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HLA MOLEKULALARINING GETERODIMER TUZILISHINI MODELLASHTIRISH TAHLILI

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РЕЗЮМЕ

Цель. *Анализ различных аллелей гетеродимерных молекул HLA DRA*01:01:01/DRB1 с помощью алгоритмов MolProbity и Clash Score в SwissModel.*

Материал и методы. *В исследовательской работе использовался биоинформатический метод SWISS MODEL. Показатели качества белка оценивали в программах MolProbity и Clash Score, QMEAN4.*

Полученные результаты. *Проанализированные аллельные варианты HLA-DRB1 представляли собой HLA-DRB1*03:08/DRA*01:01:01:01 и HLA-DRB1*01:05/DRA*01:01 согласно MolProbity и Clash Score: 01:01 соответствует высокому качеству: показатель MolProbity 0,97–0,98, показатель Clash 0,68, Z-показатель ≤ 2 представляет собой хорошее качество трехмерной структуры белка, что указывает на то, что результаты моделирования близки к природному аналогу гетеродимера.*

Ключевые слова: *HLA-DRB1, аллель, гистосовместимость, макрофаг, лимфоцит, MHC, HLA-DRA.*

SUMMARY

Objective. *Analysis of different alleles of HLA DRA*01:01:01/DRB1 heterodimer molecules by MolProbity and Clash Score algorithms in SwissModel software.*

Material and methods. *The bioinformatic method SWISS MODEL program was used in the research work. Protein quality indicators were evaluated in MolProbity and Clash Score, QMEAN4 programs.*

Results. *According to MolProbity and Clash Score, the analyzed HLA-DRB1 allelic variants were HLA-DRB1*03:08/DRA*01:01:01:01 and HLA-DRB1*01:05/ DRA*01 :01:01:01 is of high quality because MolProbity score is 0.97–0.98, Clash Score is 0.68, Z-score ≤ 2 means good quality for the 3D structure of the protein, the modeling results are close to the natural heterodimer analog.*

Keywords: *HLA-DRB1, allele, histocompatibility, macrophage, lymphocyte, MHC, HLA-DRA.*

HLA-DRB1 inson leykositlar D-β 1 antigeni inson 6-xromosomasiga joylashgan genlardan bo'lib, asosiy gistomansublik kompleksining MHC II sinf molekulalarining β-zanjirini kodlaydi. Ushbu molekulalar immunitet tizimida asosiy rol o'ynaydi, immun javob hujayralariga antigenlarni taqdim etishda ishtirok etadi [2, 6]. HLA-DRB1 ning makrofaglar, dendrit hujayralar va B-limfositlar hujayralar membranasidagi faollashtiruvchi MHC II sinf molekulalari guruhiga kiradi. MHC II molekulalari ikkita polipeptid zanjiridan iborat: α-zanjiri HLA-DRA tomonidan va β- zanjiri HLA-DRB1 geni tomonidan kodlanadi, antigenlar uchun bog'lanish joyini ta'minlaydi. Ushbu molekulalar T-hujayralari bilan o'zaro ta'sir qiladi va immun javobini faollashtirish uchun begona molekulalar haqida ma'lumot beradi [10, 13].

HLA-DRB1 Evropa populyatsiyalarida, ayniqsa AQSh, Buyuk Britaniya, Germaniya va Frantsiya kabi mamlakatlarda skleroz, revmatoid artrit kabi kasalliklarda faol o'rganilmoqda. Osiyo, xususan, Xitoy, Yaponiya va Koreyada HLA-DRB1 bilan bog'liq faol tadqiqotlar olib borilgan. Ushbu populyatsiyalarda ma'lum HLA-DRB1 allellari tizimli qizil lupus, qandli diabet I turi va turli xil autoimmun kasalliklar bilan bog'liqligi aniqlangan [5, 7, 14].

HLA-DRA va DRB1 geterodimer oqsil molekulasi HLA-DRA oqsil molekulasi 254 aminokislota qoldig'idan iborat, HLA- DRB1 266 aminokislota qoldig'idan iborat. Geterodimer molekula, B- limfositlar, makrofaglar hujayra reseptorlari tarkibida bo'ladi va antigen taqdimot etish reaktsiyalarida ishtirok etadi [1, 8, 11].

Hozirda mavjud bo'lgan bioinformatsion dasturlar SwissModel ning MolProbity asosida HLA- DRA*01:01:01:01/DRB1 turli xil allellarining geterodimer molekulalari sifat ko'rsatkichlariga baho berish imkonini beradi [4, 12], olingan natijalar HLA II sinf geterodimer molekulalarining immun javobni hosil qilishdagi antigen bilan bog'lanish sifatini ochib beradi [3, 9]. Ushbu xulosalarga tayangan holda, tadqiqotning maqsadi HLA DRA*01:01:01/DRB1 geterodimer molekulalarining turli xil allellarini SwissModel dasturida MolProbity va QEAN4 ko'rsatkichlarini tahlil qilishdan iborat. HLA DRB1 va DRA oqsilining geterodimer molekulasi 1-chi rasmda keltirilgan [15].
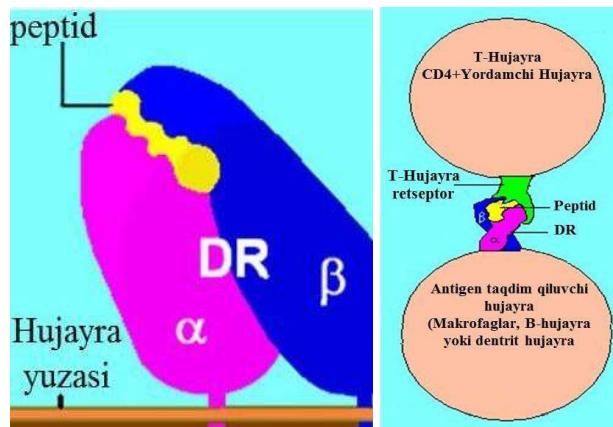
Rasm 1. HLA-DR molekulasining ligand bilan bog;lanishi, DR molekulalarining T- limfotsitlar reseptorlariga taqdim etishi.

