HemaVision®-inv16

A multiplex RT-PCR screening test for chromosome translocation inv(16)(p13;q22)(CBFB-MYH11) associated with leukemia
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User Manual
for
HemaVision®-inv16, Cat. No. HV03-inv16
25 tests per kit

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HemaVision®-inv16 is manufactured by

DNA Diagnostic A/S
Voldbjergvej 16
DK-8240 Risskov
Tel.: +45 8732 3050  Fax: +45 8732 3059  VAT: DK-66inv16815
Denmark  Mail: info@dna-diagnostic.com  Web: www.dna-diagnostic.com
1. PURPOSE OF THE TEST

HemaVision®-inv16 is a CE-marked in vitro diagnostic test for qualitative detection of the human leukemia causing chromosomal translocation inv(16)(p13;q22)(CBFB-MYH11). The test screens RNA from blood or bone marrow for breakpoints resulting in the exon fusions CBFB and MYH11 genes. HemaVision®-inv16 also detects mRNA splice variants for the inv(16)(p13;q22)(CBFB-MYH11) translocation. It is a fast 4-5 hour test. The HemaVision®-inv16 test has sensitivity (>99%) and specificity (>96%).

Limit of detection is 10⁸ µg of fusion RNA in a sample of 1 µg total RNA when the RNA quality is good.

This test brings IVD testing deeper into a detailed description of the exon organization of fusion genes originating from chromosome translocations. This information is important for predicting development of the disease and selection of treatment.

The test is for professional use only.

HemaVision®-inv16 is a qualitative test using total RNA extracted from human whole blood or bone marrow cells as starting material in the test. The test uses reverse transcription of RNA to cDNA followed by multiplex PCR (Polymerase Chain Reaction), agarose gel electrophoresis, and interpretation.

HemaVision®-inv16 identifies chromosomes, genes and exons at the breakpoint in fusion genes. Furthermore, the test identifies mRNA splice variants from fusion genes.

The HemaVision®-inv16 kit contains primers for 25 cDNA reactions, and 25 PCR tests.

Figure 1 illustrates principle for the RT-PCR reactions of the HemaVision®-inv16 kit. The tests identifies chromosomes, fusion genes and exons at the breakpoint. Only intron breakpoints for fusion genes maintaining the original translational reading frame are shown.

Blue arrow: PCR primers. Grey arrow: cDNA primer. Black arrow: Breakpoints. One, two or three dots indicate translational reading frame at end or beginning of exon.
2. PRINCIPLES OF TEST

RNA is template for synthesis of cDNA in a reaction using Reverse Transcriptase (RT) and specific cDNA primers. The cDNA is template for PCR amplifications using a hot start Taq DNA Polymerase and specific PCR primers. Many fusion genes have several breakpoints. Therefore, the PCR primers are designed to bind at positions enabling screening for all these breakpoints as illustrated in figure 1. PCR products are visualized by agarose gel electrophoresis. A Reaction Control amplicon of 983 bp is also detected in all reactions from the constitutively expressed Biotinidase (BTD) gene. This is a control for the quality of RNA and functionality of the test. The workflow of the test and an example of test results are shown in figure 2.

![Workflow and results from a test with HemaVision®-inv16, Cat. No. HV03-inv16.](image)

**Figure 2.** Workflow and results from a test with HemaVision®-inv16, Cat. No. HV03-inv16.

- **Samples:** -RNA (negative control), Patient 1, Patient 2.
- **Result:** 983 bp Reaction Control amplicon present in all lanes except the negative controls (-RNA). Sample “2B” positive for translocation specific amplicon of 417 bp.
- **Conclusion:** From the Interpretation Table 4 it can be seen patient “2” has a translocation at inv(16)(p13;q22)(CBFBex5-MYH11ex30) variant D.

**RNA Preparation**

Total RNA is prepared from whole blood, cell lines, or bone marrow cells with the QIAamp® RNA Blood Mini Kit (Qiagen Cat. No. 52304).

