

THROMBOTYPE® 1 (HPA-1)

INTENDED USE

THROMBOTYPE® 1 is an assay for the molecular determination of HPA-1 (PL^A) using PCR amplification of human genomic DNA.

For *In Vitro* Diagnostic Use

AND EXPLANATION OF THE TEST

The Human Platelet Alloantigens (HPAs), in particular HPA-1 (PL^A) are associated with amino acid changes in platelet glycoproteins. While not overtly affecting the function of the proteins, the modifications alter the proteins' local conformations. The resulting antigenic determinants can be targets for alloimmune and autoimmune antibody responses that cause life-threatening bleeding disorders such as refractoriness to platelet transfusions, post-transfusion purpura, and neonatal alloimmune thrombocytopenia. To date, serologic methods for HPA-1 platelet typing have been limited by the lack of well-characterized alloantisera and the scarcity of platelets in thrombocytopenic patients. However, with advances in platelet immunogenetics, it is now possible to genotype individuals for the single nucleotide polymorphism that characterizes the alleles of HPA-1.

THROMBOTYPE® 1 is an alternative to platelet serological testing and an adjunct to HLA matching in selecting compatible platelets for alloimmunized recipients. THROMBOTYPE® 1 contains the reagents necessary to perform allele-specific PCR on isolated genomic DNA and to identify an individual's genotype for HPA-1 using a gel endpoint.

PRINCIPLE OF THE PROCEDURE

The assay uses a modified proprietary allele specific priming polymerase chain reaction (PCR) in which a product is produced only if the allele is present. These amplifications determine the presence of alleles for platelet polymorphism HPA-1: HPA-1a (PL^{A1}) or HPA-1b (PL^{A2}). Genomic DNA is first isolated from the patient specimen, using one of the many commercial kits or published techniques that can yield high-purity genomic DNA. Sample DNA is amplified using the supplied amplification tubes and reagents. After amplification, an aliquot of each reaction is pipetted to a well of an agarose gel. A 15 – 20 minute electrophoresis step then separates PCR products by size. The gel is then examined on a UV transilluminator. Presence of a PCR product band of the correct size indicates presence of the allele in the DNA sample. Product bands from internal control primers demonstrate that acceptable conditions were present in each PCR tube. The gel may be photographed as a permanent record of the assay.

Maximum number of tests per kit: 24

All reagents should be stored as directed by the label.

PT 1a/1b 1. **HPA Primer Tubes:** PCR tubes with allele-specific primers dried on the inner surface. The tubes are enclosed resealable bags.
Ready for use.

1a Pink tubes with pink caps.

1b Yellow tubes with yellow caps.

LAD 2. **100 bp DNA Ladder:** Double-stranded DNA in discrete fragments, starting at 100 base pairs (bp) and increasing in 100 bp steps to 1000 bp, in a Tris buffer. Ready for use.

PR 3. **2X PCR Reagent:** A Tris-KCl buffer containing magnesium chloride, oligonucleotide primers, free deoxynucleotide triphosphates (dNTPs), and other proprietary components. Dilute before use.

E-Gel® 4. **E-Gel® 48:** precast agarose gels (4%) used for separation of the PCR products. Ready for use.

- Do not use reagents beyond their expiration date.
- Do not use reagents that are turbid or contaminated.
- Do not use gels that appear cracked or dried out.
- PCR tubes and reagents contained in the kit are not to be used in conjunction with any other test system.
- Substitution of components other than those provided in this kit may lead to inconsistent or erroneous results.
- Due to variations in the performance of different thermal cyclers it may be necessary for the laboratory to establish adjusted parameters for the thermal cycling program in order to achieve valid results.

