response to chemotherapy. It was demonstrated that patients with high mRNA levels of ABCA2, besides three other studied genes, were included in the group of patients with poor response to chemotherapy (53). Gillet and colleagues identified ABCA2 as one of the genes which was highly expressed in multidrug resistant cell lines of breast cancer (MCF7/CH1000), AML (HL60/AR) and T-ALL (CEM/ADR5000) [13]. Treatment of acute lymphoblastic leukemia cell lines of CCRF-CEM and Jurkat with methotrexate, vinblastine or doxorubicin caused certain increase of ABCA2 expression in Jurkat cell line, and of ABCA3 in CCRF-CEM and Jurkat cell lines (38, 70). Blocking of ABCA2 and ABCA3 genes by siRNAs showed drug sensitivity in the aforementioned cell lines [38]. A reparative mechanism is proposed relating ABCA3 to ABCA2 transporter, where the enhanced activity of one protein may compensate the dysfunction of the other one (70). In a recent study performed by our group, it is revealed that four ABC transporters are related to poor prognosis in childhood ALL (7, 17). Among them ABCA2 high mRNA levels increase the risk of MDR 15 fold more than those with lower expressions (16).

The regulation of gene expression can occur at various levels including transcriptional, post-transcriptional and post-translational levels. The post-

translational modifications may include alterations in splicing control, mRNA consistency, localization and translation[84]. For example, it is shown that in some patients with lung cancer, despite the increased mRNA levels of Mdr1 gene, no enhanced expression at protein levels was observed(85). Further investigations are required to delineate the mechanisms through which ABCA2 may influence multidrug resistance in childhood ALL.

**Conclusion:**

ALL is the most prevalent cancer in children under 15 years old. Multidrug resistance is one of the most

important obstacles of treatment in these patients. The current review article has discussed the possible role of ABC transporter, ABCA2, in MDR and the poor prognostic value of this gene in childhood ALL according to several, recent published studies in this field. It is hoped that this manuscript would help for a better understanding of this gene and its impact on multidrug resistance; the information which may improve our knowledge for choosing more effective protocols for treating acute lymphoblastic leukemia.

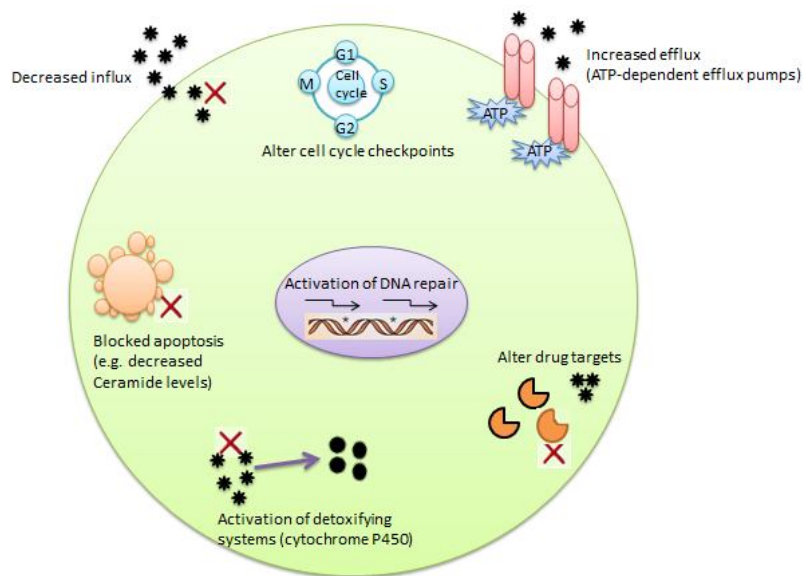


Figure 1. Several mechanisms of MDR in cancer cells. MDR can occur in cancer cells by mechanisms including (a) decreased influx of drug, (b) alteration of cell cycle checkpoints, (c) increased efflux of drugs by ATP-dependent pumps, (d) blocked apoptosis, (e) increased DNA repair, (f) altered drug targets and (g) activation of detoxification systems.