DRB genining allellari ichida populyatsiyalarda eng ko'p tarqalgan allel DRB1 hisoblanadi. DRB1 ning 7 ta allel variant aniqlangan bo'lib, gen tarkibidagi nukleotid qatorlari bir- biridan farq qiladi, kodlanadigan ekzon qatorlari ham bir- biridan farq qiladi. DRB1*01:01:01:01, DRB1 01:01:02:01 variantlarida 11101 va 11 229 nukleotid qatorlari uchraydi, kodlanadigan nukleotidlar qatori ikkala allel variantda bir xil 801 nukleotid qatoridan iborat bo'lib, kodlangan oqsil tarkibida 266 ta aminokislota qoldig'i uchraydi (jadval 1). DRB1*01:02:02, DRB1*01:05 va DRB1*01:06 allel variantlarda nukleotidlar qatori aniqlanmagan, kodlanadigan nukleotidlar qatori CDS 246 ta, oxirgi ikki allelda 270 tadan bo'lib, kodlangan oqsil tarkibida 81, 89, 89 aminokislota qoldig'i uchraydi, ya'ni gen nukleotidlar qatori, CDS va aminokislotalar qisqargan. DRB1*01:03:01:01 allel variantda nukleotidlar qatori 10956 nukleotidni tashkil qiladi, lekin kodlanadigan CDS nukleotidlar soni 801 ta bo'lib, 266 ta aminokislotadan tashkil topgan oqsilni sintezlaydi. DRB1*01 ning yana bir allel variant DRB1*01:04:01 varianti kodlanadigan nukleotidlar qatori 675 nukleotiddan tashkil topgan ya'ni HLA-DRB1*01:01variantga nisbatan qisqargan bo'lib, 224 aminokislotadan tashkil topgan oqsilni sintezlaydi.

DRB1 03 allel variant xilma- xil bo'lib, umumiy 14 xil variant aniqlangan. Shulardan DRB1*03:01:01:01 allel variant 13908 nukleotidlardan tashkil topgan bo'lib, kodlanadigan nukeotidlar soni 801 ta nukleotiddan iborat, oqsil tarkibidagi aminokislotalar soni 266 taga tengdir. DRB1*03:01:01, DRB1*03:02:01 allellar 13222 va 13209 ta nukleotid qatorlaridan iborat, lekin kodlanadigan nukleotidlar 801 ta bo'lib, oqsil tarkibidagi aminokislotalar soni 266 tani tashkil qiladi. DRB1* 03:03 da polimorfizm kuchli bo'lib, kodlanadigan nukleotidlar soni qisqargan 300 ta nukleotidni tashkil qiladi, va oqsil tarkibida 100 aminokislota qoldig'i mavjud. DRB1*03:04:01, DRB1*03:05:01, DRB1*03:06 va DRB1*03:07:01:01 allelda nukleotidlar soni DRB1*03 alleldan kuchli farq qilmaydi, kodlanadigan nukleotidlar soni 801 taga teng bo'lib, oqsil tarkibidagi aminokislotalar soni 266 taga teng. DRB1*03:08, DRB1*03:09, DRB1*03:10, DRB1*03:11, va DRB1*03:12 allel

variantlarda nukleotidlar qatorida turli xil sondagi qishqarishlar mavjud bo'lgan, kodlanadigan CDS qatorlarining soni ham qisqargan bo'lib, oqsil tarkibidagi aminokislotalar soni kamaygan.

Eng ko'p sonli allellar guruhi HLA-DRB1*04 alleli hisoblanadi, allellar doirasidagi o'zgarishlar genda nukleotidlar sonining oshishi bilan bog'liqdir. DRB1*04 genining 33 ta allel variantlari aniqlangan. DRB1*04:01:01:01, DRB1*04:02:01, DRB1*04:04:01:01, DRB1*04:05:01:01, DRB1*04:04:01:01, DRB1*04:05:01:01, DRB1*04:06:01, DRB1*04:07:01:01, DRB1*04:08:01:01, DRB1*04:09:01:01, DRB1*04:10:01, DRB1*04:11:01:01, DRB1*04:12, DRB1*04:13, DRB1*04:14, DRB1*04:15, DRB1*04:16, DRB1*04:18, DRB1*04:19, DRB1*04:25, DRB1*04:26, DRB1*04:31, DRB1*04:32 larda gen tarkibidagi nukleotidlar soni 14489 dan 15224 tagacha o'zgaradi, lekin kodlanadigan nukleotidlar qatori 801 tani tashkil qiladi va oqsillar tarkibidagi aminokislotalar qoldig'i 266 taga teng bo'ladi. DRB1*04:21 allel variantda kodlanadigan nukleotidlar soni 663 ta bo'lib, oqsil tarkibidagi aminokislotalar qoldig'i 220 taga teng bo'lgan. DRB1*04:01:02, DRB1*04:01:02, DRB1*04:17:01, DRB1*04:21, DRB1*04:22, DRB1*04:23, DRB1*04:24, DRB1*04:25, DRB1*04:26, DRB1*04:27, DRB1*04:28, DRB1*04:29 allel variantlarda kodlanadigan nukleotidlar qatori 260-270 tagacha bo'lib, oqsil tarkibidagi aminokislotalar soni 89 taga teng bo'lgan.

DRB1*07 allel variantning 4 alleli aniqlangan bo'lib, DRB1*07:01:01:01, DRB1*0702, DRB1*07:03, DRB1*07:04 allellar tarkibidagi nukleotidlar soni 15379-16110 tagacha bo'lgan. Kodlanadigan nukleotidlar soni 801 taga teng bo'lib, oqsil tarkibidagi aminokislotalar soni 801 taga tengdir.

