GenVinSet

HLA-C*06

Instructions for use

Kit for HLA-C*06 group of alleles detection

For In Vitro Diagnostic Use

References GVS-C06-48 (48 tests)
GVS-C06-24 (24 tests)

Store from –18 to –30ºC

CE

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Index

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1. Intended use

GENVINSET HLA C*06 is a kit for HLA-C*06 group of alleles determination by Real Time PCR using specific primers and hydrolysis probes (TaqMan® technology).

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2. Summary and explanation

Psoriasis vulgaris (PsV) is a chronic inflammatory disease of skin, characterised by epidermal hyperplasia, inflammatory cellular infiltration and vascular remodelling [1, 2]. It occurs approximately in 2% of the general population. The cutaneous manifestations of psoriasis are obvious, and have a negative impact on quality of life of patients. Moreover, up to 40% of psoriatics develop psoriatic arthritis; in 5% of psoriatics the psoriatic arthritis is severe and deforming [3]. It has a complex aetiology which involves both genetic and environmental factors. However, the root cause of psoriasis remains unknown.

Family studies have demonstrated that psoriasis has a genetic basis and is multifactorial in most if not all cases [4]. However, despite numerous genetic linkage studies yielding at least 19 candidate loci, the identities of the genes involved remain unclear [5]. Nevertheless, there is a general agreement that a major genetic determinant of psoriasis, designated "psoriasis susceptibility 1" (PSORS1 [MIM 177900]), resides in the major histocompatibility complex (MHC) [6].

The existence of allelic associations between psoriasis and human leukocyte antigen (HLA) genes in the MHC, has been appreciated for more than 100 years [7]. HLA-C*06 has been identified as a major psoriasis susceptibility genetic polymorphism, and identifies early-onset psoriasis (type 1) [8] and the guttate subtype of psoriasis. The worldwide HLA-C*06 allele frequency varies greatly and can range from 14,1% to 59,1%, whereas the percentage of patients with psoriasis carrying HLA-C*06 ranges from 10,5% to 77,2%, according to Chen et al. [9]. Although C*06 is highly associated with the disease, the allele frequency does not directly reflect the pathology prevalence. The pathogenesis of psoriasis integrates genetic, environmental and immunologic factors.

Biological agents represent an advanced type of psoriasis treatment. However, clinical studies have demonstrated that even highly selective drugs are not effective in all patients and could be associated with important side effects [10].

Several studies have demonstrated a significant increase in response to ustekinumab treatment in HLA-C*06 positive patients [10-14]. Talamonti et al. reported that HLA-C*06 positive patients respond faster and higher to ustekinumab than HLA-C*06 negative patients, 96.3% of them reaching PASI 75 at week 28, against the 72.7% in C*06 negative patients [10]. Similar results were found in Chinese patients, in which more C*06 positive patients reached PASI 75 and PASI 90 at 4 and 28 weeks, in comparison to C*06 negative patients [14].

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It has been shown that the presence of HLA-C*06 affects different aspects of psoriasis, from genetic susceptibility, to clinical manifestation, co-morbidity and treatment efficacy. Interestingly, although the allele positivity is usually associated with more severe and unstable form of disease, treatment response seems to be more favourable for both conventional agents and certain biologics.

All of that underline the roll of HLA-C*06 not only as a psoriasis susceptibility marker, but also as a pharmacogenetic marker of response to ustekinumab in psoriasis.

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3. Procedure principles

The detection method used by Genvinset is based in a primer specific PCR, which anneal to specific HLA- C*06 group of alleles (*) monitored by TaqMan probes.

At the same time the method amplifies and detects a control gene (ß-actin) to verify the assay's result.

This technique provides high resolution, high sensitivity, specificity and reproducibility.