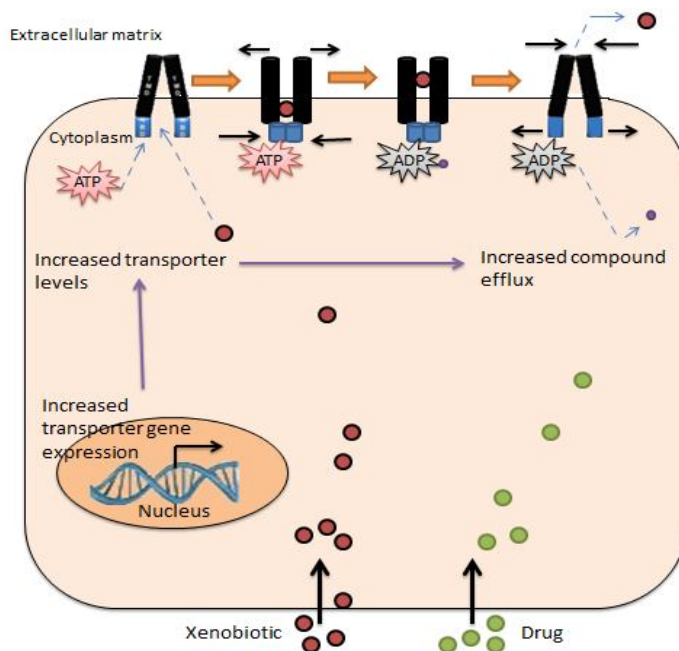


Figure 2. Function of ABC transporters in MDR and their drug efflux mechanism. The entry of drug into the cell by diffusion or active uptake leads to increased transporter gene expression, increased transporter levels and so increased compound efflux. After substrate and ATP binding to ATP-dependent pumps, the transporter effluxes substrate to extracellular matrix. In this mechanism, Phosphate group is released, and the substrate is then excreted.

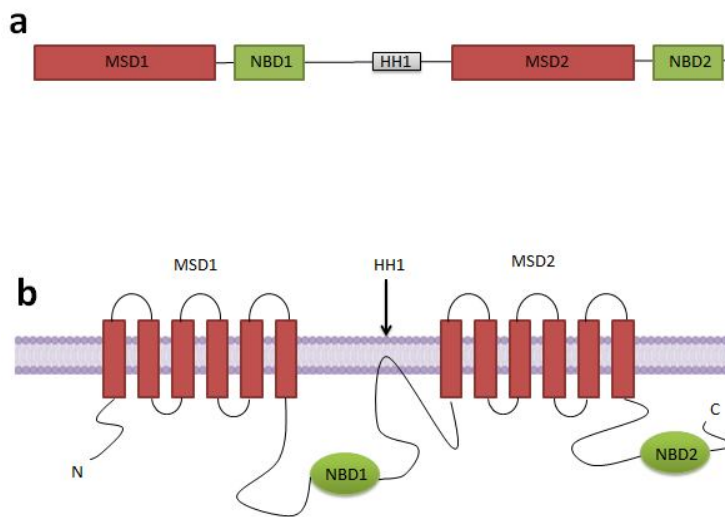


Figure 3. Gene (a) and protein (b) structure of ABCA2 transporter. There is a long cytoplasmic regulator domain between two symmetric halves of this protein that each of them contains a membrane including a spanning domain (MSD) and a nucleotide binding domain (NBD).