DRB1*08 allel genida 25 ta allel variant aniqlangan bo'lib, DRB1*08:01:01:01, DRB1*08:02:01:01, DRB1*08:03:02:01, DRB1*08:04:01:01, DRB1*08:06:01:01, DRB1*08:07, DRB1*08:08, DRB1*08:09:01, DRB1*08:10, DRB1*08:11:01:01, DRB1*08:13, DRB1*08:14, DRB* 08:16, DRB1*08:17,

DRB1*08:18 allellarda nukleotidlar soni 13199- 13841 tagacha uchragan, kodlanadigan nukleotidlar soni 801 ta bo'lib, oqsillar tarkibidagi aminokislotalar qoldig'i 266 taga teng bo'lgan. Genlarning tarkibidagi nukleotidlar qisqarilishi bilan bog'liq bo'lgan allel variantlarga DRB1*08:02:02 tarkibiga 552 kodlanadigan nukleotidlar kiradi va sintezlangan oqsil tarkibida 183 aminokislota uchraydi. DRB1*08:04:03, DRB1*08:05, DRB1*08:12, DRB1*08:15, DRB1*08:19, DRB1*08:20, DRB1*08:21 allel variantlarda 257- 270 tagacha nukleotidlar uchraydi va kodlangan oqsil tarkibida 89 ta aminokislota qoldig'i bo'ladi.

DRB1*09 allel variantlarda kodlanadigan oqsil va nukleotidlar qatorida o'zgarishlar aniqlanmagan. DRB1*10 genida allel variantlar aniqlanmagan.

DRB1*11 genida 38 ta allel variant aniqlangan bo'lib, 266 aminokislota kodlaydigan allel variantlarga DRB1*11:01:01:01, DRB1*11:01:02:01, DRB1*11:01:03, DRB1*11:02:01:01, DRB1*11:03:01, DRB1*11:04:01:01, DRB1*11:04:02, DRB1*11:05, DRB1*11:06:01, DRB1*11:08:01, DRB1*11:08:02, DRB1*11:09:01:01, DRB1*11:11:01, DRB1*11:12:01, DRB1*11:14:01:01, DRB1*11:15:01:01, DRB1*11:16:01:01, DRB1*11:17, DRB1*11:18, DRB1*11:19:01, DRB1*11:21, DRB1*11:24:01, DRB1*11:25, DRB1*11:27:01, DRB1*11:28:01:01, DRB1*11:29:01, DRB1*11:34 allellar kiradi va ular tarkibida nukleotidlar qatori 13180- 13931 tagacha bo'lishi aniqlangan, kodlanadigan nukleotidlar qatori CDS 801 ta nukleotid sonini tashkil qilgan. DRB1*11:31 allel variant tarkibida kodlanadigan CDS nukleotidlar soni 714 tani tashkil qilgan va oqsil tarkibida aminokislotalar qoldig'i 237 ta bo'lgan. Yana bir allelda DRB1*11:07:01 va DRB1*11:13:01, DRB1*11:32 da kodlanadigan nukleotidlar soni 552 va 562 tani tashkil etgan, oqsil tarkibidagi aminokislotalar qoldig'i 183 va 187, 183 tani tashkil qilgan.

DRB1*11:10:01, DRB1*11:20, DRB1*11:22, DRB1*11:23:01, DRB1*11:26, DRB1*11:30, DRB1*11:33, DRB1*11:33 allellarda 269, 270 va 240 nukleotidlardan tashkil topgan bo'lib, oqsillar tarkibidagi aminokislotalar soni 80-89 taga teng bo'lgan.

DRB1*12 genida 8 ta allel variant mavjud bo'lib, ulardan DRB1*12:01:01:01, DRB1*12:02:01:01, DRB1*12:02:02:01 larda 13105- 13857 tagacha nukleotid qatorlari mavjud va 801 kodlanadigan iRNK hosil bo'ladi, oqsil tarkibida 266 ta aminokislota qoldig'i bo'ladi. DRB1*12:06 tarkibida 628 ta kodlanadigan nukleotidlar bo'lib, 209 aminokislota qoldigidan tashkil topgan oqsil kodlanadi. DRB1*12:03:02 allel variantida 628 ta kodlanadigan nukleotidlar bor va 183 ta aminokislotali oqsil hosil qiladi. DRB1*12:04, DRB1*12:05 allellarda nukleotid qatorlari qisqargan bo'lib, 270 ta nukleotiddan iborat va 89 ta aminokislotadan iborat oqsil kodlaydi.

DRB1*13 genining 36 ta allel variant mavjud bo'lib, DRB1*13:01:01:01, DRB1*13:02:01:01, DRB1*13:03:01:01, DRB1*13:04, DRB1*13:05:01:01, DRB1*13:06, DRB1*13:07:01, DRB1*13:08, DRB1*13:10, DRB1*13:11:01, DRB1*13:12:01, DRB1*13:14:01, DRB1*13:15, DRB1*13:16:01:01, DRB1*13:17, DRB1*13:18, DRB1*13:19, DRB1*13:20:01:01, DRB1*13:21:01:01, DRB1*13:22:01:01, DRB1*13:24:01:01, DRB1*13:26:01, DRB1*13:27:01, DRB1*13:29:01:01 allel variantlarda 13171-13941 doirasida nukleotidlar qatoriga ega bo'lgan. DRB1*13:03:02, DRB1*13:07:02, DRB1*13:09, DRB1*13:13, DRB1*13:25 allellarda nukleotidlar qatori 270 atrofida bo'lgan va kodlanadigan oqsillar tarkibida 80-89 ta aminokislotalar qoldig'i uchragan.

