Ezplex®

HLA- DRB1 typing Kit

Instructions for Use (IFU)

Approved by MFDS (Ministry of Food and Drug Safety of South Korea)

24 / 48 Tests

Manufacturer:

SML GENETREE Co., Ltd.

1307~1309, 167, Songpa-daero, Songpa-gu, Seoul, Republic of Korea

TEL : +82-2-2057-7900

FAX : +82-70-7425-3950

Website : http://www.smlgenetree.com

http://www.genetree.co.kr

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I. Intended Use

The Ezplex® HLA-DRB1 NGS typing Kit is an *in-vitro* diagnostic test that identifies HLA-DRB1 alleles in high resolution among Human Leukocyte Antigens (HLA) with DNA extracted from the transplant donor's or recipient's whole blood samples. It uses PCR (Polymerase Chain Reaction) and NGS (Next Generation Sequencing) methods to support qualitative testing of histocompatibility genes for bone-marrow or organ transplants.

II. Summary and Explanation

HLA is a major antigenic system in determining the survival of transplant allografts or transfused platelets in sensitized individuals [1]. HLA class I antibodies can be formed after blood transfusions, after organ transplantations and during pregnancy [2]. HLA molecules play a key role in immunity and recognition of self versus non-self, consequently HLA typing and HLA matching is mandatory prior to most forms of transplantation. As HLA antigens restrict the specificity of T-cell mediated immune responses HLA typing can also be a useful investigative tool in any immune disorder or any immune response to pathogens, vaccines or medical treatment. HLA typing can also be used to support disease diagnosis where certain HLA alleles have been shown to be significantly associated with disease states.

III. Principles of the Procedure

DNA is first extracted from human whole blood. Exon 2 of HLA-DRB1 is then amplified by the first polymerase chain reaction (1st PCR). An adapter specific for Index and Miseq flow cells is amplified by the second polymerase chain reaction (2nd PCR). The resulting amplicon is then sequenced in Miseq DX equipment using SBS (Sequencing By Synthesis) technology. The sequencing result is generated and extracted in the 'FASTQ' file format and analyzed with the dedicated software (HLA NGT) provided with the Ezplex® HLA-DRB1 NGS typing kit to determine the type of HLA-DRB1.

IV. Kit Components and Packaging Configurations

Catalog Numbers: GNT-4009-1 24 Tests/Kit; GNT-4009-2 48 Tests/Kit

No.	Component Name	Volume 24 Tests/Kit	Volume 48 Tests/Kit	Main Ingredients
1	HLR 1st PCR Master Mixture	1vial, 315uL	1vial, 630uL	5X PCR buffer, D.D.W, dNTP, DRB1-Forward Primer, DRB1-Reverse Primer
2	Bio-prince Taq	1vial, 21ul	1vial, 41ul	Taq polymerase
3	HLR 2nd PCR Master Mixture	1vial, 580uL	1 vial, 1,150uL	5X PCR buffer, D.D.W, dNTP
4	2nd PCR Primer	1Plate, 6uL x each well (Exon 2 24-well)	1 Plate, 6uL x each well (Exon 2 48-well)	DRB1 Exon2 Index Forward Primer, DRB1 Exon2 Index Reverse Primer

Optional Materials Provided: Genetree Viewer Software (CAT No. GNT-4009-3)

V. Materials Required But Not Provided:

No.	Name	CAT No.	Manufacturer
1	Miseq® v2 Reagent Kit 500 Cycles PE – Box 1 of 2	15033625	Illumina
2	Miseq® Reagent Nano Kit v2 Box 2 of 2	15036714	Illumina
3	Qubit™ 4 Fluorometer	Q33226	ThermoFisher Scientific
4	Qubit™ dsDNA HS Assay Kit	Q32851	ThermoFisher Scientific
5	Qubit™ assay tubes	Q32856	ThermoFisher Scientific
6	MagNA Pure 96 DNA and Viral NA Large Volume Kit	06374891001	Roche
7	MagNA Pure 96 Instrument	06541089001	Roche
8	Any applicable device and materials for Electrophoresis	-	-
9	Loading Dye	-	-
10	10N NaOH	-	-
11	Tween 20	-	-
12	Any applicable 96 well PCR plate plastics for Thermal Cycler	-	-