**cDNA Synthesis**

cDNA is synthesized in a reaction containing the isolated RNA, cDNA Mix (primers) from the HemaVision®-inv16 kit Cat No. HV03-inv16 and Reverse Transcriptase, 5x Buffer, DTT, and dNTP from the reagent module HemaVision® kit Cat. No. HV06-RMP or Cat. No. HV04-RM.

**PCR**

The cDNA is used as a template for one pair of translocation specific primers and one pair of reaction control primers. The PCR reaction use Primer Mix PCR from the HemaVision®-inv16 (Cat. No. HV03-
inv16) and HemaVision DNA Polymerase, 10xbuffer, and dNTP from HemaVision®-RMP kit (Cat. No. HV06-RMP). The tube Primer Mix PCR contains one pair of translocation specific primers and one pair of reaction control primers specific for the housekeeping gene Biotinidase (BTD). The PCR products are analyzed by agarose gel electrophoresis. The 983 bp reaction control band is a positive control for using intact RNA and functionality of the RT-PCR reactions. A translocation specific band shows the test is positive for a inv(16)(p13;q22)(CBFB-MYH11) translocation. The breakpoint is determined from the Interpretation Table 4.

**Interpretation of results**

A sample is positive for a translocation when a translocation specific band and reaction control amplicons are present. Note, the reaction control band can be weak in reactions with a strong translocation specific band. The breakpoint is identified by the molecular size of the translocation specific amplicon using Interpretation Table 4. More than one translocation specific band shows presence of alternative spliced mRNA from the fusion gene.

Figure 2 shows workflow for testing blood or bone marrow samples with HemaVision®-inv16. In this example, sample “2” is positive for a translocation specific band of 417 bp in the reaction using Primer Mix PCR B. The Reaction Control amplicon of 983 bp is present in both the translocation positive sample “2” and in the translocation negative sample “1” showing the RNA was intact and the RT-PCR reactions were functional. The negative control sample “-RNA” contains no amplicons showing the reagents has not been contaminated with positive material. From Interpretation Table 4 it can be concluded, the patient “2” has a inv(16)(p13;q22)(CBFBex5-MYH11ex30) translocation and patient “1” has no inv(16)(p13;q22)(CBFB-MYH11) translocation.

### 3. KIT COMPONENTS AND STORAGE

The HemaVision®-inv16 kit Cat. No. HV03-inv16 contains a box with one white capped tube containing Primer Mix cDNA, two blue capped tubes with Primer Mix PCR A, Primer Mix B. A User Manual for instruction follows each kit. The kit is shipped at -20°C or below and the kit must be stored at -20°C by the customer. While performing the test always keep test components on ice (0°C). Each kit contains sufficient primer mixes for 25 cDNA reactions and 25 PCR reactions.

**NOTE:** It is essential for functionality of the HemaVision®-inv16 kit also to obtain and use the reagents provided in HemaVision®-RMP kit, Cat. No. HV06-RMP containing: 20 µL MMLV-Reverse Transcriptase, 100 µL 5x cDNA buffer, 50 µL DTT, 100 µL dNTP, 45 µL HemaVision DNA Polymerase, 300 µL 10x PCR buffer.

*Figure 3 shows content of HemaVision®-inv16 kit, Cat. No. HV03-inv16.*

1 x 110 µL Primer Mix cDNA (white cap)
1 x 155 µL Primer Mix PCR A (blue caps)
1 x 155 µL Primer Mix PCR B (blue caps)
4. EQUIPMENT AND MATERIALS REQUIRED BUT NOT PROVIDED

RNA extraction:
QIAamp® RNA Blood Mini Kit from Qiagen Cat. No. 52304.