DRB1*14 genida 32 ta allel variant aniqlangan bo'lib, DRB1*14:01:01:01, DRB1*14:02:01:01, DRB1*14:03:01, DRB1*14:04:01:01, DRB1*14:05:01:01, DRB1*14:06:01, DRB1*14:07:01, DRB1*14:08, DRB1*14:09, DRB1*14:10:01:01, DRB1*14:11:01:01, DRB1*14:12:01, DRB1*14:13, DRB1*14:14, DRB1*14:15, DRB1*14:16, DRB1*14:17, DRB1*14:18, DRB1*14:19, DRB1*14:20, DRB1*14:21, DRB1*14:23:01:01, DRB1*14:24 allellarda nukleotidlar soni 13108-13940 tagacha bo'lgan, kodlanadigan CDS nukleotidlar soni 801 ta bo'lib, oqsillar tarkibidagi aminokislotalar qoldig'i 266 taga teng bo'lgan. DRB1*14:13 va DRB1*14:27:01 nukleotidlar soni 687 va 663 bo'lib, oqsillar tarkibida aminokislotalar qoldig'i 228 va 220 ta bo'lgan. DRB1*14:22, DRB1*14:25:01, DRB1*14:26, DRB1*14:28, DRB1*14:29, DRB1*14:30, DRB1*14:31, DRB1*14:32:01 nukleotidlar qatori qisqargan allel variantga kiradi, kodlanadigan nukleotid qatori soni 257- 283 tagacha bo'lib, hosil bo'lgan oqsil tarkibida 84-94 tagacha aminokislota uchraydi.

DRB1*15 genida 11 allel variant uchraydi, allel variantlar tarkibidagi nukleotidlar soni DRB1 01 alleldagi nukleotidlar soniga yaqindir. DRB1* 15:01:01:01, DRB1*15:01:02, DRB1*15:02:02:01, DRB1*15:03:01:01, DRB1*15:04, DRB1*15:06:01, DRB1*15:07:01 allellarda nukleotidlar soni 10862- 11567 tagacha bo'ladi. Kodlanadigan nukleotidlar soni 801 ga teng bo'lib, oqsillar tarkibidagi aminokislotalar soni 266 taga tengdir. DRB1*15:05 allel tarkibida nukleotidlar soni 552 taga teng bo'lib, oqsil tarkibida 183 ta aminokislota mavjud. DRB1*15:02:03, DRB1*15:08 allellarda 246, 270 ta nukleotid qatorlari mavjud bo'lib, kodlanadigan oqsillar tarkibida 81 va 89 ta aminokislota aniqlangan.

DRB1*16 genida 10 ta allel variant mavjud bo'lib, DRB1*16:01:01:01, DRB1*16:02:01:01, DRB1*16:04:01, DRB1*16:05:01, DRB1*16:07 larda 10751- 11272 tagacha nukleotid qatorlari mavjud, DRB1*16:03 allel variantda kodlanadigan nukleotid qatori 785 tagacha qisqargan bo'lib, sintezlanadigan oqsil tarkibida 262 ta aminokislota qoldig'i bor. DRB1*16:01:02, DRB1*16:02:02, DRB1*16:08 tarkibida kodlanadigan nukleotidlar soni 242-270 gacha bo'lib, oqsillar tarkibida 80-89 tagacha aminokislota aniqlangan.

**HLA- DRB1 geni allel variantlari (www.ebi.ac.uk/ipd/imgt/hla/alleles)**

T/R	DRB1*01	GEN	CDS	OQSIL	
1	DRB1*01:01:01:01	11101	801	266	
2	DRB1*01:01:02:01	11229	801	266	
3	DRB1*01:02:02		246	81	
4	DRB1*01:03:01:01	10956	801	266	
5	DRB1*1:04:01		675	224	
6	DRB1*01:05		270	89	
7	DRB1*01:06		270	89	
T/R	DRB1*03	GEN	CDS	OQSIL	
1	DRB1*03:01:01:01	13908	801	266	
2	DRB1*03:01:02:01	13222	801	266	
3	DRB1*03:02:01:01	13209	801	266	
4	DRB1*03:02:02		300	100	
5	DRB1*03:03		270	89	
6	DRB1*03:04:01	13233	801	266	
7	DRB1*03:05:01	13203	801	266	
8	DRB1*03:06	13203	801	266	
9	DRB1 03:07:01:01	13204	801	266	
10	DRB1*03:08		565	188	
11	DRB1*03:09		258	86	
12	DRB1*3:10		714	237	
13	DRB1*3:11:01		269	89	
14	DRB1*03:12		240	80	
T/R	DRB1*04	GEN	CDS	OQSIL	
1	DRB1*04:01:01:01	14956	801	266	
2	DRB1*04:01:02		270	89	
3	DRB1*04:02:01	14499	801	266	
4	DRB1*04:03:01:01	15224	801	266	
5	DRB1*04:04:01:01	15150	801	266	
6	DRB1*04:05:01:01	15140	801	266	
7	DRB1*04:05:02		270	89	
8	DRB1*04:06:01	15150	801	266	
9	DRB1*04:07:01:01	14958	801	266	
10	DRB1*4:08:01:01	14489	801	266	
11	DRB1*04:09:01:01	14562	801	266	
12	DRB1*04:10:01	14945	801	266	
13	DRB1*04:11:01:01	14500	801	266	
14	DRB1*04:12	14504	801	266	
15	DRB1*04:13	14562	801	266	
16	DRB1*04:14	14435	801	266	
17	DRB1*04:15	14569	801	266	
18	DRB1*04:16	14509	801	266	
19	DRB1*4:17:01		270	89	
20	DRB1*04:18	14569	801	266	
21	DRB1*04:19	14486	801	266	
22	DRB1*04:20		222	73	
23	DRB1*04:21		663	220	
24	DRB1*04:22		246	82	
25	DRB1*04:23		270	89	
26	DRB1*04:24		270	89	
27	DRB1*04:25		801	266	
28	DRB1*04:26		801	266	
29	DRB1*04:27		260	86	
30	DRB1*04:28		270	89	
31	DRB1*04:29		270	89	