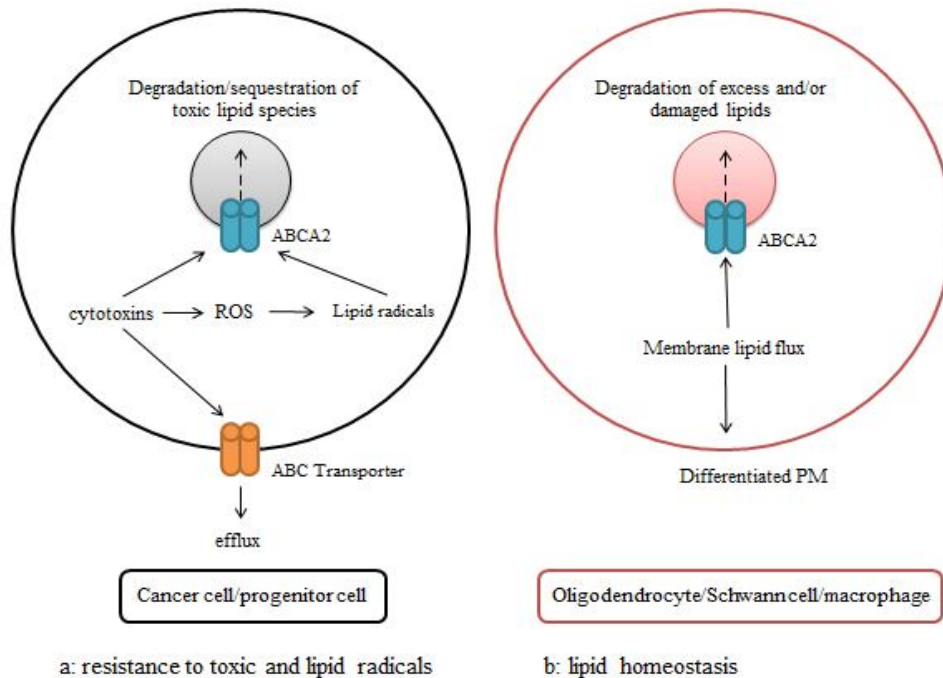


Figure 4. The function of ABCA2 protein. a: trapping of toxic lipids and/or lipid radicals in the cancer and progenitor cells for protecting the cell and degradation of toxic substance. b: contributing to the degradation of membrane lipids in cell differentiation to maintain lipid homeostasis.

## References

- Jemal, A., et al., Global cancer statistics. a cancer journal for clinicians, 2011. 61(2): p. 69-90.
- Chang, X.-b., A molecular understanding of ATP-dependent solute transport by multidrug resistance-associated protein MRP1. *Cancer and Metastasis Reviews*, 2007. 26(1): p. 15-37.
- Prasad, A., et al., Prevalence of familial malignancy in a prospectively screened cohort of patients with leukemia. *Journal of Clinical Oncology*, 2010. 28(15\_suppl): p. 6590.
- Kaatsch, P., Epidemiology of childhood cancer. *Cancer treatment reviews*, 2010. 36(4): p. 277-285.
- Styczynski, J., et al., Predictive value of multidrug resistance proteins and cellular drug resistance in childhood relapsed acute lymphoblastic leukemia. *Journal of cancer research and clinical oncology*, 2007. 133(11): p. 875-893.
- Campos-Sanchez, E., et al., Acute lymphoblastic leukemia and developmental biology: A crucial interrelationship. *Cell Cycle*, 2011. 10(20): p. 3473-3486.
- Abedi, M., et al., Evaluation of the expression profile of MDR1 gene and assessment of its prognostic value in childhood ALL. *Sci J Iran Blood Transfus Organ*, 2014. 10(4): p. 326-334.
- Entezar-e-Ghaem, M., et al., Evaluation of mRNA expression profile of ABCG2/BCRP in childhood acute lymphoblastic leukemia. *J Shahid Sadoughi Univ Med Sci* 2013. 21(5): p. 575-86.
- Swerts, K., et al., Prognostic significance of multidrug resistance-related proteins in childhood acute lymphoblastic leukaemia. *European Journal of Cancer*, 2006. 42(3): p. 295-309.
- Fletcher, J.I., et al., ABC transporters in cancer: more than just drug efflux pumps. *Nature Reviews Cancer*, 2010. 10(2): p. 147-156.
- Abedi, M. and S. Rahgozar, P- glycoprotein's role in drug resistance in epilepsy and its regulatory mechanisms. *The 1st International and 5th Annual Congress of Iranian Neurogenetic Society*, 2011: p. 88.
- Shukla, S., Z.-S. Chen, and S.V. Ambudkar, Tyrosine kinase inhibitors as modulators of ABC transporter-mediated drug resistance. *Drug Resistance Updates*, 2012. 15(1): p. 70-80.