Reagent Module:
HemaVision®-RMP kit Cat. No. HV06-RMP contains: MMLV-RT; 5x cDNA buffer; DTT; dNTP, HemaVision DNA Polymerase, 10x PCR buffer. Use two HV06-RMP kits together with each HemaVision®-inv16 kit.
Instead of using HemaVision®-RMP use HemaVision®-RM Cat. No. HV04-RM containing MMLV-RT; 5x cDNA buffer; DTT; dNTP. HotStarTaq DNA Polymerase 5U/µL is from Qiagen.

Master Mix room – No templates in this room:
Micropipettes, 0.5-10 µL, 20-200 µL,
HemaVision® kit Cat. No. HV06-RMP containing: MMLV-RT; 5x cDNA buffer; DTT; dNTP, HemaVision DNA Polymerase, 10x PCR buffer
Aerosol barrier micropipette tips, 0.5-10 µL, and 20-200 µL
Micro centrifuge
Ice bath
RNase free tubes
Disposable gloves
RNase free water
-20°C freezer for storage of kits (HemaVision®-inv16 and HemaVision®-RMP)

cDNA room:
Micropipettes, 0.5-10 µL, 20-200 µL
Aerosol barrier micropipette tips, 0.5-10 µL, and 20-200 µL
Micro centrifuge
Heating block/Water bath
Ice bath
RNase free tubes
Disposable gloves
RNase free water
-80°C freezer for storage of RNA samples

PCR room:
Micropipettes, 0.5-10 µL, 20-200 µL
Aerosol barrier micropipette tips, 0.5-10 µL, and 20-200 µL
Micro centrifuge
Thermal Cycler
Ice bath
PCR tubes (0.1 mL or 0.2 mL) and lids
Disposable gloves

Gel electrophoresis room:
Micropipettes, 0.5-10 µL
Aerosol barrier micropipette tips, 0.5-10 µL
Micro centrifuge
Equipment for agarose gel electrophoresis
Disposable gloves
Molecular size marker (e.g. 100 bp ladder)
5. PRECAUTIONS

General precautions
1. The quality of the RNA sample greatly affects the results of this test. To minimize the risk of degradation of RNA by ribonucleases, we strongly recommend lysing the cells in a denaturing solution [e.g. containing guanidinium isothiocyanate (GTC)] immediately after isolation and before freezing. Always store cell samples and aqueous RNA solutions at –80°C. Even an overnight storage at –20°C may result in RNA degradation. When working with RNA always use gloves to avoid ribonuclease contamination from hands.

2. RT-PCR is a very sensitive technique. Therefore, precautions must be taken to avoid false positive results caused by contamination with RNA, cDNA or PCR products from other samples.

   Dedicated four separate rooms to the following activities:
   1) Master Mix production – No templates in here
   2) cDNA synthesis
   3) PCR
   4) Gel electrophoresis

   A set of micropipettes, aerosol barrier pipette tips, disposable gloves and clean lab coats should be kept in each of the four rooms. The work must be organized so that mixes and reaction products only move in the direction from Master Mix room to cDNA room to PCR room to Gel electrophoresis room. NEVER move mixes or reaction products in the opposite direction.

3. Laboratory workbenches, pipettes, and lab coats must be cleaned on a regular basis.

4. Use of aerosol barrier pipette tips is highly recommended during the entire procedure. It is essential to change gloves very often when handling tubes containing RNA or DNA. After PCR tubes must be opened with extreme care to avoid spillage of high copy number DNA products.

Safety
- Read and understand the procedure before starting.
- Normal laboratory aseptic technique should be followed at all times.
- Treat each sample as if it is infectious.
- Wear eye protection and disposable gloves during all steps of the assay.

