Studying HLA class I polymorphism in brain tumour patients

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Abstract :

The present study aimed at shed light on the association between HLA-class I antigens (A, B and Cw) and brain tumours (meningioma and glioma) in the basis of their individual frequencies or two-locus association A total of 52 brain tumour patients were enrolled in this study, with an age range of 7-68 years. The patients were divided into two clinical groups; meningioma (20 cases) and glioma (22 cases), while the remaining 10 cases represented other types of brain tumour. Control samples included 47 Iraqi Arab apparently healthy blood volunteers, with an age range of 15-50 year. Three HLA antigens showed a significant increased frequency in total patients as compared to controls. They were B13 (34.6 *vs*. 6.5%), B40 (15.4 *vs*. 2.2%) and Cw3 (15.4 *vs*. 2.2%). In contrast, B5 was significantly decreased (15.4 *vs*. 34.8%). In meningioma patients, only B13 was significantly increased (35.0 *vs*. 6.5%), while in glioma patients, B13 (36.4 *vs*. 6.5%) and Cw5 (36.4 *vs*. 2.2%) were significantly increased. Variations between patients and controls have been also encountered for the observed and expected HLA-two locus associations (B13-Cw3, B13-Cw5 and B40-Cw5).

Key words: Brain tumour, HLA-class I, Two locus associations

Introduction:

Brain tumour is a mass or growth of abnormal cells in brain, which can either be originated from the brain itself or migrated from another part of the body to the brain (metastatic brain tumour) [1]. Benign tumours consist of very slow growing cells, usually have a distinct border and do not invade surrounding tissues. In contrast, malignant brain tumours are usually rabid growing, and lack distinct borders due to their tendency to seed "roots" into nearby normal tissues, and often called brain cancer. Both groups of brain tumour can cause similar symptoms that depend on their size and location in the brain [2].

Expression of HLA molecules is important for the augmentation of immune response against non-self antigens and malignant cells, and their polymorphisms may underline immunogenetic predisposition to develop different diseases, including malignancies. In this regard, association of single HLA alleles or HLA haplotype with diseases including cancers have been reported [1]. Moreover, HLA-class I expression is frequently altered or a defect in the expression and/or function in many tumour types and down regulation of HLA-class I expression is a widespread phenomenon used by

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tumour cells to escape anti-tumour T-cell mediated immune response. These alterations may play a role in the clinical course of the disease, and in Malignant Brain Tumour (MBT), different studies have targeted the subject of HLA, and positive, as well as, negative associations have been reported, and implications of these alleles in the pathogenesis of the disease have been suggested [3, 4, 5].

HLA association with diseases is a further important feature of HLA system, and since the first demonstration of a significant correlation between HLA-B27 and ankylosing spondylitis in 1973, the literatures are overwhelmed to reveal the significance of HLA molecules in conferring the individual an immunogenetic predisposition to develop diseases of different natures; autoimmune, infectious and malignant diseases. The mechanisms behind such association are subjected to different speculations [6].Concerning tumours, the association of HLA alleles with solid tumours, such as nasopharyngeal, colorectal, or thyroid carcinoma has been described, reviewed by [7]. HLA-B18 was significantly increased in patients with nasopharyngeal carcinoma [8], and in patients diagnosed with pancreatic cancer [9]. There was also a positive association between glioma and HLA-B27 and HLA-Cw6 alleles [1], while HLA-A2 allele was positively associated with meningioma [10]. Recently, [4] have discussed that a loss of MHC-class I molecules by tumour cells is thought to represent an evasion mechanism of tumours from recognition by tumour-specific CD8+T cells. The present study aimed at investigate the association between HLA-class I alleles and brain tumour (meningioms and gliomas) in a sample of Iraqi Arab patients.