13. Gillet, J.-P., et al., Microarray-based detection of multidrug resistance in human tumor cells by expression profiling of ATP-binding cassette transporter genes. *Cancer research*, 2004. 64(24): p. 8987-8993.
14. Albrecht, C. and E. Viturro, The ABCA subfamily—gene and protein structures, functions and associated hereditary diseases. *Pflügers Archiv-European Journal of Physiology*, 2007. 453(5): p. 581-589.
15. Mack, J.T., C.B. Brown, and K.D. Tew, ABCA2 as a therapeutic target in cancer and nervous system disorders. *Expert Opin Ther Targets*, 2008. 12(4): p. 491-504.
16. Rahgozar, S., A. Moafi, and M. Abedi, mRNA expression profile of multidrug-resistant genes in acute lymphoblastic leukemia of children, a prognostic value for ABCA3 and ABCA2. *Cancer biology & therapy*, 2013. 15(1): p. 35-41.
17. Abedi, M. and S. Rahgozar, The mechanisms of drug resistance in Acute lymphoblastic leukemia. The 6th Annual Congress of Iranian Blood and pediatric cancer Society, 2012: p. 61.
18. Ellinghaus, E., et al., Identification of germline susceptibility loci in ETV6-RUNX1-rearranged childhood acute lymphoblastic leukemia. *Leukemia*, 2012. 26(5): p. 902-909.
19. Chokkalingam, A.P., et al., Fetal growth and body size genes and risk of childhood acute lymphoblastic leukemia. *Cancer Causes & Control*, 2012. 23(9): p. 1577-1585.
20. Seghatoleslam, A., et al., Expression of UBE2Q2, a putative member of the ubiquitin-conjugating enzyme family in pediatric acute lymphoblastic leukemia. *Archives of Iranian Medicine (AIM)*, 2012. 15(6).
21. Jamshidi, K., A. Esmaeilzadeh, and A. Kosha, An eight-year period study of blood malignancies at Zanjan Beheshti hospital (1991-1999). *Journal of Zanjan University of Medical Sciences And Health Services*, 2004. 12(46): p. 47-53.
22. Vardiman, J.W., et al., The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*, 2009. 114(5): p. 937-951.
23. Thathia, S.H., et al., Epigenetic inactivation of TWIST2 in acute lymphoblastic leukemia modulates proliferation, cell survival and chemosensitivity. *haematologica*, 2012. 97(3): p. 371-378.
24. Pui, C.-H., M.V. Relling, and J.R. Downing, Acute lymphoblastic leukemia. *New England Journal of Medicine*, 2004. 350(15): p. 1535-1548.
25. Chokkalingam, A.P., et al., Haplotypes of DNA repair and cell cycle control genes, X-ray exposure, and risk of childhood acute lymphoblastic leukemia. *Cancer Causes & Control*, 2011. 22(12): p. 1721-1730.
26. Robison, L.L., Late effects of acute lymphoblastic leukemia therapy in patients diagnosed at 0-20 years of age. *ASH Education Program Book*, 2011. 2011(1): p. 238-242.
27. Hunger, S.P., et al., Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *Journal of Clinical Oncology*, 2012. 30(14): p. 1663-1669.
28. Pulte, D., A. Gondos, and H. Brenner, Trends in 5-and 10-year survival after diagnosis with childhood hematologic malignancies in the United States, 1990–2004. *Journal of the National Cancer Institute*, 2008. 100(18): p. 1301-1309.
29. Pui, C.-H., L.L. Robison, and A.T. Look, Acute lymphoblastic leukaemia. *The Lancet*, 2008. 371(9617): p. 1030-1043.
30. Amir, A.-H., et al., Survival Rate of Childhood Leukemia in Shiraz, Southern Iran. *Iranian journal of pediatrics*, 2013. 23(1): p. 53.
31. Chauhan, P.S., et al., Expression of genes related to multiple drug resistance and apoptosis in acute leukemia: response to induction chemotherapy. *Experimental and molecular pathology*, 2012. 92(1): p. 44-49.
32. Abedi, M. and S. Rahgozar, P-glycoprotein 170; Its clinical importance and pathophysiological role in cancer. *Journal of Isfahan Medical School*, 2013. 31(228): p. 274-293.
33. Hlavac, V., et al., The expression profile of ATP-binding cassette transporter genes in breast carcinoma. *Pharmacogenomics*, 2013. 14(5): p. 515-529.
34. Aberuyi, N. and S. Rahgozar, New approach of multi-drug resistance in acute lymphoblastic leukemia. 3th National Congress of Hematology, 2013. 3: p. 51.
35. Gottesman, M.M., T. Fojo, and S.E. Bates, Multidrug resistance in cancer: role of ATP-dependent transporters. *Nature Reviews Cancer*, 2002. 2(1): p. 48-58.
36. Fukuda, Y. and J.D. Schuetz, ABC transporters and their role in nucleoside and nucleotide drug resistance. *Biochemical pharmacology*, 2012. 83(8): p. 1073-1083.
37. Borel, F., et al., Adenosine triphosphate-binding cassette transporter genes up-regulation in untreated hepatocellular carcinoma is mediated by cellular microRNAs. *Hepatology*, 2012. 55(3): p. 821-832.
38. Efferth, T., et al., Expression profiling of ATP-binding cassette transporters in childhood T-cell acute lymphoblastic leukemia. *Molecular cancer therapeutics*, 2006. 5(8): p. 1986-1994.