No.	Name	CAT No.	Manufacturer
13	Any applicable PCR plate sealing film for Thermal Cycler	-	-
14	Any applicable barrier tips for molecular testing	-	-
15	Any applicable pipettes with several volumes	-	-
16	Any applicable 1.5mL or higher distilled vials	-	-
17	Any applicable 5mL or 15mL conical tube or higher distilled vials	-	-
18	Any applicable 8-strip tube	-	-
19	Any applicable 8-strip cap	-	-
20	Centrifuge for 8-strip	-	-
21	Latex gloves	-	-
22	Computer for installation of Genetree Viewer HLA Analysis Software	**Required System**	
		* Microprocessor: Intel(R) Core I3 2.0GHz or above * Memory: 4GB or above * OS: Microsoft Windows 10 64 bit	

VI. Instruments

- SimpliAmp Thermal Cycler (or any other similar device). Catalog Number: 4375786 ThermoFisher Scientific
- Illumina MiSeqDx Instrument.Catalog Number: DX-410-1001

VII. Storage and Handling Conditions

- All kit materials should be stored at -20+ 2°C opened and unopened.
- Use the reagents before the expiration date shown on the labeling.
- The product is disposable.
- Completely thaw the reagents before use.
- Repeated thawing and freezing should be avoided.

VIII. Warning and Precautions

- This product is intended for *in vitro* diagnostic use, and should only be used by clinical experts such as clinical pathologists and medical technologists.
- All product components shall be taken out just before use and should be stored in a freezer (below –20°C) immediately after use so that they are exposed as little as possible to ambient temperature.
- Quality control requirements must be performed in conformance with local, state, and/or federal regulations or accreditation requirements and your laboratory's standard quality control procedures.
- For each test, both positive and negative controls should be tested together and these results should be taken into account when interpreting results.
- Internal Control may not amplify when the target nucleic acid has a high concentration or an inhibitor is present, so dilute the nucleic acid appropriately and retest.
- Beware of carry-over contamination since the PCR and NGS have high sensitivity.
- Repeated freezing and thawing of reagents and specimens should be avoided since this may affect test sensitivity.
- Beware of microbe contamination when dividing the reagents. It is recommended to use a sterilized disposable filter tip.
- Do not touch the reagent container cap or the inner side of PCR tube cap with your hands.
- It is prohibited to mix the products from different Lots even in case of the same product reagent.
- Do not use the product if expired.
- Tests shall be performed in accordance with the Guideline for Laboratory Biosafety and the Laboratory Safety Management Manual.
- When handling the specimen, beware of infection through skin or inhalation. In case of human exposure, the part shall be immediately cleansed with running tap water and medical attention should be immediately sought for any symptoms including high fever and rashes.
- All spaces shall be thoroughly sterilized using 70% Ethanol or 0.5% sodium hypochlorite.
- Only the Illumina Miseq DX Instrument and the ThermoFisher Scientific SimpliAmp Thermal Cycler can be used with the Ezplex® HLA-DRB1 NGS typing Kit. These instruments should be calibrated regularly according to instrument's instructions to eliminate cross-talks between channels.
- Store assay components at the recommended storage conditions.
- Please note that accurate information cannot be obtained if this product is used in an unintentional manner or if results intersect between samples.
- Take care to avoid contamination between patient samples and unintentional contamination of reagents by DNA.
- As this product is 'disposable', reuse is prohibited.
- It is recommended to use MagNA Pure 96 DNA and Viral NA Large Volume Kit for nucleic acid extraction.

IX. Collection, Storage and Shipment of Specimens

- Whole blood samples shall be used for the test.
- Specimens must be tested within 24 hours while maintaining the minimum refrigeration condition(4℃).
- Prior to testing, ensure that the specimens do not exceed 1 day at room temperature or 3 days at 2~8 ℃ to prevent DNA degradation.
- Specimens should be divided into amounts required for one testing and stored at −70℃ or below in a freezer so as to avoid repeated thawing.
- Specimens that are no longer needed shall be put in a container for liquids and disposed as liquid medical waste.
- Specimen Collection
  - Specimens shall be collected in a dedicated container which shall be sealed to prevent leakage.
  - Adequate protective gears such as gloves and gowns shall be used to handle the specimens and protective glasses, masks, or aprons shall be worn if protection is required against specimen splatter.
  - After collecting blood into a container, mix the anticoagulant with the sample sufficiently, and shake it 8 to 10 times to avoid foaming.

X. Procedure

A. Specimen Pretreatment

The **MagNA Pure 96 DNA and Viral NA Large Volume Kit (Roche)** and **MagNA Pure 96 Instrument (Roche)** should be used for nucleic acid extraction and users should follow the protocol included in the user manual. After being extracted, nucleic acid should be divided into amounts required for 1-2 tests and be stored at in a −20 ± 2℃ freezer since extracted nucleic acid can be degraded.