Material and Methods:

This study was carried out on 52 brain tumour patients who were admitted to the Specialized Surgeries Hospital and Neurological Disorders Hospital in Baghdad for a surgical operation to resect brain tumour during the period May 2008 - February 2009. Based on a clinical evaluation (the consultant medical staff at the hospitals) and a histopathological examination, the patients were divided into two clinical groups; meningioma (20 cases) and glioma (22 cases), while the remaining 10 cases represented other types of brain tumour. Control samples included 47 apparently healthy blood volunteers. From each participant, 5 ml of venous blood was dispensed in a tube containing heparin (5000 unit/ml) to prevent coagulation and processed in less than 2 hours. Lymphocytes were collected by means of density-gradient centrifugation, and phenotyping of the cells for HLA class I (A, Band Cw) and antigens was done by the microlymphocytotoxicity method [11]. The association between a marker and a disease was expressed in terms of relative risk (RR), etiological fraction (EF) and preventive fraction (PF). The RR value can range from less than one (negative association) to more than one (positive association). If the association was positive, the EF was calculated, while if it is negative, the PF was calculated. The significance of such association (positive or negative) was assessed by Fisher's exact probability. Such assessment is more preferred, because it is not affected by small numbers (less than 5). The calculations of such parameters were carried out by using the computer Programmes for Epidemiologists (PEPI) version 4.0.The HLA system was further characterized in terms of gene frequencies of its alleles, in which the

following square-root formula was applied:

$$\text{Gene Frequency} = 1 - \sqrt{1 - \text{Antigen Frequency}}$$

From the gene frequency (GF), the expected percentage frequency of two-locus association (EPF-TLA) between two alleles was estimated by using the following formul:

$$\text{EPF - TLA (\%)} = \left(\frac{\text{GF of first Allele x GF of second Allele x Sample Size}}{100} \right)$$

Results:

HLA Class I Antigen Frequencies

The Observed numbers and percentage frequencies of HLA-A, -B and -Cw antigens in brain tumour patients (total, glioma and meningioma) and controls are given in tables 1, 2 and 3, respectively, while antigens showing significant variations between patients and controls are summarized in Table 4. Out of the 30 tested antigens (8 A, 15 B and 7 Cw), five antigens (B5, B13, B40, Cw3 and Cw5) showed a significant variation between patients and controls. HLA-B5 was present in 15.4% of total patients, while its frequency in controls was 34.8%. Such decreased frequency was significant (P = 0.05), and the associated RR and PF values were 0.34 and 0.23, respectively. A similar decreased frequency was observed in glioma and meningioma patients (18.2 and 20.0%, respectively) as compared with controls (34.8%), but neither of the two differences reached a significant level (P > 0.05) (Table 2).In contrast with HLA-B5, B13 showed a significant (P = 0.001) increased frequency in total patients as compared with controls (34.6 *vs*. 6.5%). Such variation scored an EF value of 0.30, and the associated RR was 7.59. Such observation was also consistent in glioma (36.4 *vs*. 6.5%; RR = 8.19; EF = 0.32; P = 0.007) and meningioma (35.0 *vs*. 6.5%; RR = 7.72; EF = 0.30; P = 0.01) patients (Table 4).HLA-B40 and -Cw3 antigens showed a significant increased frequency in total patients as compared with controls (15.4 *vs*. 2.2%; RR = 8.18; EF = 0.14; P = 0.05). A similar increased frequency was also observed in glioma (13.6%) and meningioma (15.0%) patients as compared with controls (2.2%), but neither of these differences reached a significant level (Table 4).The fifth antigen was HLA-Cw5, which manifested important deviation in glioma patients only, and present in 36.4% of patients, while its frequency in controls was 2.2. Such difference was significant (P = 0.001), and it was able to score an RR value of 25.71 and EF value of 0.35. Such difference was also true when the comparison was made between glioma and meningioma patients (36.4 *vs*. 10.0%).

Table 1: Observed numbers and percentage frequencies of HLA-A antigens in brain tumour patients (total, glioma and meningioma) and controls.

HLA Antigens	Brain Tumour Patients						Controls No. = 46	
	Total No. = 52		Glioma No. = 22		Meningioma No. = 20			
	No.	%	No.	%	No.	%	No.	%
A1	6	11.5	3	13.6	2	10.0	9	19.6
A2	9	17.3	4	18.2	3	15.0	15	32.6
A3	9	17.3	5	22.7	3	15.0	6	13.0
A9	13	25.0	8	36.4	4	20.0	11	23.9
A10	10	19.2	5	22.7	3	15.0	9	19.6
A11	2	3.8	ND	ND	2	10.0	6	13.0
A19	19	36.5	9	40.9	8	40.0	16	34.8
A28	3	5.8	1	4.55	1	5.0	4	8.7

ND: Not detected.

