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# Association of Caspase 8 and Caspase 10 Genetic Polymorphisms with B-cell Non Hodgkin's Lymphoma in Egypt: A Case-Control Study

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## Abstract

**Background and purpose:** Non-Hodgkin lymphomas are closely related diseases with distinctive morphologic, immunophenotypic, genetic, and clinical features. Genetic susceptibility studies of NHL are mandatory to identify at risk populations and to clarify important disease mechanisms. Caspase genes play a key role in regulation of apoptotic cell death, and dysregulation of this signaling pathway has been shown to participate in tumorigenesis. The current study aimed at defining the role of Caspase 8-D302H, Caspase 8-652 6N ins/del and Caspase 10-I522L genetic polymorphisms as risk factors for NHL and their possible role as genetic prognostic markers.

**Methods:** The present study included 100 Egyptian B-cell NHL patients and 100 healthy controls. Genotyping of the studied genes was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. Data was analyzed using SPSS statistical package version 15.

**Results:** The study revealed that CASP8-D302H mutant genotypes were significantly higher in NHL patients when compared to the controls and conferred increased risk of NHL. For CASP8-652 6N ins/del and Casp10-I522L, there was no statistical difference in the distribution of the different genotypes between NHL cases and the controls. Furthermore, there were no statistical differences between NHL patients harboring the wild or mutant genotypes of the studied genes as regards their response to therapy.

**Conclusions:** CASP8-D302H genetic polymorphism represents a genetic risk factor for NHL in Egyptian population. Hopefully, better understanding of the functional consequences of caspase genes polymorphism would provide a foundation for future studies of the possible role of these genes in lymphomagenesis.

**Keywords:** Caspase; Polymorphisms; Non Hodgkin's Lymphoma

## Introduction

Non-Hodgkin's Lymphomas (NHL) are closely related diseases, each involving the malignant transformation of lymphoid cells, but with distinctive morphologic, immunophenotypic, genetic, and clinical features [1,2]. In Egypt, it is the fifth most common cancer in both sexes. The incidence of non-hodgkin's lymphoma increased steadily from 1995 to 2004 particularly in the elderly population [3]. Thus, developing additional strategies for screening and prevention of non-Hodgkin's lymphoma becomes mandatory.

Caspases are intracellular cysteine proteases that mediate apoptosis and are categorized as initiator caspases (1, 2, 4, 5, 8, 9, 10, 11, and 12) or effector caspases (3, 6, 7, and 14) [4]. Aberrant expressions or activities are associated with many pathological conditions, including cancer [5]. Caspase 8 is a key regulator of apoptosis, an essential defense mechanism against hyper-proliferation and tumorigenesis [6]. The importance of caspase-8 in initiating death receptor-induced apoptosis and maintaining immune homeostasis and surveillance is well established. However, little is known about genetic variants in CASP8 and their role in human cancer susceptibility [5]. Lan et al. [4] suggested that SNPs in initiator caspases as CASP8 affect lymphomagenesis. They attributed their suggestion to other biological functions mediated by these genes other than apoptosis. In particular, CASP8 plays a particular role in regulating lymphocyte homeostasis, NF-kB activation and differentiation of monocytes into macrophages, all of potential relevance to NHL aetiology. Moreover, Sun et al. [5] reported that somatic mutations of CASP8 are responsible for down regulation of CASP8 expression. Somatic mutations and genetic polymorphisms in the CASP8 gene have been reported in breast cancer, gliomas, lung cancers and multiple myeloma [7-9].

In apoptotic signal transduction initiated by death receptors and their ligands such as FAS and FASL, caspase-8 cooperates with caspase-10 and the fas-associated protein with death domain-like apotosis regulator (CFLAR). CASP10 and CFLAR are adjacent to CASP8 in the human genome. Therefore, these three genes are strong candidate loci for cancer susceptibility owing to their important roles in immune regulation, including activation-induced cell death (AICD) of T lymphocytes [10].