32	DRB1*04:30		270	89	
33	DRB1*04:31		801	266	
34	DRB1*04:32		801	266	
T/R	DRB1*07	GEN	CDS	OQSIL	
1	DRB1*07:01:01:01	16110	801	266	
2	DRB1*0702				
3	DRB1*07:03	15379	801	266	
4	DRB1*07:04		801	266	
T/R	DRB1*08	GEN	CDS	OQSIL	
1	DRB1*08:01:01:01	13235	801	266	
2	DRB1*8:02:01:01	13841	801	266	
3	DRB1*08:02:02		552	183	
4	DRB1*08:03:01				
5	DRB1*08:03:02:01	13562	801	266	
6	DRB1*08:04:01:01	13219	801	266	
7	DRB1*08:04:02		228	76	
8	DRB1*08:04:03		269	89	
9	DRB1*08:05		270	89	
10	DRB1*08:06:01:01	13220	801	266	
11	DRB1*08:07	13251	801	266	
12	DRB1*08:08	13220	801	266	
13	DRB1* 08:09:01	13841	801	266	
14	DRB1*08:10	13199	801	266	
15	DRB1*08:11:01:01	13179	801	266	
16	DRB1*08:12		270	89	
17	DRB1* 08:13		801	266	
18	DRB1*08:14		801	266	
19	DRB1*08:15		270	89	
20	DRB1*08:16		801	266	
21	DRB1*08:17	13182	801	266	
22	DRB1*08:18		801	266	
23	DRB1*08:19		257	85	
24	DRB1*08:20		270	89	
25	DRB1*08:21		269	89	
T/R	DRB1*09	GEN	CDS	OQSIL	
1	DRB1*09:01:01				
2	DRB1*09:01:02:01	16042	801	266	
T/R	DRB1*10	GEN	CDS	OQSIL	
1	DRB1 10:01:01:01	13501	801	266	
T/R	DRB1*11		GEN	CDS	OQSIL
1	DRB1*11:01:01:01		13921	801	266
2	DRB1*11:01:02:01		13931	801	266
3	DRB1*11:01:03		13227	801	266
4	DRB1*11:02:01:01		13641	801	266
5	DRB1*11:03:01		13650	801	266
6	DRB1*11:04:01:01		13919	801	266
7	DRB1*11:04:02		13185	801	266
8	DRB1*11:05			801	266
9	DRB1*11:06:01		13244	801	266
10	DRB1*11:07:01			552	183
11	DRB1*11:08:01		13186	801	266
12	DRB1*11:08:02			801	266
13	DRB1*11:09:01:01		13246	801	266

14	DRB1*11:10:01		270	89
15	DRB1*11:11:01	13243	801	266
16	DRB1*11:12:01	13243	801	266
17	DRB1*11:13:01		562	187
18	DRB1*11:14:01:01	13238	801	266
19	DRB1*11:15:01:01	13249	801	266
20	DRB1*11:16:01:01	13179	801	266
21	DRB1*11:17	13229	801	266
22	DRB1*11:18	13231	801	266
23	DRB1*11:19:01	13203	801	266
24	DRB1*11:20		270	89
25	DRB1 *11:21		801	266
26	DRB1*11:22		250	82
27	DRB1*11:23:01		270	89
28	DRB1*11:24:01	13180	801	266
29	DRB1*11:25	13201	801	266
30	DRB1*11:26		240	80
31	DRB1*11:27:01	13242	801	266
32	DRB1*11:28:01:01	13182	801	266
33	DRB1*11:29:01	13181	801	266
34	DRB1*11:30		269	89
35	DRB1*11:31		714	237
36	DRB1*11:32		552	183
37	DRB1*11:33		270	89
38	DRB1*11:34	13180	801	266
T/R	DRB1*12	GEN	CDS	OQSIL
1	DRB1*12:01:01:01	13220	801	266
2	DRB1*12:02:01:01	13857	801	266
3	DRB1*12:02:02:01	13105	801	266
4	DRB1*12:03:01			
5	DRB1*12:03:02		552	183
6	DRB1*12:04		270	89
7	DRB1*12:05		270	89
8	DRB1* 12:06		628	209
T/R	DRB1*13	GEN	CDS	OQSIL
1	DRB1*13:01:01:01	13935	801	266
2	DRB1*13:02:01:01	13941	801	266
3	DRB1*13:03:01:01	13761	801	266
4	DRB1*13:03:02		270	89
5	DRB1*13:04	13251	801	266
6	DRB1*13:05:01:01	13200	801	266
7	DRB1*13:06	13249	801	266
8	DRB1*13:07:01	13822	801	266
9	DRB1*13:07:02		268	89
10	DRB1*13:08	13206	801	266
11	DRB1*13:09		270	89
12	DRB1*13:10	13181	801	266
13	DRB1*13:11:01	13199	801	266
14	DRB1*13:12:01	13205	801	266
15	DRB1*13:13		262	86
16	DRB1*13:14:01	13199	801	266
17	DRB1*13:15	13171	801	266
18	DRB1*13:16:01:01	13253	801	266
19	DRB1*13:17		801	266
20	DRB1*13:18	13250	801	266
21	DRB1*13:19	13235	801	266