(*) See Procedure Limitations (section 12)

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4. Kit contents

Reference: GVS-C06-24 (24 tests)

- GVS-C06-PM: Primer Mix (PM). 1 vial x 110 µL
- GVS-C06-MM: Master Mix (MM). 1 vial x 138 µL
- GVS-C06-C+: Positive Control (C+). 1 vial x 5 µL
- GVS-RB: Reaction Blank (RB). 1 vial x 100 µL

Reference: GVS-C06-48 (48 tests)

- GVS-C06-PM: Primer Mix (PM). 2 viales x 110 µL
- GVS-C06-MM: Master Mix (MM). 2 viales x 138 µL
- GVS-C06-C+: Positive Control (C+). 1 vial x 5 µL
- GVS-RB: Reaction Blank (RB). 1 vial x 100 µL

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5. Kit storage

All of the kit's reagents should be stored from -18ºC to -30ºC and they are stable at this temperature until its expiration date, as indicated in the bottle. Do not perform more than 3 freezing/thawing cycles to the Primer Mix (GVS-C06-PM) and Master Mix (GVS-C06-MM) vials as this could reduce the assays sensitivity and change results.

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6. Materials required but not supplied

General

- Gloves
- Lab coat

Consumables:

- Filter tips (P200, P100 & P10).
- 1.5 mL Autoclaved tubes.
- RT-PCR instrument specific reagents (in the case of using RotorGene Q, only 0.1mL tubes are allowed).

Equipment

- RT-PCR instrument, with FAM and HEX/VIC detection channels.
  Validated instruments:
  - StepOne™, Applied Biosystems™
  - LightCycler® 96 System, Roche
  - Rotor-Gene® Q, Qiagen®
  - DTlite Real-Time PCR System, DNA-TECHNOLOGY
- Vortex
- Pipettes (P200, P100 & P10)

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7. Sample collection and preparation

This test should only be performed with whole blood samples treated with EDTA anti coagulation agents or citrate. Heparin can interfere with the PCR process and should not be used in this procedure.

It is recommended to test the DNA extraction system with GENVINSET HLA C*06 before using the results for diagnostic purposes.

Caution

All biological and blood samples should be treated as possibly infectious. When manipulating them, observe all basic (universal) precautions. All sample manipulation should be done with gloves and appropriate protection.

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8. Procedures

A) PCR preparation

Precautions

- Unfreeze all of the kit components before starting the assay, mix and centrifuge.
- Work over ice or a cold block.
- The PCR should be assembled in the pre-PCR area.
- Use only filtered tips and autoclaved tubes 1.5 mL.
- Use gloves and lab coat at all times.
- In each session it is recommended to use one negative sample for HLA-C*06 and the Positive Control (C+) included in the kit.

1. Take the samples out of the freezer. Vortex.
2. Prepare the Master Mix and Primer Mix to n+1 samples:

	Vol. per sample (µL)
Master Mix	5
Primer Mix	4

3. Pipette 9 µL of this mix on the PCR wells over the cold holder and add 1 µL of DNA, or Reaction Blank in the case of the contamination control well.
4. Seal the tubes/plate with convenient sealer, spin down the volume by centrifuging 1 min. 360 x g.
5. Place the tubes/plate in the thermal cycler and start the following cycle:

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B) Thermal cycler configuration

1. Set up the next amplification program:

	Cycle number	Temperature (ºC)	Time (mm:ss)	Analysis
Desnaturalization	1	95	05:00	X
Cycle	40	95	00:15	X
		64	1:00	Single
Cooling	1	15	∞	X

2. Set up the reading channels

3. The emitted fluorescence must be read in FAM (495-520 nm) and HEX (535-554 nm) channels. Both fluorescences should be detected in every well (biplex reaction).

