GenVinSet

HLA-NARCOLEPSY

Instructions for Use

Kit for DQB1*06:02 group of alleles detection

Reference GVS-NP-48 (48 tests)
GVS-NP-24 (24 tests)

Store from –18 to –30ºC

For In Vitro Diagnostic Use CE

Rev 05 / 2020-01-30

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Intended Use

GENVINSET HLA NARCOLEPSY is a kit for determination of the HLA-DQB1*06:02 group of alleles, by Real Time PCR using TaqMan® probes technology.

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Summary and explanation

Narcolepsy is an autoimmune disorder that affects approximately between 0.02 - 0.05% of the population worldwide. Narcoleptic patients frequently have severe sleepiness and commonly have fragments of Rapid Eye Movement (REM) sleep that intrude into wakefulness, such as hypnagogic (dream-like) hallucinations as they drift off to sleep, as well as brief episodes of cataplexy (muscle paralysis) triggered by strong emotions [1–4].

One of the most important breakthroughs in elucidating the cause of narcolepsy came with the discovery of hypocretins (orexins) [5-7]. Hypocretin-secreting neurons project from the lateral hypothalamus (LH) throughout the central nervous system (CNS) to neurons involved in the regulation of feeding, sleep-wakefulness, neuroendocrine homeostasis, and autonomic regulation [8,9]. The loss of hypocretin has also been reported by numerous clinical studies of narcoleptic individuals [10-15].This loss of hypocretin-producing cells is seemingly selective, rather than general or regional destruction, as intermingling melanin-concentrating neurons appear unaffected in the same narcoleptic patients [14,15]. This specific depletion of hypocretin-secreting neurons led to the hypothesis that narcolepsy is an autoimmune driven process within the hypothalamus [16,18].

The importance of the immune system and its potential role in the onset of narcolepsy has been the focus of research and debate for many years [19-21]. With more than 98% of narcoleptic patients with low CSF hypocretin-1 carrying HLA-DQB1*06:02, frequently in combination with HLA DRB1*15:01, narcolepsy has one of the strongest known associations with HLA [22, 23]. While nearly all narcoleptic patients express DQB1*06:02, expression of DQB1*06:02 is not limited to narcoleptic individuals; between 12% and 38% of the general population are carriers of this allele [24].The significant association with DQB1*06:02 strongly suggests an interaction between a specific T cell receptor subtype leading to the destruction of hypocretin producing neurons.

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Procedure principles

The detection method used by Genvinset is based on a primer specific PCR, which anneals to specific DQB1*06:02 group of alleles monitored with Taqman® probes.

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

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

(*) See section 'Procedure limitations' (page 16).

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Kit contents

Reference GVS-NP-48 (48 tests)

- GVS-NP-PM: 2 vials x 248 µL Primer Mix (PM)
- GVS-NP-C+: 1 vial x 5 µL Positive Control (C+)
- GVS-RB: 1 vial x 100 µL Reaction Blank (RB)

Reference GVS-NP-24 (24 tests)

- GVS-NP-PM: 1 vial x 248 µL Primer Mix (PM)
- GVS-NP-C+: 1 vial x 5 µL Positive Control (C+)
- GVS-RB: 1 vial x 100 µL Reaction Blank (RB)

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Kit storage

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

Due to the reagent's photo sensitive nature, avoid continuous exposure to light.

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Materials required but not supplied

General

- Gloves
- Lab coat

Consumables

- Filter tips (P1000, P200 & P20)
- 1.5 mL autoclaved tubes
- RT-PCR instrumet specific reagents (in the case of using RotorGene Q, only 0.1mL tubes are allowed)

Equipment

- RT-PCR instrument. The next devices have been validated:
    - StepOne™, Applied Biosystems™
    - 7500 Real-Time PCR System, Applied Biosystems™
    - LightCycler® 96 System, Roche
    - LightCycler® 480, Roche
    - Rotor-Gene® Q, Qiagen®
- Vórtex
- Pipettes (P1000, P200 & P20)

Reagents

- Recombinant Taq (5U/µL) with exonuclease activity 5'—› 3' (DNA as imput sample). The next Taq have been validated:
    - Taq DNA Polymerase Roche™
    - Go Taq® G2 Flexi DNA polymerase (Promega®)
    - Axi Taq (inno-train)
    - AmpliTaq® DNA Polymerase (Applied Biosystems™)
    - MyTaq™ DNA Polymerase (Bioline™)
    - BioTaq™ DNA Polymerase (Bioline™)
    - Taq DNA Polymerase (Applichem™)

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Sample collection and preparation

This test should only be performed with complete 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.

The technique is compatible with any conventional DNA extraction system. Before emitting results with diagnostic purposes, perform a validation test of the samples obtained with the extraction system

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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Procedures

A) PCR preparation

Precautions

- Unfreeze all of the kits 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 1.5mL autoclaved tubes
- Use gloves and lab coat at all times.
- In each session it is recommended to use one negative sample for DQB1*06:02 and one positive sample (DQB1*06:02).