6. PROCEDURE

Procedural notes
- Store all test components as described in section 3: Kit Components and Storage.
- Do not mix reagents from different lots.
- Careful pipetting technique is essential for accurate results.
- This protocol is optimized with enzymes and buffers from HemaVision® kit Cat. No. HV06-RMP.
- This protocol is optimized for the ABI (Perkin Elmer) GeneAmp 9600/9700 thermal cycler. Use of another thermal cycler may require optimization by the user.
- As a positive control for RNA quality and functionality of each RT-PCR reaction a 983 bp fragment of the housekeeping gene biotinidase must be present in all lanes except in reactions positive for a translocation specific amplicon where it may be weak or missing.
- As a negative control, make the cDNA reaction without RNA template.
RNA preparation

- Use blood from venipuncture collected into a tube containing EDTA. Alternatively, use bone marrow collected into a tube containing EDTA. Do not freeze the blood or bone marrow sample or use samples collected in heparin tubes.
- Prepared mononuclear cells from whole blood or bone marrow by the Ficoll Hypaque method.
- Within 24 hours of collection, extract total RNA with QIAamp® RNA Blood Mini Kit (Qiagen Cat. No. 52304). Typically, 5-10 µg total RNA is extracted from 1 x10⁷ mononuclear blood cells.
- Measure the RNA concentration by reading the optical density at 260 nm. An absorbance of 1 unit at 260 nm corresponds to 40 µg of RNA per mL. Adjust the concentration of RNA to 0.1 µg/µL with RNase free H₂O.
- Make 20 µL (0.1 µg/µL) RNA aliquots in RNase free tubes. Store RNA aliquots at –80°C or use RNA immediately for cDNA synthesis.

**cDNA synthesis and PCR**

**Step 1 cDNA Synthesis**

1.1 In the Master Mix room prepare cDNA Synthesis Mix according to Table 1 using reagents from HemaVision®-RMP reagent module Cat. No. HV06-RMP.

<table>
<thead>
<tr>
<th>Table 1: cDNA Synthesis Mix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of samples</td>
</tr>
<tr>
<td>5x MMLV-RT Buffer (µL)</td>
</tr>
<tr>
<td>100 mM DTT (µL)</td>
</tr>
<tr>
<td>10 mM dNTP Mix (µL)</td>
</tr>
<tr>
<td>MMLV-RT (µL)</td>
</tr>
<tr>
<td>Total volume (µL):</td>
</tr>
</tbody>
</table>

1.2 In the cDNA room add 3.5 µL Primer Mix cDNA from white capped tube in the HemaVision®-inv16 kit to one 0.2 mL PCR tube containing 8 µL total RNA (0.8 µg). Mix gently and spin down for 10 seconds.

1.3 In a separate RNase free tube, add 3.5 µL of Primer Mix cDNA to 8 µL H₂O (negative control).

1.4 Incubate the tubes in a heating block or water bath at 65°C for 5 minutes. Chill tubes on ice and hold on ice.

1.5 Add 8.5 µL of the cDNA Synthesis Mix to the tube with 11.5 µL RNA+Primer Mix cDNA and the negative control tube from step 1.4. Mix gently and spin down for 10 seconds.

1.6 Incubate at 37°C for 45 minutes.

1.7 Incubate at 95°C for 5 min to inactivate the MMLV-RT enzyme.

1.8 Chill and hold the cDNA tube on ice (0°C, do not freeze) for a maximum of three days before use in PCR.
Step 2  PCR

2.1 In the Master Mix room prepare the Master Mix PCR according to Table 2 using HemaVision® reagent module Cat. No. HV06-RMP. Mix and spin down for 10 seconds.