- Do not isolate the DNA sample from heparinized blood. Heparin may interfere with PCR amplification.
- PCR is covered by patents held by Roche Molecular Systems and F. Hoffman LaRoche Ltd. For information on licenses to practice PCR, contact (in the United States) the Director of Licensing at Roche Molecular Systems, Inc., 1145 Atlantic Avenue, Alameda, California 94501, or (outside the United States) the PCR Licensing Manager, F. Hoffmann-La Roche Ltd, Grenzacherstr.124, CH-4070 Basel, Switzerland.
- PCR Laboratory Practice
 PCR's powerful ability to amplify DNA sequences makes it especially sensitive to contamination by even small amounts of extraneous DNA. Consequently, every effort should be made to avoid introducing previously amplified material into test samples. Such cross-contamination can be reduced by physically separating pre-amplification areas from post-amplification space, preferably in separate rooms, or across a room at minimum. A biological cabinet can be used for DNA preparation to minimize the formation of potentially contaminating aerosols. A "dead air box" in the pre-amplification area can provide a more controlled work space for PCR setups. For post-amplification processing, perform all work on plastic-backed absorbent paper to trap splashouts. The paper should be discarded to biohazard waste. Each work area should have its own set of dedicated pipettors. Sharing of lab equipment between pre- and post-amplification areas should be minimized, and any equipment from the "post" area should be cleaned with a DNA-inactivating agent (for example, fresh 10% bleach) before transfer to the "pre" area. Use a new pipet tip for each pipetting step, and use aerosol barrier tips if not using positive displacement pipettors. Wear a separate lab covering for each work area, and frequently change gloves while working. Finally, when performing the assay place the kit control and environmental control (negative control – water instead of genomic DNA as sample) after patient samples.
- When finished with the assay, dispose of waste materials as biohazardous waste and decontaminate non-disposable materials with 10% household bleach or other DNA-inactivating agent.
- The UV transilluminators used to visualize the PCR product bands emit powerful ultraviolet light, which can damage eyes and skin. Always wear protective clothing and UV-blocking glasses or face shield when operating the UV transilluminator.
- E-Gel[®]s contain a small amount of ethidium bromide as a DNA stain. Ethidium bromide is a known human mutagen. Do not open the gel cassettes. Dispose of gels according to local hazardous waste regulations.

COLLECTION

- Isolate DNA using a published method or a commercial kit manufactured for that purpose.
- Resuspend the DNA in sterile water or 10 mM Tris at pH 8.0 – 9.0. Samples should **not** be rehydrated in solutions containing greater than 0.5 mM EDTA or other chelating agents. These may interfere with PCR.
- DNA samples may be assayed immediately after isolation or stored in a non-defrosting freezer at or below –20°C for an extended period (one year or more) without affecting results. THROMBOTYPE[®]1 testing of frozen (-20°C) samples diluted in Tris/EDTA buffer (10 mM Tris, pH 8.0 -9.0/0.5 mM EDTA) and stored in screw-top tubes with O-ring caps showed 100 % agreement with results from DNA sequencing of the samples. Additional data on stability of samples when stored frozen are available from two manufacturers of DNA isolation kits, (refer to Gentra Systems and QIAgen web sites).
- DNA samples should be in the range of 10 – 100 ng/μL, with a 260nm/280nm ratio between 1.60 and 1.90.
- Presence of excess contaminating protein or RNA, heparin, EDTA or other chelating agents may interfere with PCR amplification of the purified DNA.

NOTE: *Vials may contain more reagent than described on the labels. Be sure to measure the reagent with an appropriate device when making dilutions.*

Materials Provided

Packaged for storage at 2 to 8°C

1. Three resealable bags containing
 - 8 X HPA-1a (PL^{A1}) Amplification Tubes (pink with pink caps)
 - 8 X HPA-1b (PL^{A2}) Amplification Tubes (yellow with yellow caps)
2. 2 x 450 μL 2X PCR Reagent
3. 1 x 200 μL 100 bp DNA Ladder
4. 3 x foil sealers
5. Negative Control Tubes: one resealable pouch containing 1 x 8 empty PCR tubes for setting up negative control amplifications

Packaged for storage at 15 to 30°C

1. 3 x 4% E-Gel[®]48

Materials Required (but not provided)

A. For PCR

- Taq Polymerase, either native or recombinant, 5U/μL. Do not use other thermostable polymerases or “hot start” preparations of Taq polymerase.
- Programmable thermal cycler with block sized to accept 0.2 mL PCR tubes.
- Silicone spacer pad
- Adjustable micropipets to deliver 1 - 1000 μL and sterile barrier tips
- DNA- and DNase-free water
- Ice bath or cold blocks to fit 0.6 mL or 1.5 mL tubes and 0.2 mL PCR tubes
- PCR (0.2 mL) tube rack
- Vortex mixer
- Snap-top conical polypropylene microcentrifuge tubes (0.5 - 1.7 mL), DNA- and DNase-free
- 10% bleach or other DNA-inactivating agent