39. Aberuyi, N., S. Rahgozar, and A. Moafi, Prediction of involved microRNAs in modulation of ABCA2 transporter in order to confront multi drug resistance in acute lymphoblastic leukemia using bioinformatic methods. 8th Congress of Iranian Pediatric Hematology & Oncology Society, 2014. 8: p. 85.
40. Turton, J. and K. Morgan, ATP-Binding Cassette, Subfamily A (ABC1), Member 7 (ABCA7), in Genetic Variants in Alzheimer's Disease. 2013, Springer. p. 135-158.
41. Davis Jr, W., et al., Reciprocal regulation of expression of the human adenosine 5'-triphosphate binding cassette, sub-family A, transporter 2 (ABCA2) promoter by the early growth response-1 (EGR-1) and Sp-family transcription factors. *Nucleic acids research*, 2003. 31(3): p. 1097-1107.
42. Wolf, S.J. and C.G. Lee, ABC Drug Transporters and Their Impact on Drug Disposition/Drug Sensitivity and Resistance. in *Encyclopedia of Drug Metabolism and Interactions*, A.V. Lyubimov, 2012, Wiley.
43. Vulevic, B., et al., Cloning and characterization of human adenosine 5'-triphosphate-binding cassette, sub-family A, transporter 2 (ABCA2). *Cancer research*, 2001. 61(8): p. 3339-3347.
44. Michaki, V., et al., Down-regulation of the ATP-binding cassette transporter 2 (Abca2) reduces amyloid- $\beta$  production by altering Nicastrin maturation and intracellular localization. *Journal of Biological Chemistry*, 2012. 287(2): p. 1100-1111.
45. Zhou, C.-J., et al., Atp-binding cassette transporter ABC2/ABCA2 in the rat brain: a novel mammalian lysosome-associated membrane protein and a specific marker for oligodendrocytes but not for myelin sheaths. *The Journal of Neuroscience*, 2001. 21(3): p. 849-857.
46. Davis Jr, W., The ATP-binding cassette transporter-2 (ABCA2) regulates esterification of plasma membrane cholesterol by modulation of sphingolipid metabolism. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids*, 2014. 1841(1): p. 168-179.
47. Chen, Z.J., et al., Association of ABCA2 expression with determinants of Alzheimer's disease. *The FASEB journal*, 2004. 18(10): p. 1129-1131.
48. Takenaka, S., T. Itoh, and R. Fujiwara, Expression pattern of human ATP-binding cassette transporters in skin. *Pharmacology Research & Perspectives*, 2013. 1(1).
49. Neidle S., *Cancer drug design and discovery*. Academic Press, 2011: p. 406