Table 2: Master Mix PCR

<table>
<thead>
<tr>
<th>Number of samples</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PCR reactions</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>10x PCR buffer (µL)</td>
<td>5.0</td>
<td>10.0</td>
</tr>
<tr>
<td>dNTP mix (µL)</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>HemaVision DNA Polymerase (µL)</td>
<td>0.8</td>
<td>1.6</td>
</tr>
<tr>
<td>H2O (µL)</td>
<td>27.2</td>
<td>44.4</td>
</tr>
<tr>
<td>Total volume (µL):</td>
<td>34.0</td>
<td>68.0</td>
</tr>
</tbody>
</table>

2.2 Label two 0.2 mL PCR tubes for each patient with sample number plus “A” and “B” respectively.

2.3 Add 17 µL Master Mix PCR to each marked PCR tubes.

2.4 Transfer 5 µL Primer Mix PCR A from the blue-capped tube in HemaVision®-inv16 to the PCR tube marked “A”. Similarly, transfer 5 µL Primer Mix PCR B from the blue-capped tube in HemaVision®-inv16 to the PCR tube marked “B”.

2.5 In the PCR room add 3 µL cDNA (from step 1.8) to each of the PCR tubes from step 2.4. Close the tubes, mix and spin for 10 seconds. Volume per tube 25 µL.

2.6 Transfer the tubes to a thermal cycler and start the PCR amplification using the PCR cycling parameters in Table 3. Notice during the first 15 cycles, the annealing temperature is reduced by 0.2°C per cycle starting at 65°C and ending at 62°C.

Table 3: PCR Amplification Parameters

<table>
<thead>
<tr>
<th>Step</th>
<th>Time/Temperature</th>
<th>Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15 minutes at 95°C</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>30 seconds at 95°C 60 seconds at 65°C minus 0.2°C/cycle. (Touch down program to reduce unspecific amplification) 90 seconds at 72°C</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>30 seconds at 95°C 30 seconds at 62°C. 90 seconds at 72°C</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>Hold at 4°C</td>
<td>1</td>
</tr>
</tbody>
</table>

Step 3  Gel electrophoresis

3.1 Prepare a 1.5 % (w/v) agarose gel at least 10 cm long in 1X TBE buffer. Add ethidium bromide to a final concentration of 0.5 µg/mL.

3.2 In the Gel Electrophoresis room, carefully open the PCR tubes without contaminating gloves and surroundings with drops containing high copy numbers of amplicon.
3.3 Add 3 μL of 10x loading buffer into each PCR tube. Load approximately 14 μL per slot in the gel. Finally load a molecular size marker to the gel.

3.4 Run the gel in 1X TBE buffer until the Bromophenol blue dye has migrated approximately 3/4 of the gel.

3.5 Examine the gel with UV-light and document result by photography.

7. INTERPRETATION

- The HemaVision®-inv16 kit tests for inv(16)(p13;q22)(CBFB-MYH11) chromosome translocations associated with leukemia. After agarose gel electrophoresis do interpretation as follows:
- Look for a positive for the Biotinidase (BTD) reaction control band (983 bp) in all PCR reactions. The reaction control band can be weak or missing in the lane containing a strong translocation specific band. The reaction control band is a control for the quality of the used total RNA and the functionality of the performed RT-PCR reactions.
- Look for a translocation specific band. Identify the translocation with Interpretation Table 4.
- The PCR is negative for a translocation specific band. The PCR is positive for the reaction control band (983 bp). Then the test must be interpreted as negative for a inv(16)(p13;q22)(CBFB-MYH11) translocation.
- The PCR is negative for both reaction control band (983 bp) and a inv(16)(p13;q22)(CBFB-MYH11) translocation band. The test failed and it must be repeated. New RNA may need to be prepared also.