B. For Electrophoresis and Analysis

- E-Base Motherbase (GTI cat. #EZT-24DEV)
- PCR (0.2 mL) tube rack
- Adjustable micropipets to deliver 1 - 20 μL and sterile barrier tips
- Plastic-backed absorbent paper for lab bench
- UV transilluminator (GTI cat. #EZT-ILLUM)
- 10% bleach or other DNA-inactivating agent
- Deionized water
- Gel documentation system (GTI cat. # EZT-CAM, EZT-HOOD)

Optional

- Adjustable multichannel micropipet to deliver 5 μL and 10 μL and sterile barrier tips
- Electronic pipet or repeater pipet capable of delivering 20 – 25 μL and sterile barrier tips

Test Procedure

A. In Advance

1. Isolate genomic DNA from all samples to be tested. Each sample should have a DNA concentration in the range of 10 – 100 ng/μL and a 260nm/280nm ratio between 1.60 and 1.90.
2. Program a thermal cycler with the THROMBOTYPE®1 PCR program. The program is as follows:

94°C	30 seconds	
94°C	1 second	
57°C	30 seconds	6 cycles
72°C	10 seconds	
94°C	1 second	
65°C	30 seconds	27 cycles
72°C	10 seconds	
72°C	12 seconds	
4°C	Hold	

NOTE: *This cycling program was developed on the ABI PE9700 running in Max mode. Due to differences in individual thermal cyclers, each instrument must be validated by amplifying known samples to assess the performance. If bands are faint, increase the time of both annealing steps by an initial 3 seconds, then in 1 sec. increments, until product yield is acceptable. If faint “readthrough” bands or troublesome primer dimer bands appear, reduce both annealing times by an initial 3 seconds, then in 1 sec. increments until the “readthrough” or dimer bands no longer appear.*

B. PCR

3. Turn on the thermal cycler in advance of setup to ensure that the heated lid has time to reach its operating temperature. Check the cycling program to be sure it has not been changed.

4. Keep Taq polymerase and the 2X PCR Reagent on ice or a cold block.
5. Prepare work surfaces and pipettors before use by wiping with 10% household bleach or other DNA-inactivating agent.
6. Determine the number of tests to be performed. Total tests should include all unknown samples to be tested plus a negative (water) control. Each sample requires one (1) of each type of Amplification tube – one 1a (PL^{A1}, pink with pink caps) and one 1b (PL^{A2}, yellow with yellow caps) - a total of two (2) per sample. The negative control requires at least one negative control tube.
7. Make a PCR setup map showing the positions of each tube for each sample.
8. Remove Amplification tubes from the kit, separate the number required for the assay, and place them in an ice bath or PCR (0.2 mL) tube cold block in the pattern shown on the map. Return remaining tubes to the resealable bag(s) and store at 2 to 8°C.
9. Remove the Negative Control Tubes from the kit, and separate at least one tube for an assay. Place the tube(s) in the cold block. Return the remaining tubes to the resealable bag and store at 2 to 8°C.

NOTE: *If more than one negative control is set up for an assay, the volumes in the PCR setup methods described below must be adjusted for the extra tube(s).*

10. A method is described below. An individual master mix that includes all necessary components is prepared for each sample; a 25 µL aliquot of each mix is then pipetted to one 1a primer tube and one 1b primer tube. A separate negative control master mix is also prepared and 25 µL of this mix is pipetted to the negative control PCR tube(s).

An alternate protocol may be developed by the user if the protocol results in an amplification mix that delivers **per PCR tube**:

- 12.5 µL 2X PCR Reagent
- 0.5 Unit Taq polymerase
- 40 – 400 ng human genomic DNA (80 – 200 ng recommended)
- DNA-free water to a final volume of 25 µL

Such a protocol must be validated by the user with known positive and negative samples.

11. Prepare a master mix for each sample.
 - a. Label a microcentrifuge tube for each DNA sample, one for the negative control, and one for preparing the Taq dilution.
 - b. Prepare a dilution of Taq polymerase to 0.5 Units/µL in DNA-free water. Each sample master mix requires 2.4 µL and the negative control requires 1.6 µL. Use table below as a reference.