NOTE – Special settings for Rotor Gene Q:

a. Open the Rotor-Gene Q – Pure Detection software. Select the tab "Advanced" in the window New Run, and click "New".

b. Select the type of rotor used (only 0.1 mL tubes accepted, see section 6). Select the "Locking Ring Attached" box and continue by clicking "Next".

c. Type the "Reaction Volume" as 10 uL, and identify the operator and the sample.

d. Click "Edit Profile" and set up the amplification program (see section 8.C.1). Select the step 60 sec at 64 ºC, and click "Acquiring to Cycling A". Select the channels for fluorescence acquisition "Green" and "Yellow". Then "OK". Click "OK" to accept and close the "Edit Profile" window.

e. Clic "Gain Optimisation" in the "Run New Wizard" dialog box to open the "Auto-Gain Optimization Setup" window. In the scroll menu of "Channel Settings" select "Acquiring Channels" and then "Add". In the window "Auto-Gain Optimisation Channel Settings", set the following parameters for each channel ("Green" and "Yellow"):

- Tube position = 1
- Target Sample Range: 5 FI up to 10 FI
- Acceptable Gain Range: -10 to 10

f. Activate the option "Perform Optimisation Before 1st Acquisition", and click "Close".

g. Select "Next" and then "Start Run" in the "New Run Wizard" window.

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9. Results

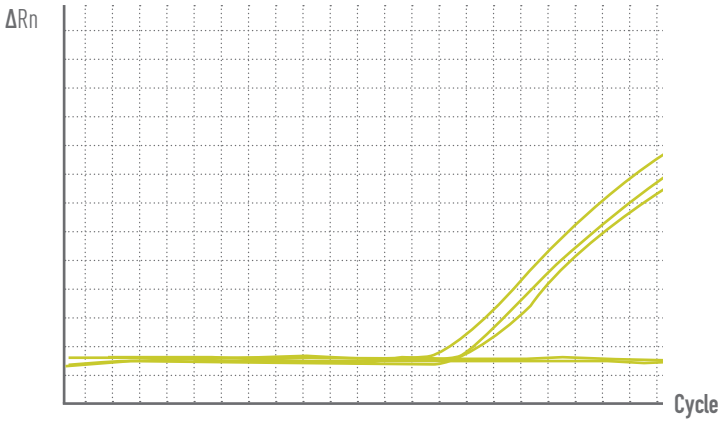
GENVINSET HLA is a qualitative technique to identify presence or absence of HLA-C*06 group of alleles.

It is not necessary to select any passive reference.

The results of this technique can be obtained as follows:

HLA-C*06 results

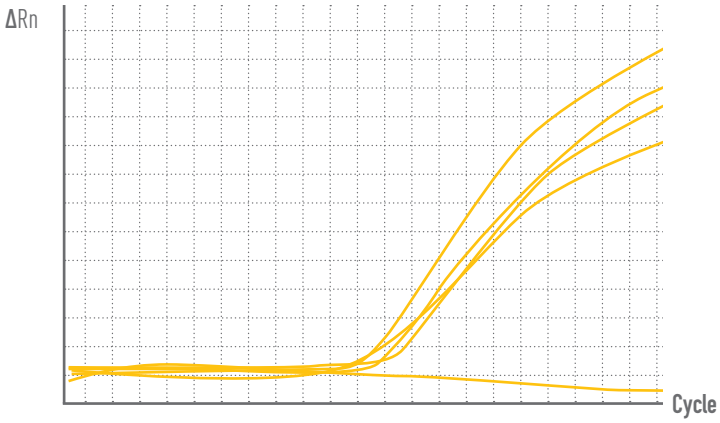
Selecting FAM channel in Amplification Plot, we can see next graphic:



Samples generating an amplification curve are C*06 positive and they are identified by a numeric value called Crossing Point (Cp) corresponding with the cycle in which the fluorescence can be detected.

ß-actin results (internal Positive Control):

Selecting VIC/HEX channel in Amplification Plot, we can see next graphic:



Samples generating an amplification curve are positive for internal control (ß-actin). All DNA samples should be positive for this gene, showing the presence of sample in the corresponding well and the correct amplification.