B. 1st PCR

1) Prepare the 1st PCR Master Mixture and Bio-Prince Taq, and make a mixture to dispense 12uL into each well. (1st PCR Master Mixture: 11.75uL + Bio-Prince Taq: 0.25uL)
2) Dispense 12uL of the mixture prepared in the process of '1)' into a 96-well plate.
3) Dispense DNA 3uL each into the 96-well plate to make a total volume of 15uL.
4) Perform PCR as shown in [Table 1].

[Table 1] 1st PCR Conditions

Step	Temperature / Time	Cycle
1	98°C / 20sec	1 cycle
2	98°C / 5sec	7 cycles
	65°C / 30sec	
	72°C / 2min	
3	98°C / 5sec	31 cycles
	60°C / 30sec	
	72°C / 2min	
4	72°C / 10min	1 cycle
5	4°C / ∞	-

5) Apply electrophoresis to the amplified PCR product to check its band to confirm that PCR was successful.
(Mix Product 3uL + Dye 2uL and perform loading at 2.2% Agarose Gel for 10 minutes.)
6) To proceed with the 2nd PCR with the amplified PCR Product, dilute 1st PCR Product 5uL with D.D.W 145uL.

C. 2nd PCR

1) Prepare the 2nd PCR Master mixture and Bio-prince Taq, and make a mixture to dispense 21uL into each well. (2nd PCR Master mixture: 20.5uL + Bio-prince Taq: 0.5uL)
2) Dispense 21uL of the mixture prepared in '1)' into the plate well where the 2nd PCR Primer is dispensed by 6uL each, to make a total volume of 27uL.
3) Dispense 3uL of the 1st PCR product each and perform pipetting 10 times.
4) The 2nd PCR should be performed under conditions specified in [Table 2] and electrophoresis applied to check its band to confirm that PCR is successful.

[Table 2] 2nd PCR Conditions

Step	Temperature / Time	Cycle
1	98°C / 20sec	1 cycle
2	98°C / 5sec	8 cycles
	65°C / 30sec	
	72°C / 2min	
3	98°C / 5sec	32 cycles
	60°C / 30sec	
	72°C / 2min	
4	72°C / 10min	1 cycle
5	4°C / ∞	-

D. NGS Run Preparation #1(Miseq Cartridge and Sample Preparations)

1) Bring out the Miseq Reagent Cartridge kept frozen (at -20℃). Pour water into an icebox and put the Cartridge in the water so that the arrow marked on its side sinks, which will warm the Cartridge (1 hour).
2) Dispense distilled water 50uL to an empty 96-well PCR plate.
3) Place the Product with the 2nd PCR completed onto a plate with 10uL of distilled water and spin down.
4) 5uL of the Product diluted in distilled water is collected into a 5uL-tube.

E. NGS Run Preparation #2 (Equipment Maintenance Wash)

1) Perform Maintenance Wash prior to running the equipment. (For 30 minutes, 3 times)
2) Turn on power and click “Perform Wash” on the first screen. Conduct washing 3 times with a Cartridge for Wash and Bottle for PR2 Buffer filled with tween20 0.5%.
3) When washing is completed, prepare a Sample Sheet and Batch File which will be saved in the “Sample Sheet” folder.
   NOTE: Maintenance Wash does not need to be performed for every run. Instead, it can be performed every 30 days.

F. NGS Run Preparation #3 (Sample Dilution)

1) Prepare the collected Sample 5mL Tube in ‘D’ and five 0.5mL-Tubes.
   (S1, S2 Control, Sample1, Sample 2(4nM), Sample 3 (in case needed for retesting)).
2) Prepare the Qubit dsDNA HS Assay Kit’s Solution for 5 tubes as shown below.
   *** dsDNA HS Buffer - 199uL X 5 = 995uL, dsDNA HS reagent - 1uL X 5 = 5uL**
3) Dispense 190uL of the Mixture prepared in the previous stage into the S1 and S2 Control Tubes and 198 uL of it to the Sample Tube (1~3).
4) Add S1 and S2 control DNA 10uL to the S1 and S2 Control Tubes, and add 2uL of the sample collected in ‘D’ into the Sample1 Tube.
5) After vortexing, measure the concentration after 2 minutes of reaction (in order of S1→S2→Sample1).
6) Based on the measured Sample1 concentration, dilute the collected sample with 4nM into other Sample tubes (since the level of concentration decreases more, set the DW quantity a little less.)
7) Add 2uL of the sample diluted with 4nM. Then, after vortexing, measure the concentration after 2 minutes of reaction.
8) The final concentration should be set between 4.1~4.6nM.