Single nucleotide polymorphism in the coding region of CASP8-D302H has been reported. The aspartate to histidine change at residue 302 on the surface of caspase 8 is hypothesized to influence its autoprocessing or interactions with antiapoptotic molecules, such as the fas-associated protein with death domain-like apotosis regulator (CFLAR) [11]. The ins/del polymorphism (-/CTTACT, a 6bp/ del) in the promoter region of CASP8 gene was suggested to remove the stimulatory protein 1 binding site and to be associated with reduced susceptibility to many cancers including lung, esophageal, gastric, colorectal, cervical, and breast cancer [12]. Caspase 10 is homologous

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to caspase 8. Inherited CASP 10 mutations underline defective lymphocyte and dendritic cell apoptosis and may contribute to the pathogenesis of NHL [13].

The aim of the current study was to investigate the association of Caspase 8-D302H, Caspase 8-652 6N ins/del and Caspase 10-I522L genetic polymorphisms as risk factors for NHL and their possible role as prognostic markers for B-cell NHL in Egypt. The chosen SNPs were a common SNP in exon 9 of caspase 8 (D302H, G>C), SNP at the promoter region of caspase 8 (-652 6N del, -/CTTACT) and a common SNP in exon 8 of caspase 10 (I522L, A>T). This combination was chosen as recommended by the National Center for Biotechnology information dbSNP database [14].

## Material and Methods

### Study population

This study comprised 100 adult Egyptian B-cell NHL patients and 100 age and gender matched healthy controls. Cases were selected from the Department of Medical Oncology, National Cancer institute (NCI), Cairo University, Egypt. Patients were either newly diagnosed cases or attending the NCI for follow-up. They were 40 females and 60 males and their ages ranged from 18-71 years with a mean age of 40 years. The research protocol was approved by the research Ethics committee of the Departments of Clinical pathology and Medical Oncology, Cairo University. Diagnosis of B-NHL was based on lymph node excision biopsy from the affected group of lymph nodes. Histopathological and immunohistochemical studies were done to confirm the diagnosis and for proper sub-typing according to the WHO classification [15]. Bone marrow biopsy was done for staging. The extent of the disease was categorized according to the Ann Arbor classification and the performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) criteria [16]. All patients under study were subjected to full history taking with special attention to B symptoms (fever, night sweats and loss of weight), symptoms denoting site of affection, or family history of similar condition. Thorough clinical examination according to the standard sheet of hematological malignant disorders of the NCI was done with careful notation and assessment of clinical signs relevant to NHL. Radiological assessment was done for all patients for proper diagnosis and staging. Laboratory investigations included complete blood count, liver and kidney functions, serum uric acid, LDH and Beta2 microglobulin. The clinical and laboratory characteristics of NHL patients are presented in (Table 1).

### Genotyping of caspase 8-D308H, caspase 8-6N 652 ins/del and caspase 10-1522L

Genomic DNA extraction from peripheral blood leucocytes was done using Gene JET Genomic DNA purification kit (Fermentas, Lithuania) following the manufacturer's instructions. DNA samples were routinely stored at -20°C. Genotypic analysis of the candidate genes was performed by polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) method. The primer sequences and the restriction enzymes used are presented in (Table 2). All PCR reactions were performed in a total volume of 25 µl containing 2-3 µl genomic DNA, 12.5 µl 2X Dream Taq Green PCR Master Mix, 1 µl of each forward and reverse primers (20 pM) (Fermentas, Lithuania). The thermocycler programs conducted for amplifying the candidate genes and the restriction enzymes used for genotyping are presented in (Table 3). The PCR products were visualized by agarose gel electrophoresis [17].

### Treatment regimen for non-hodgkin lymphoma

All patients were subjected to the standard protocol of treatment of NHL (NCI). Non- bulky (<10 cm) stages IA and IIA cases including extra-nodal presentations can be successfully managed by 3 to 4 cycles of a doxorubicin containing regimen (e.g. CHOP followed by involved field radiotherapy (IFRT). Cycle is repeated every 21 days. The treatment protocol was intravenous Cyclophosphamide (750 mg/m2), Doxorubicin (50 mg/m2) and Vincristine (2 mg/m2) at day 1 with oral Prednisone (100 mg) as a total dose from day 1 to 5.