22	DRB1*13:20:01:01		13180	801	266
23	DRB1*13:21:01:01		13204	801	266
24	DRB1*13:22:01:01		13229	801	266
25	DRB1*13:23:01			552	183
26	DRB1*13:24:01:01		13179	801	266
27	DRB1*13:25			270	89
28	DRB1*13:26:01			801	266
29	DRB1*13:27:01			801	266
30	DRB1*13:28:01			270	89
31	DRB1*13:29:01:01		13255	801	266
32	DRB1*13:30			253	84
33	DRB1*13:31			663	220
34	DRB1*13:32			270	89
35	DRB1*13:33:01			246	81
36	DRB1*13:34			270	89
T/R	DRB1*14		GEN	CDS	OQSIL
1	DRB1*14:01:01:01		13936	801	266
2	DRB1*14:02:01:01		13630	801	266
3	DRB1*14:03:01		13816	801	266
4	DRB1*14:04:01:01		13940	801	266
5	DRB1*14:05:01:01		13933	801	266
6	DRB1*14:06:01		13812	801	266
7	DRB1*14:07:01		13835	801	266
8	DRB1*14:08		13252	801	266
9	DRB1*14:09		13206	801	266
10	DRB1*14:10:01:01		13251	801	266
11	DRB1*14:11:01:01		13204	801	266
12	DRB1*14:12:01		13816	801	266
13	DRB1*14:13			687	228
14	DRB1*14:14			801	266
15	DRB1*14:15		13257	801	266
16	DRB1*14:16		13201	801	266
17	DRB1*14:17		13258	801	266
18	DRB1*14:18		13181	801	266
19	DRB1*14:19		13228	801	266
20	DRB1*14:20		13085	801	266
21	DRB1*14:21		13253	801	266
22	DRB1*14:22			270	89
23	DRB1*14:23:01:01		13108	801	266
24	DRB1*14:24			801	266
25	DRB1*14:25:01			283	94
26	DRB1*14:26			270	89
27	DRB1*14:27:01			663	220
28	DRB1*14:28			257	85
29	DRB1*14:29			270	89
30	DRB1*14:30			270	89
31	DRB1*14:31			253	84
32	DRB1*14:32:01			270	89
T/R		DRB1*15	GEN	CDS	OQSIL
1		DRB1*15:01:01:01	11080	801	266
2		DRB1*15:01:02	10898	801	266
3		DRB1*15:02:01:01			
4		DRB1*15:02:02:01	10862	801	266
5		DRB1*15:02:03		246	81
6		DRB1*15:03:01:01	11567	801	266
7		DRB1*15:04	11480	801	266

8	DRB1*15:05		552	183
9	DRB1*15:06:01	10898	801	266
10	DRB1*15:07:01	10902	801	266
11	DRB1*15:08		270	89
T/R	DRB1 16	GEN	CDS	OQSIL
1	DRB1*16:01:01:01	11272	801	266
2	DRB1*16:01:02		255	85
3	DRB1*16:02:01:01	11005	801	266
4	DRB1*16:02:02		242	80
5	DRB1*16:03		785	262
6	DRB1*16:04:01		801	266
7	DRB1*16:05:01	10751	801	266
8	DRB1*16:06			
9	DRB1*16:07		801	266
10	DRB1*16:08		270	89
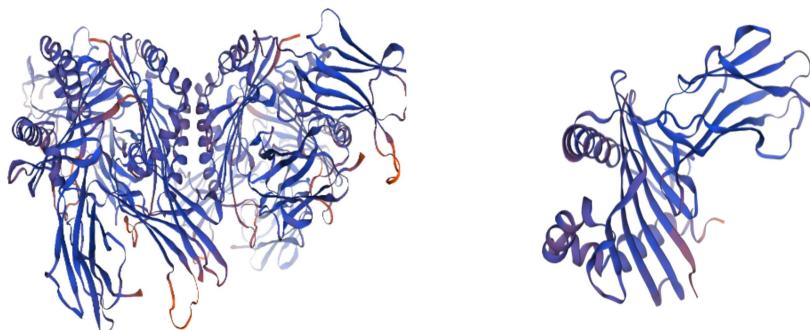
A) HLA DRB1*01:01:01:01/DRA1*01:01:01:01   B) HLA DRB1*01:05/DRA*01:01:01:01
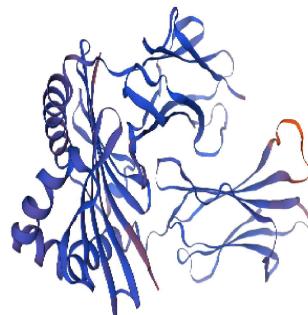
C) HLA-DRB1*03:08/DRA*01:01:01:01

Rasm 1. 266, 183 va 89 ta aminokislotalardan iborat bo'lgan oqsil molekulasining konformatsion strukturasi.

Rasm 1 da keltirilgan ma'lumotlarga ko'ra, DRB1 01 allelida umumiy nukleotidlar soni turlicha bo'lishi, oqsil strukturasida 89 dan 266 tagacha aminokislotalarga ega bo'lgan oqsil strukturasining sintezlanishiga olib keladi. Hosil bo'lgan oqsil strukturasining konformatsion tuzilishida, 3 ta namunada farqlar kuzatigan bo'lsada, HLA DRB1 allel variantlari antigenlar epitoplari bilan bog'lanish strukturasi yaxshi takomillashgan.