Table 2: Observed numbers and percentage frequencies of HLA-B antigens in brain tumour patients (total, glioma and meningioma) and controls.

HLA Antigens	Brain Tumour Patients						Controls No. = 46	
	Total No. = 52		Glioma No. = 22		Meningioma No. = 20			
	No.	%	No.	%	No.	%	No.	%
B5	8	15.4	4	18.2	4	20.0	16	34.8
B7	ND	ND	ND	ND	ND	ND	5	10.9
B8	4	7.7	2	9.1	1	5.0	4	8.7
B12	6	11.5	2	9.1	3	15.0	6	13.0
B13	18	34.6	8	36.4	7	35.0	3	6.5
B14	2	3.8	2	9.1	ND	ND	3	6.5
B15	2	3.8	ND	ND	2	10.0	3	6.5
B16	5	9.6	3	13.6	2	10.0	2	4.3
B17	3	5.7	2	9.1	1	5.0	1	2.2
B18	ND	ND	ND	ND	ND	ND	3	6.5
B21	2	3.8	2	9.1	ND	ND	1	2.2
B27	1	1.9	ND	ND	ND	ND	1	2.2
B35	3	5.8	1	4.5	1	5.0	9	19.6
B40	8	15.4	3	13.6	3	15.0	1	2.2
B41	4	7.7	2	9.1	2	10.0	3	6.5

ND: Not detected.

Table 3: Observed numbers and percentage frequencies of HLA-Cw antigens in brain tumour patients (total, glioma and meningioma) and controls.

HLA Antigens	Brain Tumour Patients						Controls No. = 46	
	Total No. = 52		Glioma No. = 22		Meningioma No. = 20			
	No.	%	No.	%	No.	%	No.	%
Cw1	5	9.6	2	9.1	3	15.0	1	2.2
Cw2	3	5.8	1	4.5	2	10.0	3	6.5
Cw3	8	15.4	3	13.6	3	15.0	1	2.2
Cw4	5	9.6	2	9.1	2	10.0	11	23.9
Cw5	12	23.1	8	36.4	2	10.0	1	2.2
Cw6	13	25.0	7	13.8	4	20.0	10	21.7
Cw7	7	13.5	4	18.2	2	10.0	4	8.7

Table 4: HLA antigens showing significant variations between brain tumour patients (total, glioma and meningioma) and controls.

HLA Antigens	No.	%	No.	%	RR	EF	PF	P
Total Brain Tumour Patients *versus* Controls								
B5	8	15.4	16	34.8	0.34	-	0.23	0.05
B13	18	34.6	3	6.5	7.59	0.30	-	0.001
B40	8	15.4	1	2.2	8.18	0.14	-	0.05
Cw3	8	15.4	1	2.2	8.18	0.14	-	0.05
Glioma Patients *versus* Controls								
B13	8	36.4	3	6.5	8.19	0.32	-	0.007
Cw5	8	36.4	1	2.2	25.71	0.35	-	0.001
Meningioma Patients *versus* Controls								
B13	7	35.0	3	6.5	7.72	0.30	-	0.01
Glioma Patients *versus* Meningioma Patients								
Cw5	8	36.4	2	10.0	-	-	-	0.05

RR: Relative risk; EF: Etiological fraction; PF: Preventive fraction; P: Two-tailed Fisher's exact probability.

HLA Two-Locus Association

To reach a better understanding of HLA role in the aetiology of brain tumour, the antigens that showed a significant increased frequency (B13, B40, Cw3 and Cw5) in total patients or their clinical subgroups (glioma and meningioma) were encountered in terms of two-locus associations (co-occurrence of two alleles) in patients and controls (observed percentage frequency). Then, their frequencies were estimated from the gene frequencies of the respective alleles (Tables 5, 6 and 7), which are given as expected frequency of two-locus association. Accordingly, three HLA two locus associations were inspected in brain tumour patients and controls, and they were B13-Cw3, B13-Cw5 and B40-Cw5.

Table 5: Gene frequency of HLA-A alleles in brain tumour atients (total, glioma and eningioma) and controls.