G. Sample Pooling

1) Prepare three 2mL tubes.
2) Perform serial dilutions of 10N NaOH to generate 0.2N NaOH.
3) Mix 5uL of the sample diluted with 4nM with 0.2N NaOH 5uL and generate a reaction for 5 minutes (2nM Sample).
4) Add the reacted 2nM Sample 10uL into the Pre-Chilled HT1 buffer 990uL (20pM Sample).
5) In reference to the table below, establish a proper concentration of pM and perform pooling of samples.

Final Pooling Conc.	Method
7pM	20pM Sample 210 uL + Pre-Chilled HT1 buffer 390 uL
8pM	20pM Sample 240 uL + Pre-Chilled HT1 buffer 360 uL
9pM	20pM Sample 270 uL + Pre-Chilled HT1 buffer 330 uL
12pM	20pM Sample 360 uL + Pre-Chilled HT1 buffer 240 uL

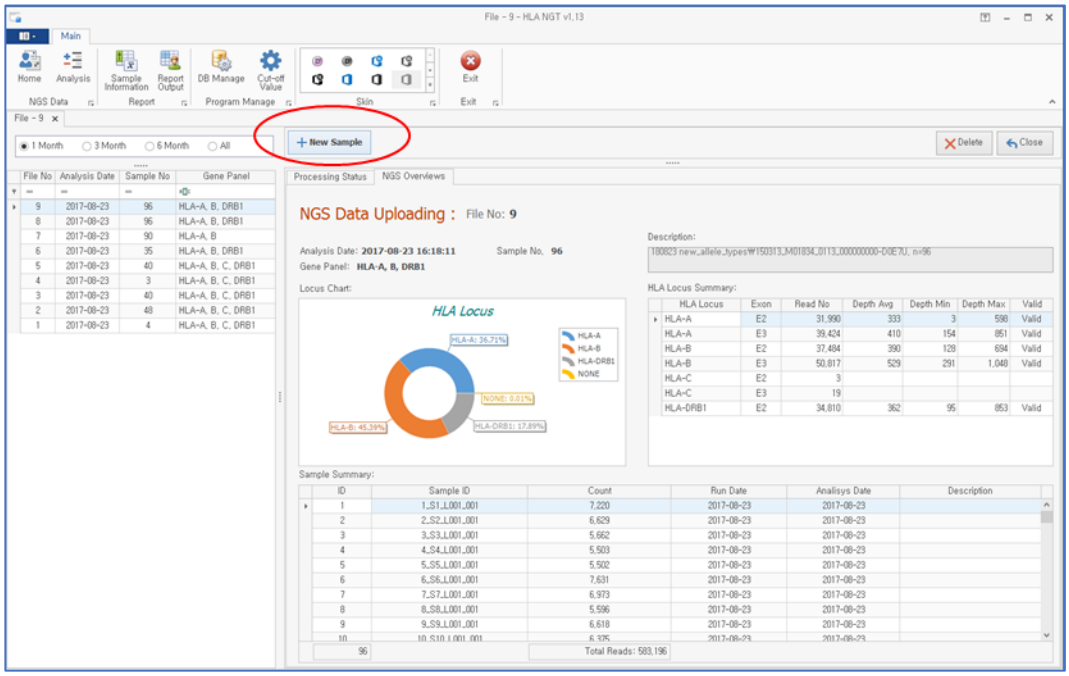
6) Keep the completed Library on ice.