### Response to therapy

Complete remission (CR) was defined as normalization of clinical and radiological abnormalities, relevant laboratory data and bone marrow picture for four weeks after the last cycle of chemotherapy.

| Item | | | NHL Patient (number-%) | |
|---|---|---|---|---|
| **Sex (Male/Female)** | | | 60 /40 | 3 : 2 |
| **B- symptoms:** Fever, night sweats, weight loss | | | 30/100 | 30% |
| **Lymphadenopathy** | | | 74 /100 | 74 % |
| **Groups of lymph nodes involved** | - | Cervical | 46/100 | 46% |
| | - | Axillary | 32/100 | 32% |
| | - | Inguinal | 27/100 | 27% |
| | - | Abdominal | 17/100 | 17% |
| | - | Submandibular | 15/100 | 15% |
| | - | Para-aortic | 13/100 | 13% |
| | - | Mesenteric | 3/100 | 3% |
| **Extranodal involvement** (GIT, bone, kidney, skin or liver) | | | 51/100 | 51 % |
| **Splenomegaly** | | | 36/100 | 36% |
| **Hepatomegaly** | | | 23/100 | 23% |
| **Clinical Stage:** | | | | |
| IA | | | 15/100 | 15% |
| IB | | | 1/100 | 1% |
| IIA | | | 12/100 | 12% |
| IIB | | | 4/100 | 4% |
| IIIA | | | 20/100 | 20% |
| IIIB | | | 10/100 | 10% |
| IVA | | | 22/100 | 22% |
| IVB | | | 16/100 | 16% |
| **Performance status:** | | | | |
| Score 0 | | | 2/100 | 2% |
| Score I | | | 70/100 | 70% |
| Score II | | | 16/100 | 16% |
| Score III | | | 9/100 | 9% |
| Score IV | | | 3/100 | 3% |
| **Pathological subtypes:** | | | | |
| Diffuse large B-cell lymphoma (DLBCL) | | | 78/100 | 78% |
| Follicular lymphoma (FL) | | | 7/100 | 7% |
| Small lymphocytic lymphoma (SLL) | | | 7/100 | 7% |
| T-cell rich B-cell lymphoma | | | 4/100 | 4% |
| Mantle Zone Lymphoma (MZL) | | | 4/100 | 4% |
| **IPI** | | | | |
| 0 | | | 13/100 | 13% |
| 1 | | | 29/100 | 29% |
| 2 | | | 35/100 | 35% |
| 3 | | | 18/100 | 18% |
| 4 | | | 5/100 | 5% |
| **Response to treatment:** | | | | |
| Complete remission (CR) | | | 12/100 | 12% |
| Partial remission (PR) | | | 14/100 | 14% |
| Partial disease (PD) | | | 6/100 | 6% |
| Relapse | | | 33/100 | 33% |
| Died | | | 5/100 | 5% |
| Stopped treatment upon request | | | 9/100 | 9% |
| Unavailable | | | 21/100 | 21% |

IPI: International prognostic index

**Table 1:** The demographic characteristics of NHL patients at presentation.

| Gene | Primer sequence | PCR product | Reference |
|---|---|---|---|
| *CASP8-D302H* | F: 5′-CATTTTGAGATCAAGCCCCG-3′<br>R: 5′-CCCTTGTCTCCATGGGAGAGGA-3′ | 132 bp | [16] |
| *CASP8- 625 6N* | F: 5′-CTGCATGCCAGGAGCTAAGT-3′<br>R: 5′-GCCATAGTAATTCTTGCTCTGC-3′ | 171 bp | [17] |
| *CASP10 -1522L* | F: 5′-GAGTGGACAAACAGGGAACAAA-3′<br>R: 5′-AGAACCAACAAAAACTCTCTGCAATA-3′ | 122 bp | [16] |

**Table 2:** The primer sequences applied for amplification of Caspase 8-D302H, Caspase 8-652 6 N ins/del and Caspase 10-1522L genes.

| Gene | Thermocycler program | Restriction enzyme | Genotypes | Restriction fragments |
|---|---|---|---|---|
| ***CASP8-****D302H* | 94°C for 1 min., 35 cycles of 94°C for 40 sec, 60°C for 40 sec, 7°C for 40 sec., then final extension at 72°C for 5 min. | *BstUI* | Wild genotype<br>Homotype<br>Heterotype | 132 bp<br>112+20 bp<br>132+112+20 bp |
| ***CASP8-*** *625 6N* | | *BfaI* | Wild genotype<br>Homotype<br>Heterotype | 171 bp<br>146+ 31 bp<br>171+146+31 bp |
| ***CASP10-*** *1522L* | 94°C for 1 min., 30 cycles 94°C for 40 sec, 50°C for 40 sec, 72°C for 40 sec., then final extension step at 72°C for 5 min. | *SspI* | Wild genotype<br>Homotype<br>Heterotype | 122 bp<br>97+25 bp<br>122+97+25 bp |