HLA Alleles	Brain Tumour Patients			Controls No. = 46
	Total No. = 52	Glioma No. = 22	Meningioma No. = 20	
A*1	0.059	0.070	0.051	0.103
A*2	0.090	0.063	0.078	0.179
A*3	0.090	0.121	0.078	0.067
A*9	0.134	0.202	0.106	0.128
A*10	0.101	0.121	0.078	0.103
A*11	0.019	ND	0.051	0.067
A*19	0.203	0.231	0.225	0.193
A*28	0.029	0.022	0.025	0.044
Others	0.275	0.170	0.308	0.116

ND: Not detected.

Table 6: Gene frequency of HLA-B alleles in brain tumour patients (total, glioma and meningioma) and controls.

HLA Alleles	Brain Tumour Patients			Controls No. = 46
	Total No. = 52	Glioma No. = 22	Meningioma No. = 20	
B*5	0.080	0.096	0.106	0.193
B*7	ND	ND	ND	0.056
B*8	0.039	0.047	0.025	0.044
B*12	0.059	0.047	0.078	0.067
B*13	0.191	0.203	0.194	0.033
B*14	0.019	0.047	ND	0.033
B*15	0.019	ND	0.051	0.033
B*16	0.049	0.070	0.051	0.022
B*17	0.029	0.047	0.025	0.011
B*18	ND	ND	ND	0.033
B*21	0.024	0.047	ND	0.011
B*27	0.001	ND	ND	0.011
B*35	0.019	0.029	0.025	0.103
B*40	0.049	0.070	0.078	0.011
B*41	0.039	0.096	0.051	0.033
Others	0.383	0.250	0.316	0.306

ND: Not detected.

Table 7: Gene frequency of HLA-Cw alleles in brain tumour patients (total, glioma and meningioma) and controls.

HLA Alleles	Brain Tumour Patients			Controls No. = 46
	Total No. = 52	Glioma No. = 22	Meningioma No. = 20	
Cw*1	0.049	0.046	0.078	0.011
Cw*2	0.029	0.023	0.051	0.033
Cw*3	0.080	0.070	0.078	0.011
Cw*4	0.049	0.046	0.051	0.033
Cw*5	0.123	0.203	0.051	0.033
Cw*6	0.134	0.174	0.106	0.117
Cw*7	0.070	0.096	0.051	0.033
Others	0.466	0.342	0.534	0.729

- **HLA-B13-Cw3 Association**

None of the control subjects had B13-Cw3, while its expected frequency was. 04%. In contrast, the observed frequency in total patients was 7.7%, and the corresponding frequency in glioma and meningioma patients was 4.5 and 5.0%, respectively. Such observed frequencies were higher than the corresponding expected frequencies in total (1.53%), glioma (1.42%) or meningioma (1.51%) patients (Figure 1).

- **HLA-B13-Cw5 Association**

Glioma patients scored the highest observed percentage frequency of B13-Cw5, which was 13.6%, followed by total (9.6%) and meningioma (5.0%) patients. The corresponding expected frequencies were lower and they were 4.12, 2.35 and 0.99%, respectively. In controls, the observed frequency was 0.0%, and its expected frequency was 0.11% (Figure 2).

- **HLA-B40-Cw5 Association**

Total brain tumour patients, as well as, glioma patients shared the highest observed percentage frequency of B40-Cw5 (3.8 and 4.5, respectively), and both frequencies were higher than the corresponding expected frequencies (0.6 and 1.42%, respectively). Meningioma patients and control subjects shared a similar observed frequency (0.0%; the occurrence of two alleles was not detected), as well as, similar expected frequencies, which were 0.40 and 0.36%, respectively (Figure 3).

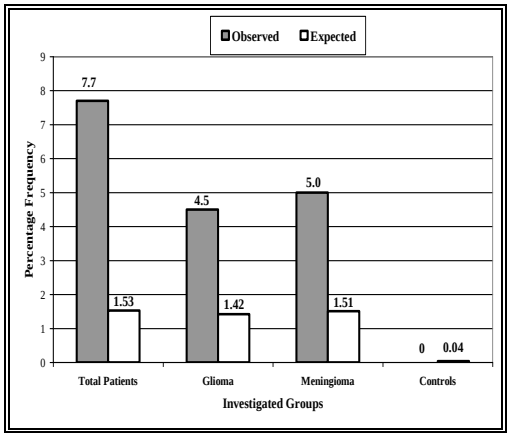

Fig.1: Observed and expected percentage frequencies of HLA-B13-Cw3 association in brain tumour patients (total, glioma and meningioma) and controls.