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10. Quality control

Due to the qualitative nature of this test, it will not be necessary to perform a calibration.

It is recommended to perform a contamination control by replacing the DNA for the Reaction Blank, and also include the Positive Control, both supplied in the kit.

The following criteria should be known for the assay to be considered valid:

- The contamination control (Reaction Blank) must provide negative results both for C*06 and for ß-actin. Cp (Crossing Point) values >35 would be consider as negative result. Cp values <35 inform us about a contamination in the session so results should be discarded.
- A positive control sample must provide positive results for both C*06 and for ß-actin.
- DNA samples should always be positive for ß-actin (Cp<35).
- DNA samples generating results with Cp>35 for ß-actin and/or C*06 must be considered as doubtful and must be retested performing a new extraction of DNA.

The assay must be made according to the kits recommendations, as well as other quality control procedures that comply with local, federal and/or certifying agencies specifications.

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11. Specific operation data

1. Analytical specificity

The alignment of primers and probes in the most common HLA database (IMGT-HLA) has revealed the absence of non specific bindings. No cross-reaction phenomena with genomic DNA have been reported.

Specificity of the analysis reactions are detailed at Section 12.

2. Analytical sensitivity

Once performed a dilution assay using 1:2 serialized dilutions of one DNA samples HLA-C*06 positive and another sample HLA-C*06 negative, obtained by conventional extraction system, at a concentration of 83 and 98 ng/µL, the following results were obtained as for analytical sensitivity of the HLA-C*06 allele detection:

- DNA sample obtained by conventional extraction system: Detection Limit = 1,30 ng/µL (*)

  (*) Cp < 35

3. Diagnostic sensitivity and specificity

In three studies of human genomic DNA, 153 samples obtained from two clinical laboratories were analyzed. They were previously typed by HLA-SSO (Sequence Specific Oligonucleotide) in Luminex platform or by massive sequencing (NGS).

Out of 153 samples tested, all of them were validated (positive amplification of the ß-actin control gene), and 24 of them were found to be C*06 positive (amplification in FAM channel).

	Genvinset HLA C*06			
	Samples	C*06 +	C*06	b-actin
SSO/ NGS	C*06 +	24	0	24
	C*06 -	0	129	129

There is a 100% match in the results obtained with GENVINSET HLA C*06 and the typing previously obtained with the SSO (Sequence Specific Oligonucleotide probes) methodology or NGS.

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12. Alleles detected by GENVINSET HLA C*06 (IMGT-HLA 3.33.0)

C*06:02:01:01	C*06:02:16	C*06:02:43	C*06:15
C*06:02:01:02	C*06:02:17	C*06:02:44	C*06:16N
C*06:02:01:03	C*06:02:18	C*06:02:45	C*06:17
C*06:02:01:04	C*06:02:19	C*06:02:46	C*06:18
C*06:02:01:05	C*06:02:20	C*06:02:47	C*06:19
C*06:02:01:06	C*06:02:21	C*06:02:48	C*06:20
C*06:02:01:07	C*06:02:22	C*06:02:49	C*06:21
C*06:02:01:08	C*06:02:23	C*06:02:50:01	C*06:22
C*06:02:01:09	C*06:02:24	C*06:02:50:02	C*06:23
C*06:02:01:10	C*06:02:25	C*06:02:51	C*06:24
C*06:02:01:11	C*06:02:26	C*06:02:52	C*06:25
C*06:02:01:12	C*06:02:27	C*06:02:53	C*06:26
C*06:02:01:13	C*06:02:28	C*06:02:54	C*06:27
C*06:02:01:14	C*06:02:29	C*06:03:01	C*06:28
C*06:02:03	C*06:02:30	C*06:03:02	C*06:29
C*06:02:04	C*06:02:31	C*06:04:01	C*06:30
C*06:02:05	C*06:02:32	C*06:04:02	C*06:31
C*06:02:06	C*06:02:33	C*06:05	C*06:32
C*06:02:07	C*06:02:34	C*06:06	C*06:33
C*06:02:08	C*06:02:35	C*06:07	C*06:34:01
C*06:02:09	C*06:02:36	C*06:08	C*06:34:02
C*06:02:10	C*06:02:37	C*06:09	C*06:35
C*06:02:11	C*06:02:38	C*06:10	C*06:36
C*06:02:12	C*06:02:39	C*06:11	C*06:37
C*06:02:13	C*06:02:40	C*06:12	C*06:38
C*06:02:14	C*06:02:41	C*06:13	C*06:39
C*06:02:15	C*06:02:42	C*06:14	C*06:40