Ushbu ma'lumotlarni MHC II sinfining bog'lanish bashoratini IEDB analitik resursining NetMHCIIpan (versiya 4.1) dan foydalangan holda ishlab chiqildi. Natijalarga ko'ra, MHC II sinf HLA DRA*01:01:01:01/ DRB1 ning DRB1*03:08 va DRB1*01:05 allel variantlari aminokislatalar qatori qisqargan bo'lib, DRB1*03:08 da 188 ta aminokislota qoldig'ini va DRB1*01:05 da 89 ta aminokislota qatoriga ega bo'lgan. Lekin ushbu ikkala allel variantda molekulalarning ligand bog'lovchi qismlari ko'p bo'lib, faolligini yo'qotmagan.
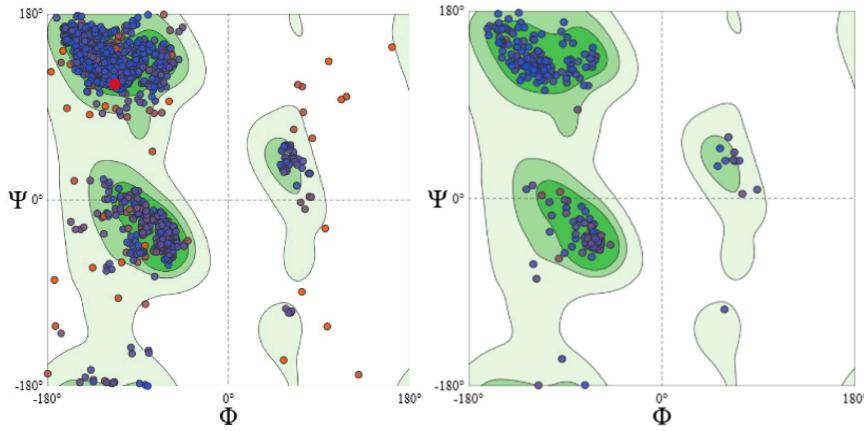
A) HLA DRB1*01:01:01:01/DRA* 01:01:01:01   B) HLA DRB1*01:05/DRA*01:01:01:01
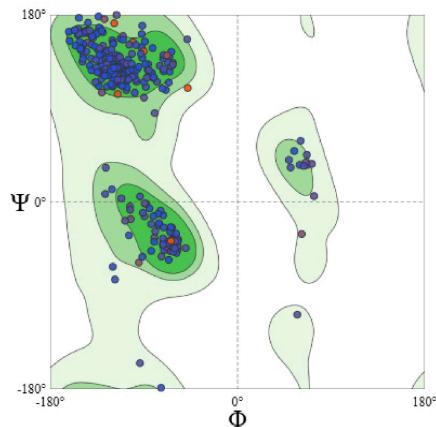
C) HLA-DRB1*03:08/DRA*01:01:01:01

Rasm 2. Geterodimerlar MolProbity ko'rsatkichlari (Ramachandran xaritasi).

HLA DRB1*01:01:01:01/DRA1*01:01:01:01

Rasm 2 da keltirilgan Mol Probity ko'rsatkichlariga ko'ra, MolProbity Score 1.36, Clash Score 1.53, Ramachandran ijobiy bahosi 93.90%, Ramachandran anomaliyalari: 1,54% ga teng bo'lgan.

C27 LYS, B137 PRO, G167 ASP, D27 ALA, A167 ASP, H212 PRO, D26 LEU, B142 ASN, A108 THR, F134 LYS, D139 GLN, F140 HIS, F138 LEU, B136 GLN, H140 HIS, H26 LEU, B26 LEU, F28 LEU, F26 LEU, D136 GLN, D137 PRO, F136 GLN, F137 PRO

Rotamer chiqishlari: 1.18%, D104 VAL, A141 VAL, F32 THR, B141 HIS, H198 GLU, G141 VAL, H189 MET, B50 THR, E27 LYS, D142 ASN, G60 ASP, C141 VAL, E184 ASP, G80 GLU, D28 LEU, E141 VAL

C-Beta og'ishlar: 13, F32 THR, F26 LEU, C107 ILE, B26 LEU, F136 GLN, D139 GLN, D136 GLN, C108 THR, D28 LEU, E184 ASP, D62 ASN, D183 THR, D134 LYS

Salbiy bog'lar: 12700 bog'dan 4 tani tashkil qilgan: C107 ILE-C108 THR, F25 PRO, H25 PRO

Salbiy burchaklar soni: 17296 ta burchakdan 133 tasi salbiy burchak 133 /17296:

Cis pozitsiyadagi Prolinar soni 88 tadan 12 bo'lgan: 12 / 88: (F152 TYR-F153 PRO), (B152 TYR-B153 PRO), (D152 TYR-D153 PRO), (H152 TYR-H153 PRO), (A40 ASN-A41 PRO), (A138 THR-A139 PRO), (C40

ASN-C41 PRO), (C138 THR-C139 PRO), (E40 ASN-E41 PRO), (E138 THR-E139 PRO), (G40 ASN-G41 PRO), (G138 THR-G139 PRO).

Buralgan prolinlar 88 tadan 1 ta bo'lgan: 1 / 88, (A176 LEU-A177 PRO)

HLA DRB1*03:08/DRA*01:01:01:01

Mol Probity baholash: 0,98

Clash Score-to'qnashuvlar soni: 0,68 (B71 ASP-B75 ARG)

Ramachandran ijobiy bahosi: 96.23%

Ramachandran anomaliyalari: 0%

Rotamer chiqishlari: 0,81 % A 72 GLN, Б 22 LEU

C- beta og'ishlar: 4 ta, A 206 ASP, B 40 ARG, A 104 TYR, A 43 GLN

Salbiy bog'lar: 1/2316, A174

Salbiy burchaklar: 26/3145

A206 ASP, B71 ASP, B11 HIS, (A138 THR-A139 PRO), A28 GLU, A91 ASP, (B50 ARG-B51 PRO), A50 ASP, A149 ASN, A174 HIS, A170 PHE, A202 HIS, (A179 LEU-A180 PRO), B76 HIS, (A120 SER-A121 PRO), (A126 GLU-A127 PRO), B61 ASP, (A176 LEU-A177 PRO), A168 HIS, A160 THR, A192 HIS, (A205 PHE-A206 ASP), B24 ARG

*Cis prolin aminokislotalar soni:* 2/14, (A40 ASN-A41 PRO), (A138 THR-A139 PRO)

HLA DRB1*01:05/DRA*01:01:01:01

MopProbity baholash: 0,97

Clash Score- to'qnashish soni: 0, 68(B71 ASP-B75 ARG)