1. Take the samples out of the freezer. Vortex (or use finger knocks).

2. Prepare the Taq and primer mix to n+1 samples:

	Vol. per sample (µL)
Taq (5U/µl)	0.1
Primer Mix	9

NOTE - Use any recombinant Taq (5U/µL) with exonuclease activity 5´—› 3´

3. Pipette 9 µL of this mix into the wells and add 1µL of DNA or negative control in the contamination control well.

4. Seal the plate with convenient sealer, spin down the volume by centrifuging for 1 minute at 360 x g.

5. Place the 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)	Ramp (%)	Analysis
Denaturation	1	95	05:00	100	X
Cycles	40	95	00:15	100	X
		64	1:00	100	Single
Cooling	1	15	∞	100	X

2. Set up the reading channels

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 'Materials required but not supplied', page 8).Select the "Locking Ring Attached" box and continue by clicking "Next".

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

d. Click "Edit Profile" and set up the amplification program (see subsection 'Thermal cylcer configuration'). 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. Click "Gain Optimisation" in the "Run New Wizard" dialog box to open the "Auto-Gain Optimisation 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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Results

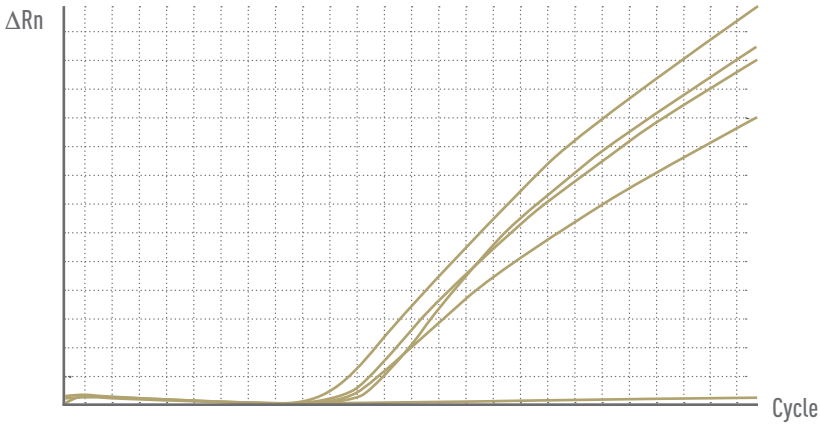
GENVINSET HLA NARCOLEPSY is a qualitative technique to identify presence or absence of the HLA-DQB1*06:02 group of alleles.

It is not necessary to select any passive reference.

The results of this technique can be obtained as follows:

DQB1*06:02 results

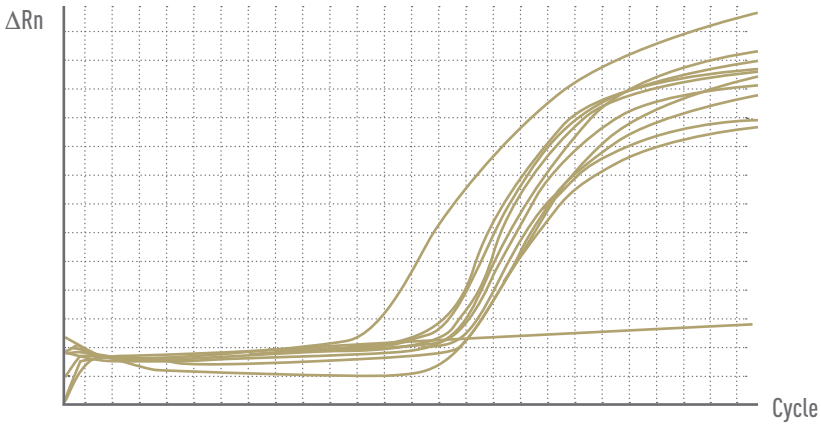
Selecting FAM channel in Amplification Plot, we can see the next graphic:



Samples generating an amplification curve are DQB1*06:02 positive and they are identified by a numeric value called Crossing Point (Cp), corresponding with the cycle in that fluorescence can be detected.

ß-globin results

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



Samples generating an amplification curve are positive for internal control (ß-globin).

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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 negative control supplied in the kit and a positive control (sample with HLA DQB1*06:02 typing).

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

- The contamination control (Reaction Blank) must provide negative results both for DQB1*06:02 and for ß-globin. Cp (Crossing Point) values >35 should be considered as a negative result. Cp values <35 inform us about a contamination in the session so results should be discarded.
- The Positive Control sample must provide positive results for both DQB1*06:02 and for ß-globin.
- DNA samples should always be positive for ß-globin (Cp<35).
- DNA samples generating results with Cp >35 for ß-globin and/or DQB1*06:02 must be considered as doubtful and must be retested by 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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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 'Procedure limitations', page 15.