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- Detected Allele
- Non detected Allele
- Non tested Allele. Possible weak amplification
- **CWD alleles marked in bold and italics**

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12. Alleles detected by GENVINSET HLA C*06 (IMGT-HLA 3.33.0)

C*06:41	C*06:65	C*06:90	C*06:115
C*06:42:01	C*06:66	C*06:91	C*06:116N
C*06:42:02	C*06:67	C*06:92	C*06:117
C*06:43:01	C*06:68	C*06:93	C*06:118
C*06:43:02	C*06:69	C*06:94	C*06:119
C*06:44	C*06:70:01	C*06:95	C*06:120
C*06:45	C*06:70:02	C*06:96	C*06:121
C*06:46N	C*06:71	C*06:97	C*06:122
C*06:47	C*06:72	C*06:98	C*06:123
C*06:48	C*06:73	C*06:99	C*06:124
C*06:49N	C*06:74Q	C*06:100	C*06:125
C*06:50	C*06:75	C*06:101	C*06:126
C*06:51	C*06:76:01	C*06:102:01	C*06:127:01:01
C*06:52	C*06:76:02	C*06:102:02	C*06:127:01:02
C*06:53:01	C*06:77	C*06:103	C*06:127:02
C*06:53:02	C*06:78	C*06:104	C*06:128N
C*06:54	C*06:79N	C*06:105	C*06:129
C*06:55	C*06:80	C*06:106:01	C*06:130
C*06:56	C*06:81	C*06:106:02	C*06:131
C*06:57	C*06:82	C*06:107	C*06:132:01
C*06:58	C*06:83	C*06:108	C*06:132:02
C*06:59	C*06:84	C*06:109	C*06:133
C*06:60	C*06:85	C*06:110	C*06:134N
C*06:61	C*06:86	C*06:111	C*06:135
C*06:62	C*06:87	C*06:112	C*06:136
C*06:63	C*06:88	C*06:113	C*06:137
C*06:64	C*06:89	C*06:114	C*06:138

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- Detected Allele
- Non detected Allele
- Non tested Allele. Possible weak amplification
- **CWD alleles marked in bold and italics**

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12. Alleles detected by GENVINSET HLA C*06 (IMGT-HLA 3.33.0)

C*06:139	C*06:167	C*06:196
C*06:140	C*06:168	C*06:197
C*06:141	C*06:169	C*06:198
C*06:142	C*06:170	C*06:199
C*06:143	C*06:171N	C*06:200Q
C*06:144	C*06:172	C*06:201
C*06:145	C*06:173	C*06:202
C*06:146	C*06:174	C*06:203
C*06:147	C*06:175N	C*06:204
C*06:148	C*06:176	C*06:205
C*06:149	C*06:177	C*06:206
C*06:150	C*06:178	C*06:207
C*06:151	C*06:179	C*06:208N
C*06:152N	C*06:180	C*06:209
C*06:153	C*06:181	C*06:210
C*06:154	C*06:182	C*06:211N
C*06:155:01:01	C*06:183	C*06:212
C*06:155:01:02	C*06:184	C*06:213
C*06:156	C*06:185	C*06:214
C*06:157	C*06:186	C*06:215N
C*06:158	C*06:187	C*06:216
C*06:159	C*06:188	C*06:217
C*06:160	C*06:189	C*06:218
C*06:161	C*06:190	C*06:219
C*06:162	C*06:191	
C*06:163	C*06:192	
C*06:164	C*06:193	
C*06:165	C*06:194	
C*06:166	C*06:195	