H. NGS Run

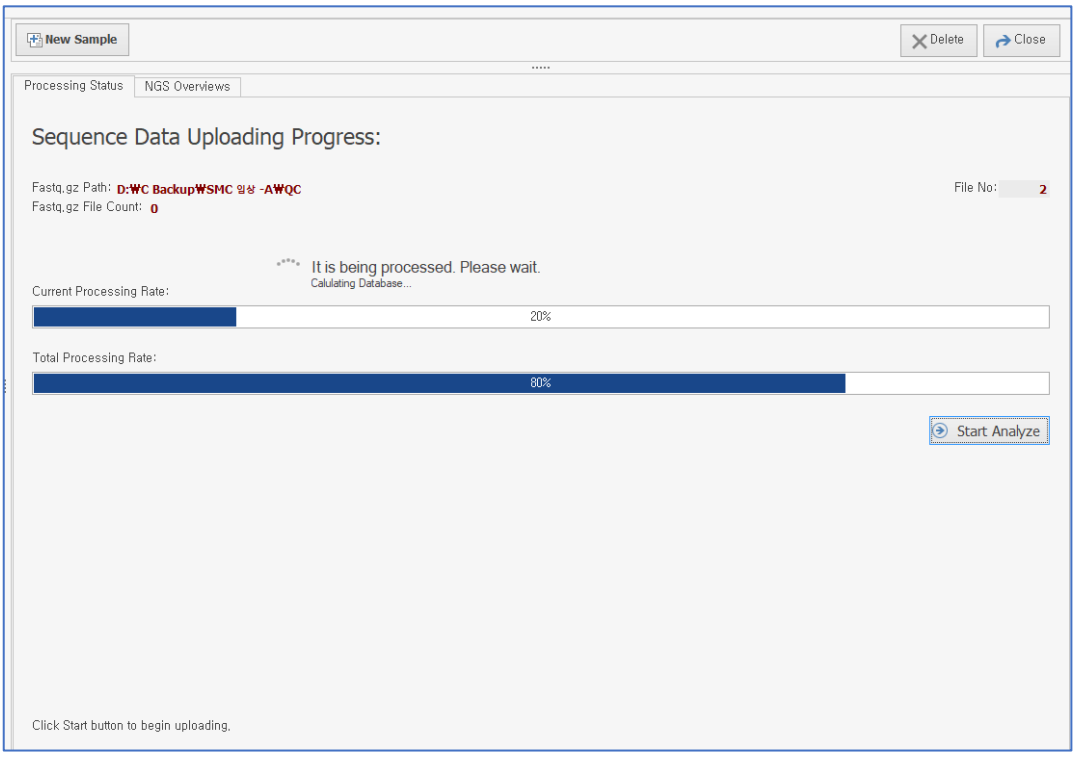
1) Prepare a Nano Kit that is kept refrigerated (consists of PS2 buffer and flow cell).
2) Click “Sequence” of Miseq equipment and login to “Base Space”
3) Properly wash D.W with the flow cell and make sure that there is no water and stain. Then, load it onto Miseq equipment.
4) Shake the PS2 buffer and attach it onto the equipment.
5) Shake the Miseq Reagent Cartridge and hit the bottom to remove bubbles. Then, add the prepared Library 600uL and place it into the equipment.
6) Re-check the Sample Sheet information displayed on the Miseq screen and perform Pre-Run.
7) When no malfunctioning is found in Pre-Run, Start Run will be performed.
8) After 60~70 minutes, check the Sequencing Screen to identify any fault.
9) Then, perform Sequencing for 24 hours.
10) When NGS Run is completed, conduct Post Run Wash. (30 minutes, 1 time)

I. Data Analysis (Genetree Viewer HLA-NGT Software)

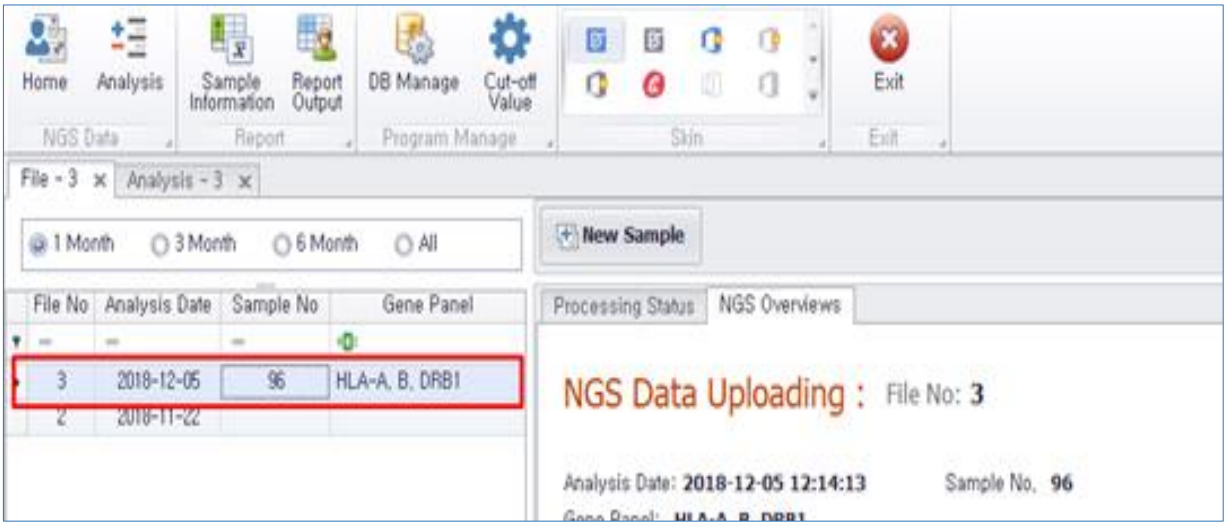
1) Transfer the Fastq File from Miseq with the Run completed to a computer for analysis.
2) Execute an analysis program and open Fastq File with the “New Sample” button.