Ramachandran ijobiy bahosi: 96.24%

Ramachandran anomaliyalari: 0,00%

*Rotamer chiqishi:*0, 81%, A 144 VAL, Б 22 LEU

*C- beta og'ishi:*3, A 207 ASP, A 104 TYR, B 40 ARG

Salbiy bog'lar: 0/2323

Salbiy burchaklar: 22/3151, A207 ASP, B71 ASP,

(A138 THR-A139 PRO), B11 HIS, (B50 ARG-B51 PRO), A28 GLU, A91 ASP, A175 HIS, A50 ASP, (A180 LEU-A181 PRO), A171 PHE, B76 HIS, A203 HIS, (A120 SER-A121 PRO), (A126 GLU-A127 PRO), A161 THR, A169 HIS, (A177 LEU-A178 PRO), A192 GLU, A193 HIS

Cis-Prolinlar: 1/254, (A40 ASN-A41 PR), (A138 THR-A139 PRO)

Rasm 3. HLA DRB1*01:05/DRA*01:01:01:01 oqsil α va β zanjirlarining QMEAN4 dasturi bahosi.
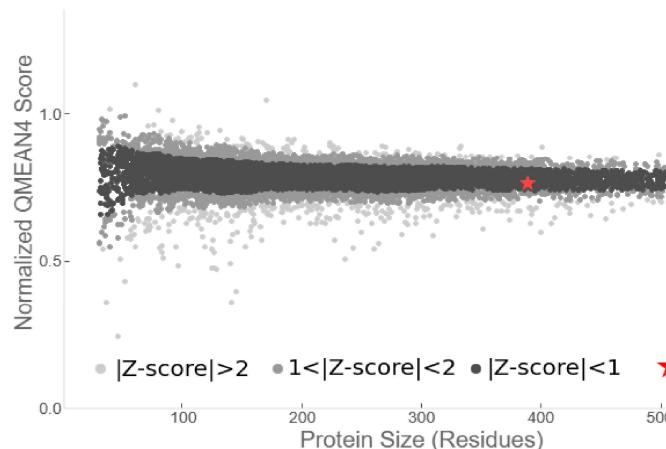
Rasm 4. HLA DRB1*01:05/DRA*01:01:01:01 geterodimer oqsilining QMEAN4 dasturi bahosi.

89 aminokislota qoldig'iga ega bo'lgan oqsil QMEAN4 dasturi bahosi rasm 3, 4 da keltirilgan. Dastur bahosiga ko'ra, oqsil strukturasi modeli ijobiy bahoga ega bo'lgan. QMEAN4 bu oqsil strukturasini sifatini turli xilomillarga asoslanib baholaydigan kompleks ko'rsatkich bo'lib, oqsilning moslik darjsini baholaydi.

XULOSA

Keltirilgan ma'lumotlar bir nechta HLA geterodimer struktur modeli MolProbity, Clash Score, Ramachandran Plot, Rotamer Outliers, C-Beta og'ishlar, salbiy bog'lar va burchaklar kabi ko'rsatkichlar baholanishini o'z ichiga olgan va baholangan. Keltirilgan birinchi oqsil 266 ta aminokislota qoldig'idan tashkil topgan bo'lib, Mol Probity bahosi 1,36, ikkinchi 183 ta aminokislota qoldig'i va uchinchi oqsillarda 89 ta aminokislota qoldig'idan tashkil topgan struktura 0,98 va 0,97 ga teng bo'lgan. MolProbity qiymatlari kichik bo'lishi yaxshi konstruktsiyali oqsil sifatini bildiradi. Clash Score ko'rsatkichi birinchi oqsilda 1,36 va ikkinchi va uchunchi oqsilda 0,68 ga teng. Ramanchandran tasnifiga ko'ra birinchi oqsil uchun 93,90% bo'lib ijobiy baholangan va ikkinchi,

uchinhi oqsil uchun 96,23% bo'lib juda yaxshi baholangan. Huddi shundan rotamer og'ishi ikkinchi va uchinchi oqsillarda juda yaxshi baholangan. B-beta og'ishlar birinchi oqsilda 13 ta, ikkinchi oqsilda 4 va to'rtinchi oqsilda 3 ta uchragan. Salbiy bog'lar soni birinchi oqsilda ko'p 4 ta, ikkinchi va uchinchi oqsilda 1 va 0 ta. Salbiy burchaklar soni ikkinchi va uchinchi oqsilda 26, 22 ta, birinchi oqsilda 133 ta. Cis- prolinlar soni birinchi va uchinchi oqsillar tarkibida 1 ta va ikkinchi oqsil tarkibida 2 ta uchragan. Tahlil qilingan MolProbity baholashlari va Clash Score ko'rsatkichlariga ko'ra, ikkinchi va uchinchi oqsillar HLA-DRB1 03:08/DRA 01:01:01:01 va HLA-DRB1 01:05/DRA 01:01:01:01 yuqori sifatga ega, chunki MolProbity bahosi 0,97–0,98 yoki Clash Score 0,68, Z-ko'rsatkich ≤ 2 oqsilning 3D strukturasi uchun yaxshi sifatni va modellashtirish natijalari yaqinligini anglatadi.

Shu bilan birga, MHC II sinfining ligand bog'lanish bashoratini IEDB analitik resursing NetMHCIIpan (versiya 4.1) dan foydalangan holda ishlab chiqish natijalarga ko'ra, DRB1*03:08 da 188 ta aminokislota qoldiqli va DRB1*01:05 da 89 ta aminokislota qatoriga

ega bo'lib, ikkala allel variantda molekulalarning ligand bog'lovchi qismlari ko'p bo'lib, faolligini yo'qotmagan.

Yuqorida keltirilgan ma'lumotlarga ko'ra, HLA molekulalari mutatsiyasi natijasida yuzaga kelgan allel variantlari oqsil molekulasining qisqarishi bilan bog'liq bo'lgan modifikatsiyalari II sinf molekulalarining faolligi saqlanib qolgan, nukleotidlar ko'payishi bilan bog'liq bo'lgan modifikatsiyalar oqsil strukturasini tabiiy 266 aminokislota qoldig'i strukturani saqlab qoladi.

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