Table 1: Dilution of Taq polymerase

A	B
# Patient Samples	Diluted Taq
2	1.0 μL Taq <u>9.0 μL</u> water 10 μL
3	1.2 μL Taq <u>10.8 μL</u> water 12 μL
4	1.6 μL Taq <u>14.4 μL</u> water 16 μL
5	1.8 μL Taq <u>16.2 μL</u> water 18 μL
6	2.0 μL Taq <u>18.0 μL</u> water 20 μL
7	2.4 μL Taq <u>21.6 μL</u> water 24 μL
8	2.6 μL Taq <u>23.4 μL</u> water 26 μL
Greater than 8 patient samples use multiples or combination of above.	

- c. Prepare Master Mixes as described in Table 2.

Table 2: Master Mix for individual DNA Sample

Water volume	2X PCR Reagent	Taq polymerase (0.5 U/ μL)	Sample DNA	Total Volume of Master Mix
18 μL	30 μL	2.4 μL	9.6 μL	60 μL

- d. Prepare a negative control master mix by combining 20 μL 2X PCR Reagent + 1.6 μL Taq polymerase (0.5 U/ μL) + 18.4 μL DNA-free water.
- e. Cap all master mixes, and mix by vortexing 3 – 5 seconds.
- f. Pipet 25 μL of each sample master mix to one 1a primer tube and one 1b primer tube.
Pipet 25 μL of the negative control master mix to the negative control PCR tube(s).

12. Cover all tubes with a foil sealer trimmed to fit the PCR tubes.

13. Examine the PCR tubes after the foil sealer is in place. Dislodge any bubbles in the bottoms of PCR tubes. Force any hanging drops down into the reaction volume. This may be performed by gently tapping tubes on the benchtop or by a brief centrifugation in a swinging-bucket centrifuge with a microwell plate carrier.

NOTE: It is critical that no bubbles are trapped in the base of PCR tubes and that no droplets are left clinging to the sides of the PCR tubes. Failure to attend to this may result in loss of the allele-specific amplification.

14. Start the THROMBOTYPE[®]1 program on the thermal cycler. Once the block reaches 70°C, pause or hold the program. Transfer the tubes from the ice bath or cold block to the block of the thermal cycler. Place one or more strips of empty PCR tubes in the block opposite the assay tubes as a spacer.

15. Place the silicone pad securely over the foil sealer to cover each tube; be sure to align the pad correctly and be certain the pad does not shift when securing the thermal cycler heated lid.

NOTE: It is important to maintain even pressure on the foil sealer atop the PCR tubes to avoid venting during the high-temperature steps in the program. To achieve this, extra PCR tubes should be placed in the block around the assay tubes so the heated lid is supported at all edges when it is closed. The silicone pad helps to maintain adequate pressure and compensates for small variations in the height of the PCR tubes.

16. Resume the cycling program. The program takes ~ 55 minutes.
17. When the thermal cycler has reached the last step of the program (the 4°C hold), remove the tubes from the thermal cycler and transfer them to a PCR tube rack. If electrophoresis will not be performed immediately, store the tubes refrigerated (2 to 8°C) for up to 3 days or in a freezer below -20°C for up to 7 days.

C. Detection

NOTE: Detection steps must be performed in an area separate from that used as the pre-PCR area. Devices should not be shared between these areas to avoid carryover contamination.

18. Prepare a work area by setting down plastic-backed absorbent paper and setting up the E-Base Motherbase, deionized water, 100 bp DNA Ladder, and pipettors at this spot.
19. If PCR tubes were frozen, remove from the freezer and allow to thaw prior to use.
20. Remove the E-Gel[®] from its foil pouch and remove the combs. Clean the gel's upper plate with a damp laboratory wipe if necessary. Label the gel's upper plate using a laboratory marker.
21. Slide the gel under the two electrodes on the E-Base Motherbase and seat the gel so its electrodes make contact with the device electrodes.
22. Pipet 10 µL deionized water to each well needed for a PCR product (2 wells for each sample plus one for each negative control). Do not add water to the 4 outer wells (marked M) for the 100 bp DNA Ladder.