2. Analytical sensitivity

A dilution assay was performed using 1:4 serialized dilutions of two DNA samples, one DQB1*06:02 positive and another one DQB1*06:02 negative, obtained by a conventional extraction system, at a concentration of 42,4 and 40,8 ng/µL. The following results were obtained as for analytical sensitivity of the DQB1*06:02 allele detection:

- DNA sample obtained by conventional extraction system:
  Detection Limit = 0.66 ng/µL (*)

  (*) Cp < 35

3. Diagnostic sensitivity and specificity

In one studie of human genomic DNA, 94 samples obtained from two clinical laboratories were analyzed. They were previously typed by HLA-SSO in Luminex platform or SSP+serology.

Out of the 94 samples tested, all of them were validated (positive amplification of the ß-globin control gene), and 12 of them were found to be DQB1*06:02 positive:

Genvinset HLA Narcolepsy			
SSO / SSP Serología	Muestras	DQB1*06:02 +	DQB1*06:02-
	DQB1*06:02 +	12	0
	DQB1*06:02 -	0	82

There is a 100% match in the results obtained with GENVINSET HLA NARCOLEPSY and the typing previously obtained with the SSO (Sequence-Specific Oligonucleotide typing), SSP (Sequence-Specific primed typing) or serology methodologies.

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Alleles (IMGT-HLA 3.32.0) detected by GENVINSET HLA NARCOLEPSY

06:01:13	06:02:24	06:192	06:47
06:02:01:01	06:02:25	06:197	06:48
06:02:01:02	06:02:26	06:198	06:49
06:02:01:03	06:02:27	06:19:01	06:50
06:02:01:04	06:02:28	06:19:02	06:51:01
06:02:02	06:11:01	06:20	06:51:02
06:02:03	06:11:02	06:200	06:68
06:02:04	06:11:03	06:201	06:70
06:02:05	06:131	06:211	06:71
06:02:06	06:136	06:213	06:72
06:02:07	06:137	06:215	06:73
06:02:08	06:138	06:216N	06:74
06:02:09	06:13:01	06:219	06:75N
06:02:10	06:13:02	06:224	06:76
06:02:11	06:147	06:225	06:77N
06:02:12	06:150	06:226	06:78
06:02:13	06:152	06:227	06:79:01
06:02:14	06:16	06:228	06:79:02
06:02:15	06:161	06:232	06:80
06:02:16	06:166	06:235	06:81
06:02:17	06:173	06:236	06:83
06:02:18	06:175	06:237	06:84
06:02:19	06:176	06:24	06:95
06:02:20	06:179N	06:240	06:97
06:02:21	06:182	06:249	
06:02:22	06:183	06:33	
06:02:23	06:188	06:37	

- Detected allele
- **Common allele of the CWD Catalogue**
- Non tested allele. Possible weak amplification
- Non detected Allele

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Procedure limitations

- The described conditions for the PCR should be precisely controlled. Deviations from these parameters can lead to poor results.
- Mutations or polymorphisms at annealing primer/probe sites are possible and may result of the lack of allele definition. Other technologies could be necessaries to resolve the typing.
- All GENVINSET work must be made according to general laboratory 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 manufacturer´s recommendations and should be used in accordance to manufacturer´s 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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Troubleshooting guide

Reaction Blank (H2O) is positive

- **Primer Mix/Reaction Blank contamination**
  - Repeat the experiment with new Primer 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 (1.5 mL tubes, pipette tips)
  - Confirm there is no Taq contamination
- **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**
  - Repeat the sample extraction verifying each step (Hemoglobin can interfere with the PCR)
- **Blood processed without previous frozen step**
  - Repeat extraction with a new blood aliquot previously frozen
- **Samples with very low DNA concentration**
  - Check the cellular lysate DNA concentration
- **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 kits correct storage (Primer Mix vial stored in darkness)
  - Avoid more than 3 freeze/unfreeze cycles of the primer mix vial
  - Aliquot the reagent if necessary
  - Repeat the series with new reagents

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- **Taq has lost activity**
  - Confirm Taq's activity
  - Repeat with new Taq

Negative control sample (DQB1*06:02 neg.) is positive

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

Positive control sample (DQB1*06:02 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**
  - Always wear gloves when manipulating the plates
- **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 technical 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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Changes to version 04

Version	Description of the modification
Rev. 04	Reduction of number of PCR cycles

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Explanation of symbols used on the labels

For in vitro diagnostic use

This product fulfills the requirements of Directive 98/79/EC on in vitro diagnostic medical device

Catalogue number

Lot number

Expiration date

Contents sufficient for <n> tests

Manufactured by

Store at

Keep away from sunlight

Positive control

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