**Table 3:** Genotyping of Caspase 8-D302H, Caspase 8-652 6 N ins/del and Caspase 10-1522L genes by PCR-RFLP assay.

| Gene | NHL Patients (number-%) | Controls (number-%) | OR | 95% CI | P value |
|---|---|---|---|---|---|
| ***CASP8 D302H*** | | | | | |
| • *Wild genotype CC* | 9(9%) | 49(49%) | Reference | | |
| • *Heterotype* CG | 7(7%) | 6(6%) | 1.179 | 0.382-3.641 | 0.774 |
| • *Homotype GG* | 84(84%) | 45(45%) | 6.417 | 3.303-12.466 | **<0.001** |
| • *CG and GG* | 91(91%) | (51%) | 9.715 | 4.413-21.387 | **<0.001** |
| ***CAS8 6N 652 ins/del*** | | | | | |
| • *Wild genotype ins/ins* | 19(19%) | 20(20%) | Reference | | |
| • *Heterotype ins/del* | 44(44%) | 46(46%) | 0.966 | 0.55-1.677 | 0.887 |
| • *Homotype del/del* | 37(37%) | 34(34%) | 1.140 | 0.639-2.035 | 0.658 |
| • *Ins/del and del/del* | 81(81%) | 80(80%) | 0.886 | 0.508-1.546 | 0.671 |
| ***CASP 10 I522L*** | | | | | |
| • *Wild genotype TT* | 48(48%) | 45(45%) | Reference | | |
| • *Heterotype* TA | 43(43%) | 41(41%) | 1.08 | 0.619-1.904 | 0.774 |
| • *Homotype AA* | 9(9%) | 14(14%) | 0.608 | 0.250-1.476 | 0.268 |
| • *TA and AA* | 52(52%) | 55(55%) | 0.938 | 0.466-1.889 | 0.858 |
| ***Dual CASP8 D302H / CASP8-652 6N ins/ del mutation*** | 74(74%) | 40(40%) | 4.269 | 2.344-7.777 | <0.0001 |
| ***Dual CASP 8 D302H / CASP10 I522L mutation*** | 47(47%) | 31(31%) | 1.974 | 1.108-3.517 | 0.020 |
| ***Dual CASP 8-652 6N ins/del /CASP 10 I522L mutation*** | 39(39%) | 40(40%) | 0.959 | 0.959-0.554 | 0.885 |
| ***Triple mutation*** | 35(35%) | 24 (24%) | 1.705 | 0.921-3.157 | 0.088 |

p-value <0.05=significant

**Table 4:** The frequency of CASP8- D302H, CASP8- 652 6N ins/del, and CASP10- I522L genotypes in NHL patients and controls.

Patients were classified as having partial remission (PR) if they have at least a 50% reduction in the sum of the product of the greatest cross-sectional diameters of measurable lesions. New lesions or more than 25% increase in an individual lesion over one treatment cycle was categorized as progressive disease (PD). Appearance of new lesions or the reappearance of old lesions in patients who achieved complete remission was categorized as relapse [18].

## Statistical analysis

Data was analyzed using SPSS statistical package version 15. Numerical data were expressed as mean, standard deviation and range. Qualitative data were expressed as frequency and percentage. Chi-square test (or Fisher's exact test) was used to examine the relation between qualitative variables. Odds ratio (OR) and 95% confidence interval (CI) were calculated for risk estimation. A p-value less than 0.05 was considered significant.

## Results

The frequency of the studied genes among NHL patients and controls are presented in Table 4. The frequency of CASP8-D302H mutant genotypes was statistically significantly higher in NHL patients when compared to the controls. Calculated risk estimation revealed that the homomutant genotype conferred six fold increased risk of NHL. For CASP8-652 6N ins/del and Casp10- I522L, there was no statistically significant difference in the distribution of the different genotypes between NHL cases and the controls. Dual mutant genotype of CASP8- D302H and CASP8- 652 6N ins/del was significantly higher among NHL patients and conferred fourfold increased risk of NHL. Dual mutant genotypes of CASP8- D302H and CASP10- I522L were significantly higher in NHL patients and conferred almost two fold increased risk of NHL. For dual mutant genotypes of CASP8-6N 652 ins/del and CASP10- I522L and triple mutant genotypes, there was no statistical difference noticed in the distribution of the mutant genotypes between the patients and the controls (Table 4). Further analysis of the influence of the studied genetic polymorphisms on the clinic-pathological characteristics of the disease revealed that there was no statistically significant difference as regards the age, gender, clinical

and laboratory data or response to therapy between NHL patients harboring the wild or mutant genotypes (Data not shown).