50. De Grouw, E., et al., Preferential expression of a high number of ATP binding cassette transporters in both normal and leukemic CD34<sup>+</sup>; CD38<sup>-</sup> cells. *Leukemia*, 2006. 20(4): p. 750-754.
51. Raaijmakers, M., ATP-binding-cassette transporters in hematopoietic stem cells and their utility as therapeutical targets in acute and chronic myeloid leukemia. *Leukemia*, 2007. 21(10): p. 2094-2102.
52. Maeß, M.B., et al., Evidence for an alternative genomic structure, mRNA and protein sequence of human ABCA13. *Gene*, 2012. 515(2): p. 298-307.
53. Steinbach, D., et al., ABCA3 as a possible cause of drug resistance in childhood acute myeloid leukemia. *Clinical Cancer Research*, 2006. 12(14): p. 4357-4363.
54. Mack, J., et al., The ATP-binding cassette transporter ABCA2 as a mediator of intracellular trafficking. *Biomedicine & pharmacotherapy*, 2006. 60(9): p. 587-592.
55. Davis Jr, W., et al., Human ATP-binding cassette transporter-2 (ABCA2) positively regulates low-density lipoprotein receptor expression and negatively regulates cholesterol esterification in Chinese hamster ovary cells. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids*, 2004. 1683(1): p. 89-100.
56. Luciani, M.F., et al., Cloning of two novel ABC transporters mapping on human chromosome 9. *Genomics*, 1994. 21(1): p. 150-159.
57. Kaminski, W.E., et al., Complete coding sequence, promoter region, and genomic structure of the human ABCA2 gene and evidence for sterol-dependent regulation in macrophages. *Biochemical and biophysical research communications*, 2001. 281(1): p. 249-258.
58. Zhou, C.J., et al., ATP-binding cassette transporter ABCA2 (ABC2) expression in the developing spinal cord and PNS during myelination. *Journal of Comparative Neurology*, 2002. 451(4): p. 334-345.
59. Beljanski, V., et al., Characterization of the ATPase activity of human ATP-binding cassette transporter-2 (ABCA2). *In Vivo*, 2005. 19(4): p. 657-660.
60. Minster, R.L., S.T. DeKosky, and M.I. Kamboh, No association of DAPK1 and ABCA2 SNPs on chromosome 9 with Alzheimer's disease. *Neurobiology of aging*, 2009. 30(11): p. 1890-1891.
61. Allikmets, R., et al., Characterization and mapping of three new mammalian ATP-binding transporter genes from an EST database. *Mammalian Genome*, 1995. 6(2): p. 114-117.
62. Davis Jr, W., The ATP-binding Cassette Transporter-2 (ABCA2) Promotes Amyloidogenic Processing of Amyloid Precursor Protein by Glu11 Site Cleavage. *Current Alzheimer research*, 2010. 7(7): p. 566.