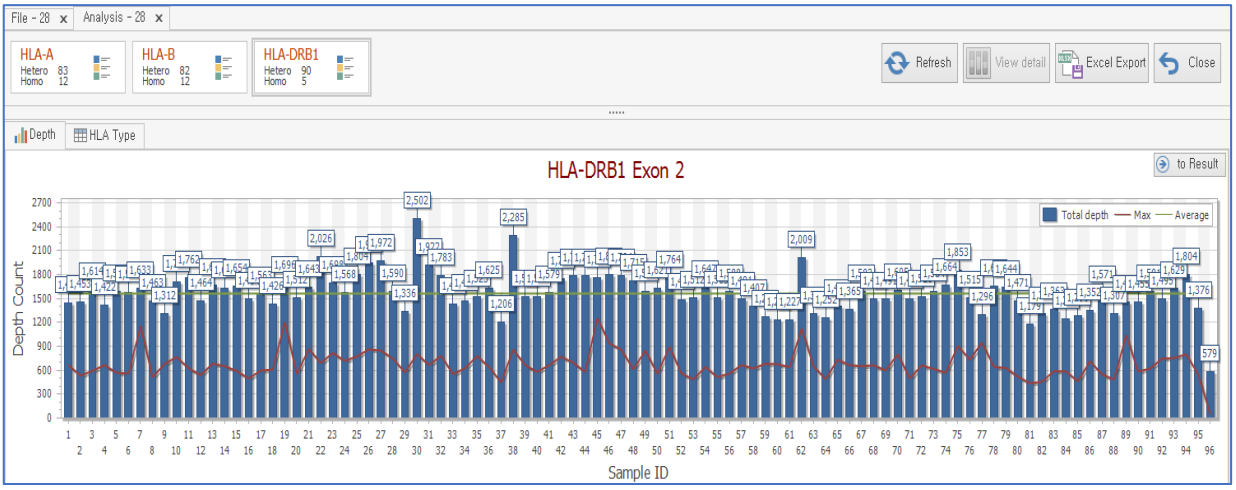
3) Press the “Start Analyze” button to open the file for analysis and check the analysis result.



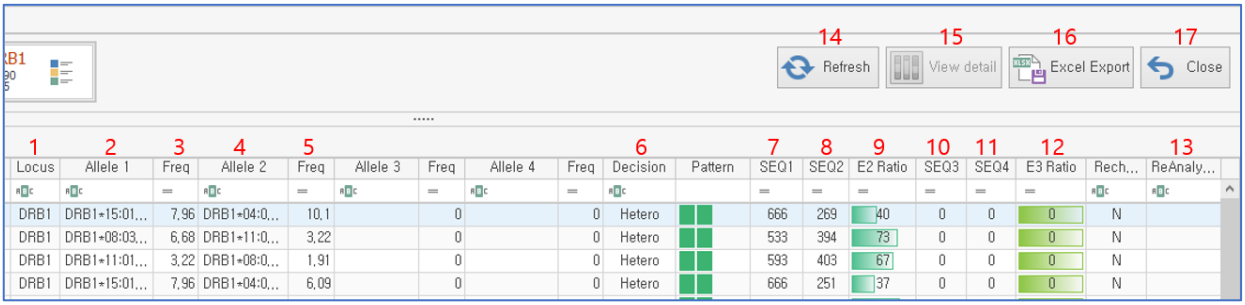
4) When the analysis is completed, check the sample summary from the [NGS Overview] tab. Double click a file from the left menu to check the result.



5) An overview on total depth count of samples for each Locus is displayed on the [Depth] tab.



6) The details on samples for each Locus are found in the [HLA Type] tab.