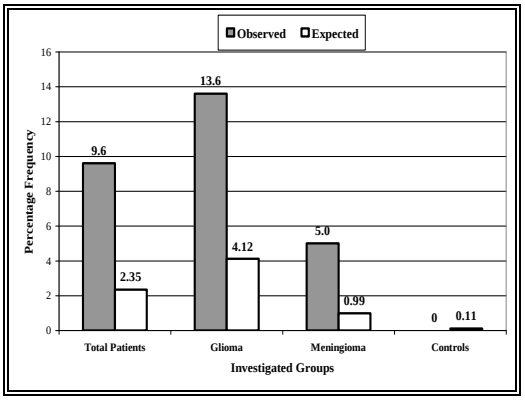

Fig. 2: Observed and expected percentage frequencies of HLA-B13-Cw5 association in brain tumour patients (total, glioma and meningioma) and controls.

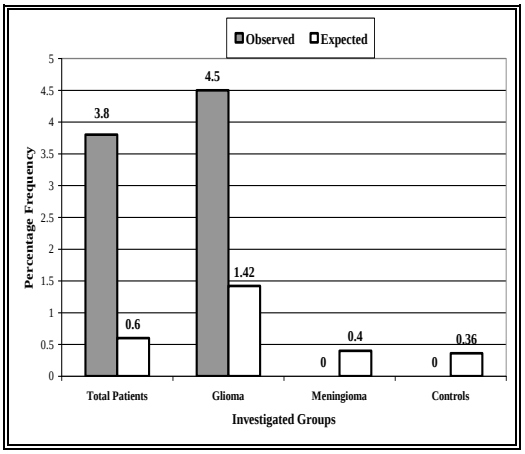

Fig. 3: Observed and expected percentage frequencies of HLA-B40-Cw5 association in brain tumour patients (total, glioma and meningioma) and controls.

Discussion:

These findings augmented the view that certain HLA alleles may impact the immunogenetic background of human brain tumour in terms of predisposition and protection, and such conclusion is subjected to the consideration whether the brain tumour is considered as one disease or a group of diseases. When total patients have been considered as one group, three alleles were important in this regard (B5, B40 and Cw3). The first allele was associated with a reduced frequency in the patients (i.e. protective role of B5 is suggested); while a reverse outcome was observed for B40 and Cw3 alleles. The latter two alleles can be considered as predisposing markers for the development of brain tumour in general, and their RR value (8.18) may justify such consideration. A further a predisposing allele that showed consistent increased frequency in total patients and their clinical subgroups was B13. Such allele scored EF value range of 0.30-0.32, and in a statistical term, approximately 30% of the aetiological factors involved in brain tumour (total or clinical subgroups) are linked to B13. However, glioma patients were further characterized with the allele Cw5, which was associated with RR value of 25.71, and such allele was present in only 10% of meningioma patients; an observation that may suggest the immunogeneticheterogeneity of both tumours in terms of their aetiological factors.

Examining HLA-class I allele frequencies in other world populations of brain tumour patients revealed the importance of these alleles in the aetiopathogenesis of brain tumour progression, although the findings were either consistent or not. In this regard, B13 was found to be significantly increased in glioma patients [12]; a finding that confirms the results of