- Detected Allele
- Non detected Allele
- Non tested Allele. Possible weak amplification
- **CWD alleles marked in bold and italics**

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13. Procedure limitations

- The described conditions for the PCR should be precisely controlled. Deviations from these parameters can lead to poor results.
- All GENVINSET work must be made according to general lab best practices and be adjusted to local regulations, like the EFI standard (European Federation of Immunogenetics)
- The RT-PCR thermal cycler must be calibrated according to the manufacturers´ recommendations and should be used in accordance to manufacturers' instructions.
- Do not mix components from other kits or lot numbers.
- Do not use the kit after its expiration date.
- Do not use the kit if there are suspicions of possible loss of reactivity, contamination, container deterioration or any other incidence that might affect the kits performance.
- Due to the complexity of HLA typing, data and result interpretation should be revised by qualified personnel.
- Eliminate expired reagents according to applicable regulations.

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14. Troubleshooting guide

Reaction Blank (H2O) is positive

- **Primer Mix/Master Mix/Reaction Blank contamination**
  - Repeat the experiment with new Primer Mix/Master Mix/ Reaction Blank aliquots
  - Perform the kit components manipulation always according to usually accepted practices to avoid contamination.
  - Verify manipulation and storage conditions.
  - Discard contaminated reagents
- **Pre-PCR area is contaminated**
  - Confirm that all necessary precautions in the PCR area have been followed
  - Check for possible contamination problems in other PCR techniques
  - Confirm suitability of the used reagents (tubes, pipette tips)
- **Pipetting error**
  - Always check that the added sample matches the sample sheet

Low or no signal in all samples. Control samples (+/-) are OK.

- **Bad quality of DNA samples**
  - Repeat the sample extraction verifying each step (Hemoglobin can interfere with the PCR)
- **Samples with very low DNA concentration**
  - Check the DNA concentration and repeat the extraction if necessary
- **DNA samples with high concentration**
  - Perform a DNA extraction method validation assay testing some dilution of the DNA samples.

Fluorescence intensity too low

- **Kit degradation (Primer Mix vial)**
  - Confirm the correct storage of the kit (Primer Mix vial stored in darkness)
  - Avoid more than 3 freeze/unfreeze cycles of the Primer Mix vial
  - Aliquote the reagents if necessary
  - Repeat the series with new reagents

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- **Kit degradation (Master Mix vial)**
  - Confirm the kits correct storage
  - Avoid more than 3 freeze/unfreeze cycles of the Master Mix vial
  - Aliquote the reagents if necessary
  - Repeat the series with new reagents

Negative control sample (C*06 neg.) is positive

- **Cross contamination**
  - Handle the kit's components always with all currently contamination avoidance practices
- **Pipetting error**
  - Always check that the added sample matches the sample sheet

Positive control sample (C*06 pos) is negative

- **Pipetting error**
  - Always check that the added sample matches the sample sheet

Fluorescence intensity varies

- **There is dirt on the outside which interferes with the signal**
  - Manipulate the plates always wearing gloves
- **The volume is not at the bottom of the well or there is an air bubble**
  - Centrifuge to make sure the sample is at the bottom of the well and there are no air bubbles, according to the technics protocol
- **Pipetting error**
  - Verify the volume added in each well is correct

There is no fluorescence signal

- **Incorrect reading channels selected**
  - Configure the correct reading channels
- **Pipetting error or reagent absence**
  - Control the pipetting and the reactions configuration
  - Repeat the PCR
- **No reading channel was selected in the thermal cycler's program.**
  - Revise and modify the thermal cycler program

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