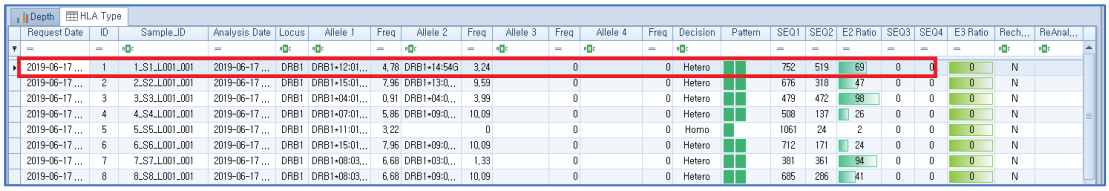


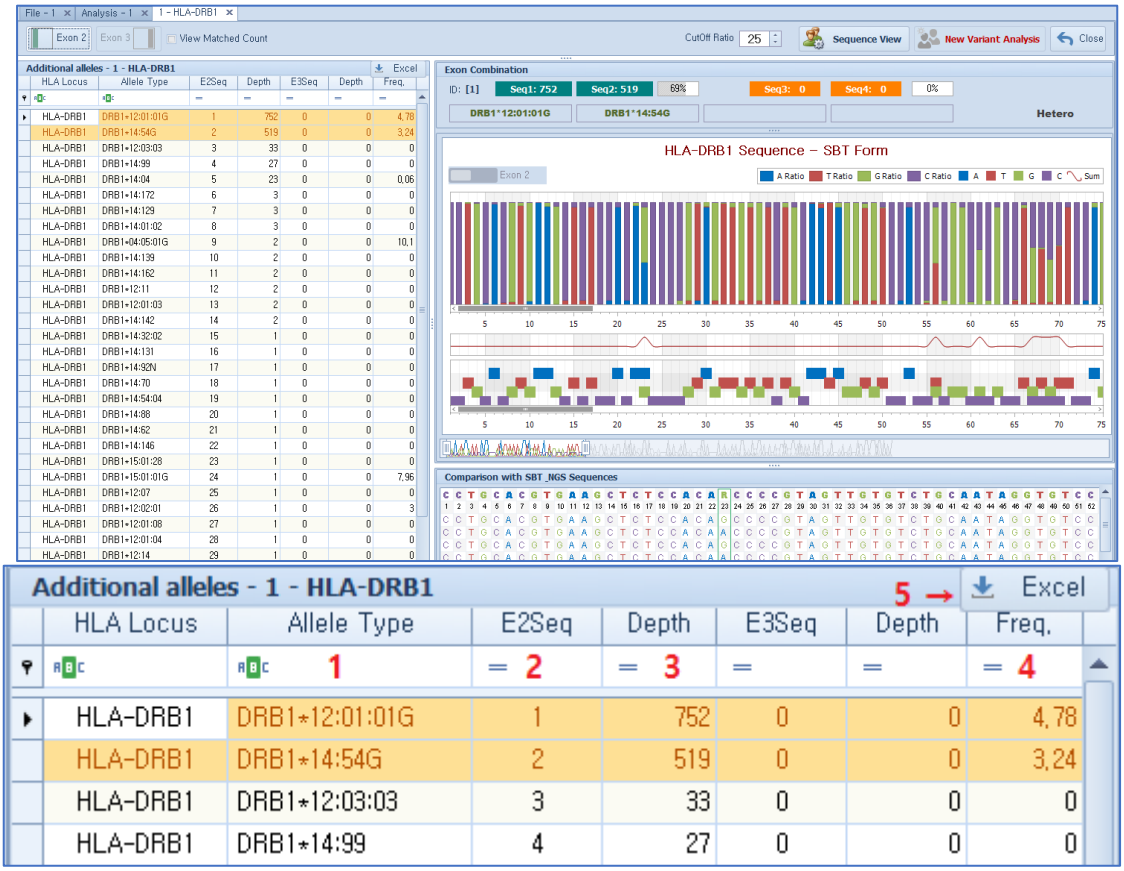
Item Description

No.	Item	Description
1	Locus	Indication of analyzed Locus
2	Allele1	HLA Typing Results for Allele1
3	Freq	Domestic frequency (KONOS) for the results of Allele1
4	Allele2	HLA Typing Results for Allele2
5	Freq	Domestic frequency (KONOS) for the results of Allele2
6	Decision	Hetero and Homo results display
7	Seq1	Depth of Allele1 in Exon 2
8	Seq2	Depth of Allele2 in Exon 2
9	E2 Ratio	Depth ratio of Allele2 to Allele1 in Exon 2
10	Seq3	Depth of Allele1 in Exon 3
11	Seq4	Depth of Allele2 in Exon 3
12	E3 Ratio	Depth ratio of Allele2 to Allele1 in Exon 3
13	Reanalyze	Mixed type check mark
14	Refresh	Refresh Results
15	View detail	Details of the results
16	Excel export	Excel extraction of results
17	Close	Close Results

*KONOS(Korean Network for Organ Sharing) : Statistics on the results of histocompatibility tests of organ donors and recipients of KONOS

7) Double click on the individual result to check the following HLA type details.