## Discussion

Apoptosis, a controlled process of programmed cell death plays an important role in the development and maintenance of tissue homeostasis [6], and has a principal role in the pathogenesis of malignancies when the genes controlling the apoptotic pathways are altered by mutations [19]. Previous studies have demonstrated that Caspase genes play a key role in regulation of apoptotic cell death, and dysregulation of this signaling pathway has been found to increase the risk of a number of human malignancies [20,21].

Searching for genes and pathways that contribute to NHL may help to identify at risk population. This would be of value in choosing therapeutic regimens that track or block these pathways to improve the future clinical practice. The current study aimed at investigating the influence of genetic polymorphisms of caspase 8 and caspase 10 on the susceptibility to B-cell NHL and the possible role of these genetic variants as prognostic markers.

Genotypic analysis revealed that CASP8-D302H GG homotype was significantly higher in NHL patients and conferred six fold increased risk of NHL. Our results are in accordance to Lan et al. [4]. Analysis of the influence of the CASP8-D302H genetic polymorphism on the clinic-pathological characteristics of the disease revealed that there was no statistically significant difference between NHL patients with wild or mutant genotypes as regards their age, gender, clinical or laboratory data or their response to therapy. Although the relapse rate was higher among NHL patients harboring the mutant genotypes, it did not reach a statistically significant level.

Genotyping of CASP8-652 6N ins/del polymorphism revealed that the frequency of CASP8-652 6N ins/del genotype was 44%, while the del/del genotype was 19%. These frequencies were higher than that reported by [12] in Chinese population. Different genetic background might account for this discrepancy. There was no statistical difference encountered in the distribution of the mutant genotypes between NHL patients and the controls, thus CASP8- 652 6N ins/del polymorphism could not be considered as a genetic risk factor for NHL in Egypt. This is in accordance with the results of Xiao et al. [12].

Genotyping of Caspase10-I522L gene revealed that the frequency of the mutant genotypes was slightly higher in NHL patients compared to controls, yet it did not reach a statistically significant level. We could not detect an association between this genetic polymorphism and susceptibility to NHL. This is in agreement with the study of Lan et al. [4]. Comparing NHL patients harboring the wild genotype and the mutant genotypes of CASP8-652 6N ins/del and Caspase10-I522L, we found no statistically significant difference between the two groups as regards their age, gender, presenting symptoms, clinical and laboratory data or their response to therapy for both genetic polymorphisms.

Combined genotype analysis revealed that co-inheritance of caspase 8-D302H with either and caspase 8-652 6N ins/del or caspase 10-I522L was associated with increased risk of NHL. However, this could be attributed to the effect of caspase 8-D302H polymorphism by itself which conferred six folds increase NHL risk.

## Conclusion

Caspase 8-D302H genetic polymorphism represents a genetic risk factor in the pathophysiology and the development of NHL in Egyptian population. So, better understanding of the functional consequences of caspase genes polymorphism would provide a foundation for future studies of the possible role of these genes in the lymphomagenesis, or on the response to anti-neoplastic therapy with the ultimate goal of identifying novel prevention approaches. Further studies with larger samples are required to clarify the role of this genetic polymorphism as a contributor for lymphomagenesis and to confirm its association with NHL.

### Author's Contributions

Mervat Khorshied was responsible for designing of the study, provided the genotyping and performed the statistical analysis of the results; Mona Hazem collected the samples and the data of the participants; Hanaa Arnaout critically reviewed the manuscript; Ola Khorshid was responsible for the clinical assessment and follow up of the patients. All authors participate in data analysis, writing the manuscript and approved the final version of the manuscript submission.

### Conflict of Interest Statement

All authors have no financial support or conflict of interest to disclose.

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