### Table 4: Interpretation table

<table>
<thead>
<tr>
<th>PCR</th>
<th>TRANSLOCATION</th>
<th>GENES</th>
<th>Primer</th>
<th>BREAKPOINT</th>
<th>AMPLICON</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HV03- inv16</td>
<td>inv(16)(p13;q22)</td>
<td>CBFB (16q22.1) MYH11 (16p13.11)</td>
<td>A</td>
<td>CBFB ex4 – MYH11 ex 34 (F)</td>
<td>415 bp</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CBFB ex5 – MYH11 ex 34 (A)</td>
<td>511 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CBFB ex4 – MYH11 ex 33</td>
<td>628 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CBFB ex5 – MYH11 ex 33 (B)</td>
<td>724 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CBFB ex4 – MYH11 ex 32</td>
<td>877 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CBFB ex5 – MYH11 ex 32</td>
<td>973 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>CBFB ex4 – MYH11 ex 31</td>
<td>216 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CBFB ex5 – MYH11 ex 31</td>
<td>312 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CBFB ex4 – MYH11 ex 30 (G)</td>
<td>321 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CBFB ex5 – MYH11 ex 30 (D)</td>
<td>417 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CBFB ex4 – MYH11 ex 29</td>
<td>528 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CBFB ex5 – MYH11 ex 29 (E)</td>
<td>624 bp</td>
<td></td>
</tr>
</tbody>
</table>

Table 4 is used for interpretation of results observed from agarose gel electrophoresis of PCR. The table shows the translocation, involved genes, exons at breakpoint, and molecular size of PCR amplicons. Numbering of exons has been updated year 2014 according to GenBank http://www.ncbi.nlm.nih.gov/genbank/. Only breakpoints maintaining the original translational reading frame from the involved genes are presented.

**Note:** A PCR amplicon with a molecular size not listed in Table 4 can appear as a consequence of amplification across an unpublished breakpoint or splice variant. Further characterization of this/these amplicons by DNA sequencing can be done free of charge by DNA Diagnostic A/S. Purify the amplicon and send it to DNA Diagnostic A/S.

**Note:** The interpretation table has been updated according to the HUGO Gene Nomenclature Committee (HGNC) see section “8. GENE ABBREVIATIONS ACCORDING TO THE HGNC”.

HemaVision®-inv16

www.dna-diagnostic.com

Revision 2014.02.28
8. **GENE ABBREVIATIONS ACCORDING TO THE HGNC:**

The HUGO Gene Nomenclature Committee (HGNC) approves a *unique* and *meaningful* name for every known human gene (read more at [www.genenames.org](http://www.genenames.org)). Table 5 shows: the old abbreviation and the corresponding present HGNC abbreviation for the gene names, the chromosome position for the gene, HGNC ID number for the protein and NCBI ACCESSION number for the DNA sequence encoding the mRNA. For details go to the NCBI web site ([www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)).

<table>
<thead>
<tr>
<th>Old Abbreviation</th>
<th>HGNC Abbreviation</th>
<th>Chromosome</th>
<th>HGNC ID</th>
<th>NCBI ACCESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBFβ</td>
<td>CBFB</td>
<td>16q22.1</td>
<td>1539</td>
<td>NM_022845</td>
</tr>
<tr>
<td>MYH11</td>
<td>MYH11</td>
<td>16p13.11</td>
<td>7569</td>
<td>NM_001040114</td>
</tr>
<tr>
<td>BTD</td>
<td>BTD</td>
<td>3p25</td>
<td>1122</td>
<td>NM_000060</td>
</tr>
</tbody>
</table>

9. **REFERENCES**


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**Symbols used on tubes and boxes**

- **CE**: "Conformité Européenne" ("European Conformity")
- **IVD**: In vitro Diagnostic Medical Device
- **REF**: Catalogue Number
- **LOT**: Lot number
- **CONT**: Contents
- **Storage temperature**
- **Expiry Date**
- **Manufacturer**
Availability / questions
Our team and distributors are always at hand to answer all your questions.
Contact us to find your nearest HemaVision® partner.

For more information, contact
DNA Diagnostic A/S
Voldbjergvej 16          Tel. +45 8732 3050
DK-8240 Risskov          info@dna-diagnostic.com
Denmark                  www.dna-diagnostic.com

DNA Diagnostic A/S (previously named DNA Technology A/S) was established in 1992. DNA Diagnostic A/S is a developer, manufacturer, and worldwide supplier of PCR based in vitro diagnostic kits.