NOTE: An outer well (marked M) may be used for the negative control if all other wells are used for patient samples.

23. For each sample, puncture the foil sealer of each PCR tube with a fresh pipet tip. Pipet 5 µL of the product to the appropriate well of the gel. Do not puncture the foil sealer of a PCR tube until ready to transfer the product to a gel.

NOTE: A small-volume multichannel pipettor speeds up the sample loading and makes an error in the loading order less likely.

NOTE: For each sample, pipetting the a and b amplifications to adjacent wells on the gel aids in interpretation of results.

24. Puncture the foil sealer of the negative control and pipet 5 µL of the product to the designated well.
25. Pipet 15 µL of the 100 bp DNA Ladder to each of the four outer wells (marked M) unless reserved for negative control.

NOTE: All samples run on a gel should always be bracketed by lanes containing the 100 bp DNA Ladder so that product band sizes can be accurately determined.

26. Plug in the Motherbase. A red light will come on and the time display will light up. Use the power button (right button) to toggle to EG mode (instead of EP mode).
27. Use the left button to set the timer for 17 minutes.

NOTE: Adequate band separation can be obtained with a run time as short as 15 minutes. However, band separation is improved by running for 17 - 20 minutes. Do not run longer than 20 minutes.

28. Press the power button (right button) to begin electrophoresis. The red light will change to green while the run is in progress.
29. At the end of the electrophoresis the green light will change to a red flashing light and an alarm will sound. Press the power button to stop the run. The flashing red light will become a steady red light. Unplug the device and remove the gel from the Motherbase.
30. Take the gel to the UV transilluminator for observation of product bands. The gel should be viewed and recorded within 20 minutes. If a record of the assay is desired, a photo of the gel should be taken using a gel documentation system.

QUALITY CONTROL

The internal control primer set produces an 85 bp product if 40 ng or more of amplifiable human DNA is loaded to a PCR reaction. This band should appear in all lanes for any amplification except the negative control. However, **allele-specific** amplification competes with the internal control PCR; the internal control product may be faint or absent in lanes positive for an allele. Thus, absence of the internal control band from a lane in which an allele-specific band appears is not cause for concern. However, if DNA was loaded to a PCR tube and no control or allele-specific bands are observed in its lane, amplification failure is strongly indicated. Such amplification failures can result from deterioration of a reagent, an incorrectly-programmed thermal cycler, poorly purified sample DNA, insufficient quantity of sample DNA loaded to the PCR, or failure to load a reactant to the PCR during setup. Results are invalid for such amplifications. Such samples should be reassayed, preferably with a fresh DNA isolate.

The 100 bp DNA Ladder provides an objective size indicator for the PCR product bands; 100 bp DNA Ladder wells bracketing the PCR wells should be included in every electrophoresis. The bands of the 100 bp DNA Ladder should appear sharp and well-separated. Any assay where the bands of the 100 bp DNA Ladder appear smeared or compressed together should be repeated. The results should not be reported.

Primer dimer bands can be formed with certain DNA samples and thermal cyclers. These bands of less than 85 bp do not affect typing by THROMBOTYPE® 1. If the dimer bands are a concern, adjustments to the cycling program as described in the section on programming the thermal cycler can minimize their appearance.

The negative (water) control lane should have no PCR product bands, allele-specific or internal control. Presence of any specific PCR products in negative control lanes indicates technical error or a contaminated reagent. If either control does not perform as expected, results are invalid and the assay should be repeated. In this instance sample results should not be reported.

INTERPRETATION OF RESULTS

The presence of an allele-specific band of the correct size in a lane is a positive result for that allele. Sizes of the PCR products for THROMBOTYPE® 1 are listed below. Absence of the allele-specific product band from a lane indicates absence of that allele from the sample (negative result) IF the internal control band is present as an indication of successful amplification. A PCR product missing both the control band and allele-specific band indicates amplification failure. The sample must be retested for that allele.