present study. However, [13] were unable to confirm this, but instead, described a negative association between Cw5 and glioma, while in the present study this allele was positively associated with glioma. However, further earlier studies shared that neither B13 nor Cw5 had a significant role in the aetiology of brain tumour, but they concentrated on the role of HLA-A alleles. The results of the present study showed no significant association between HLA-A alleles and brain tumour of both types; meningioma and glioma, while [14, 15, 16] reported that A24 is more common in this tumour, and additionally, [1] demonstrated an increased frequency of A24 and A25 alleles in glioma patients. In contrast, [17] found that A3 was increased in patients with neuroepithelial brain tumours, and [18] showed a negative association between A23 and high grade glioma. In Iraqi asrocytoma patients, further conflicting findings have been found; in which A12 was increased while A3 was decreased [19]. These conflicting results may reflect the immunogenetic heterogeneity of brain tumour, and the role of different environmental factors in triggering the immunogenetic background of the disease. Furthermore, HLA alleles shows different frequencies in different populations, including Iraqis, and this may impact HLA-disease association studies [20].The tendency for certain alleles at two different gene loci to occur in the population significantly more frequently in the same haplotype than would be expected on the basis of chance alone is called linkage disequilibrium, which is a hallmark of human MHC and extended from HLA-A through HLA-DQ locus [21]. Such allelic association is useful to refine the location of major genes prior to a positional cloning, and this has been the main use of association studies to map the disease predisposing gene that is presumed to be in linkage disequilibrium with the associated gene, and to proceed to a positional cloning of the real predisposing disease gene [22]. Differences between the observed and expected percentage frequencies of B13-Cw3, B13-Cw5 and B40-Cw5 have been observed in total and glioma patients, with the exception of B40-Cw5 that showed no difference in meningioma patients. The studies in this regard have not overwhelming, but (8) suggested that individuals A3, which is in linkage disequilibrium with B38, might have an increased risk to develop astrocytoma. [10] suggested a further to locus-association (A2-DRB1) that may increase the risk of meningioma. A positive association between B7-CW7 and high grade glioma was also reported [12]. Concerning CNS tumours, three-locus association was suggested, in which A3-B7-DRB15 and A3-B5-DRB1 combinations were significantly increased in the patients [10], while [13] suggested a protective influence of the combination A1-B8-DRB3 against primary CNS lymphoma. With respect to such type of studies, they require further investigations especially if they are based on family evaluations of patients.

Conclusion:

HLA alleles are important immunogenetic factors that may confer susceptibility to the development of brain tumour, and in this regard B13, B40 and Cw3 alleles were important susceptibility markers in total brain tumour patients, while in glioma patients a better risk was associated with B13 and Cw5 alleles, and the latter allele may represent an immunogenetic heterogeneity marker that discriminate between glioma and meningioma patients. Equally important, B5 allele might be considered as a protective

marker against the development of brain tumour.

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دراسة مستضدات خلايا الدم البيض البشرية (HLA) الصنف الأول لمرضى اورام الدماغ

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الخلاصة:
هدفت الدراسة الحالية إلى إلقاء الضوءعلى المصاحبة بين مستضدات خلايا الدم البيض البشري (HLA) الصنف الأول (A وB وCw) واورام الدماغ (الاورام السحائية واورام الخلايا الدبقة) وعلى اساس تكراراتها الفردية أو على أساس العلاقة بين موقعين من مواقع الجينات Two-locus association درس 52 مريضاً من مرضى اورام الدماغ وتراوحت أعمارهم بين 7 و 68 سنة في وقت البحث. حيث تم إحالة هؤلاء المرضى الى مستشفى الجراحات التخصصية ومستشفى الجملة العصبية في بغداد لغرض اجراء عملية استئصال ورم الدماغ للفترة من ايار الى شباط 2009. تم تقسيم مجموعة المرضى الى مجموعتين سريرية ; مجموعة الاورام السحائية (20 حالة) و مجموعة اورام الخلايا الدبقة (22 حالة), شملت عينات السيطرة 47 عراقي عربي اصحاء ضاهرياً وبأعمار (15- 50 سنة) بينما الحالات الباقية تمثل الانواع الاخرى لاورام الدماغ.
أظهرت ثلاث مستضدات (HLA) زيادة معنوية في تكرار المرضى الكلي مقارنة بالسيطرة. كما أظهرت المستضدات B13 (34.6 مقابل 6.5%)، B40 (15.4 مقابل 2.2%) و Cw3 (15.4 مقابل 2.2%). في مرضى الاورام السحائية كانت هناك زيادة في تكرار المستضد B13 فقط (35.0 مقابل 6.5%), بينما في مرضى الخلايا الدبقة كان (35.0 مقابل 6.5%) وCw5 (36.4 مقابل 2.2%) وقد كانت الزيادة معنوية. لقد تم احتساب التغايرات بين مجاميع المرضى والسيطرة للنسب المتوقعة أو الملاحظة بين موقعين من مواقع الجينات (B13-Cw3, B13-Cw5 و B40-Cw5).