63. Broccardo, C., et al., ABCA2 is a marker of neural progenitors and neuronal subsets in the adult rodent brain. *Journal of neurochemistry*, 2006. 97(2): p. 345-355.
64. Sakai, H., et al., ABCA2 deficiency results in abnormal sphingolipid metabolism in mouse brain. *Journal of Biological Chemistry*, 2007. 282(27): p. 19692-19699.
65. Tarling, E.J., T.Q. Vallim, and P.A. Edwards, Role of ABC transporters in lipid transport and human disease. *Trends in Endocrinology & Metabolism*, 2013. 24(7): p. 342-350.
66. Wang, Y., et al., Expression of ABCA2 protein in human vestibular schwannoma and peripheral nerve. *Journal of the neurological sciences*, 2005. 232(1): p. 59-63.
67. Li, G., H.M. Gu, and D.W. Zhang, ATP-binding cassette transporters and cholesterol translocation. *IUBMB life*, 2013. 65(6): p. 505-512.
68. Abuznait, A.H. and A. Kaddoumi, Role of ABC Transporters in the Pathogenesis of Alzheimer's Disease. *ACS chemical neuroscience*, 2012. 3(11): p. 820-831.
69. Wolf, A., B. Bauer, and A.M. Hartz, ABC transporters and the Alzheimer's disease enigma. *Frontiers in Psychiatry*, 2012. 3(45).
70. Efferth, T., *Inhibition of ATP-Binding Cassette Transporters by Chinese Herbs and Phytochemicals, in Evidence and Rational Based Research on Chinese Drugs*. 2013, Springer. Vienna, p. 283-331.
71. Barbet, R., et al., Expression of the 49 human ATP binding cassette (ABC) genes in pluripotent embryonic stem cells and in early-and late-stage multipotent mesenchymal stem cells: Possible role of ABC plasma membrane transporters in maintaining human stem cell pluripotency. *Cell Cycle*, 2012. 11(8): p. 1611-1620.
72. Baldrige, R.D. and T.R. Graham, Two-gate mechanism for phospholipid selection and transport by type IV P-type ATPases. *Proceedings of the National Academy of Sciences*, 2013. 110(5): p. E358-E367.
73. Mack, J.T., et al., Ablation of the ATP-binding cassette transporter, Abca2 modifies response to estrogen-based therapies. *Biomedicine & Pharmacotherapy*, 2012. 66(6): p. 403-408.
74. Mack, J.T., et al., ABCA2 transporter deficiency reduces incidence of TRAMP prostate tumor metastasis and cellular chemotactic migration. *Cancer letters*, 2011. 300(2): p. 154-161.
75. Marzac, C., et al., ATP Binding Cassette transporters associated with chemoresistance: transcriptional profiling in extreme cohorts, and their prognostic impact in a cohort of 281 acute myeloid leukemia patients. *haematologica*, 2011. 96: p. 1293-1301.
76. Schmitz, G. and W. Kaminski, ABCA2: a candidate regulator of neural transmembrane lipid transport. *Cellular and Molecular Life Sciences CMLS*, 2002. 59(8): p. 1285-1295.
77. Aberuyi, N., S. Rahgozar, and A. Moafi, Roles of ABCA2 in Alzheimer's disease. *2nd Basic and Clinical Neuroscience Congress 2013*, 2013. 2: p. 235.
78. Dhooge, C., et al., P-glycoprotein is an independent prognostic factor predicting relapse in childhood acute lymphoblastic leukaemia: results of a 6-year prospective study. *British journal of haematology*, 1999. 105(3): p. 676-683.
79. Wattel, E., et al., Expression of the multidrug resistance P glycoprotein in newly diagnosed adult acute lymphoblastic leukemia: absence of correlation with response to treatment. *Leukemia*, 1995. 9(11): p. 1870-1874.
80. Coelho, A.C. and P.C. Cotrim, The Role of ABC Transporters in Drug-Resistant Leishmania, in *Drug Resistance in Leishmania Parasites*. 2013, Springer. p. 237-258.
81. Boonstra, R., et al., Mitoxantrone resistance in a small cell lung cancer cell line is associated with ABCA2 upregulation. *British journal of cancer*, 2004. 90(12): p. 2411-2417.
82. Shukla, A., et al., Blocking of ERK1 and ERK2 sensitizes human mesothelioma cells to doxorubicin. *Mol Cancer*, 2010. 9: p. 314.
83. Kelter, G., et al., Role of transferrin receptor and the ABC transporters ABCB6 and ABCB7 for resistance and differentiation of tumor cells towards artesunate. *PLoS One*, 2007. 2(8): p. e798.
84. Blencowe, B.J., et al., Post-transcriptional gene regulation: RNA-protein interactions, RNA processing, mRNA stability and localization. *Pacific Symposium on Biocomputing*, 2009. 14: p. 545-548.
85. Roy, S., et al., MDR1/P-glycoprotein and MRP-1 mRNA and protein expression in non-small cell lung cancer. *Anticancer research*, 2007. 27(3A): p. 1325-1330.