<u>Product</u>	<u>PCR Product Size (bp)</u>
HPA-1	124
Control	85

Note that for any sample the 1a and 1b amplifications produce relatively the same amount of PCR product if the allele is present. Heterozygous samples should produce 1a and 1b product bands of nearly the same intensity. A sample where one allele-specific product band is faint compared to the other allele-specific band is probably not heterozygous. Instead the faint band is probably due to a technical error or to “read-through”. “Read-through” is low-level amplification by the allele-specific primers from a DNA sample lacking that allele. Such samples should be reassayed using a smaller amount of sample DNA. Upon reassay, appearance from the tube in question of a band similar in intensity to the alternate allele indicates a positive result for the reaction in question, and the sample should be typed as positive for the allele, a true heterozygote. This result suggests a technical error as the cause of the original suspect result. Appearance of the faint band upon reassay indicates a true “read-through” or false positive, and the sample should be scored as negative for that allele.

LIMITATIONS

- THROMBOTYPE® 1 contains materials for the amplification of sequences in genomic DNA by the polymerase chain reaction and the subsequent qualitative detection of HPA-1 allele-specific sequences by agarose gel electrophoresis. Unknown variations in the relevant gene sequences may adversely affect results.
- To ensure optimal results in the THROMBOTYPE® 1 assay, DNA samples should have a concentration between 10 ng/μL and 100 ng/μL with a 260/280 ratio of 1.60 – 1.90. Poor amplification may result from insufficient DNA added to a PCR reaction, or from poorly-purified sample DNA.
- False negative results may result from improperly handled specimens, procedural errors, amplification inhibitors, inadequate genomic DNA as sample, or from inadequate mixing of genomic DNA into the master mix especially when adding DNA directly to the PCR tubes. In this case, the control bands may or may not still be present and allele specific amplification may fail.
- Contamination from carryover nucleic acids, excessive genomic DNA loaded to amplifications, or failure to use indicated temperatures/times may result in false-positive results.
- This assay was developed with adult human DNA. It has not been validated for use with prenatal samples.
- This assay has been demonstrated to perform properly when amplified using the ABI PE9700, 9600, and 2720 thermal cyclers, the MJ Research (now Bio-Rad) PTC-200 or Mini Cycler with heated lid, and the Eppendorf Mastercycler and Mastercycler EP.

Some adjustments to the indicated cycling parameters may be required for use of the assay in other thermal cyclers. Thermal cyclers should be calibrated and maintained according to the manufacturer's instructions.

SPECIFIC PERFORMANCE CHARACTERISTICS

Accuracy

The accuracy of the THROMBOTYPE®1 assay was assessed by three different comparison studies:

Comparison of THROMBOTYPE®1 and GTI PAT assay

A comparison of methods study was performed between the THROMBOTYPE®1 assay and the GTI – PAT assay. Briefly, the HPA 1a/b genotype was determined for 15 samples using the THROMBOTYPE®1 assay and the GTI – PAT assay (n = 30 results). The allele distribution for the samples was as follows: eight HPA – 1 a/a; three HPA – 1 b/b; and four HPA – 1 a/b. The results showed 100% agreement between the two methods.

Comparison of THROMBOTYPE®1 and DNA Sequencing

DNA sequencing was performed to determine the HPA – 1a/b genotype of 46 samples with the following distribution of alleles: 33 HPA – 1a/a; four HPA – 1 b/b; and nine HPA – 1 a/b. The samples were also tested in the THROMBOTYPE®1 assay. The results from the THROMBOTYPE®1 assay showed 100% agreement with the results obtained by DNA sequencing.

Comparison of THROMBOTYPE®1 and a DNA based molecular typing assay

Thirty – six samples with the following distribution of alleles were used for the study: twenty two HPA – 1 a/a; seven HPA – 1 b/b; and seven HPA – 1 a/b. The samples were tested in the THROMBOTYPE®1 and by another PCR based molecular typing method in an independent external evaluation (n = 72). The analysis of the 72 assay results showed 100% agreement between the comparison method and the THROMBOTYPE®1 method.

Assay Precision

The reproducibility of the THROMBOTYPE®1 assay was determined. Briefly, three samples representing a range of alleles were tested in duplicate in the THROMBOTYPE®1 assay on nine separate days. The results demonstrated 100% agreement between the duplicates tests and the day to day to results.

REFERENCES

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THROMBOTYPE®1

- For *In Vitro* Diagnostic Use
- STORE AT 2 to 8°C
- STORE AT 15 to 30°C

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