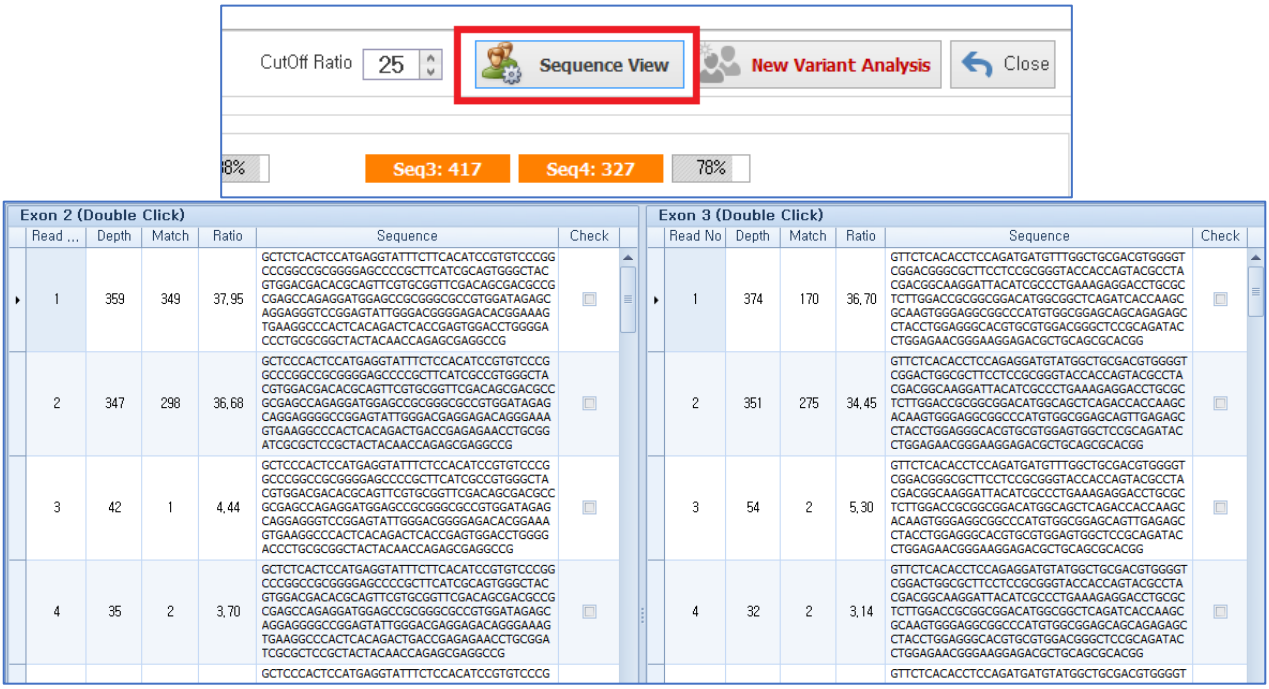




Item Description

No.	Item	Description	No.	Item	Description
1	Allele Type	HLA Typing Results for Samples	4	Freq.	Domestic frequency rate for Allele type (KONOS)
2	E2Seq	Depth ranking in Exon 2	5	Excel	Excel extract function
3	Depth	Depth in Exon 2	-	-	-

8) Click on [Sequence View] to check the detailed Sequence for each Read. Insert [Ctrl + C] to copy the Sequence.



Item Description

No.	Item	Description
1	Read No.	A number assigned to each Read (a lower number assigned to Read with a higher Depth)
2	Depth	The Depth of each Read
3	Match	The number of Sequences that Match with the Reference Sequence for each Read
4	Ratio	The ratio of Depth for each Read that accounts for the Total Depth (%)

9) With the [Export Excel] function, the final result can be exported to Excel as shown below.

HLA Locus	Allele Type	E2Seq	Depth	E3Seq	Depth	Freq.
HLA-DRB1	DRB1*12:01:01G	1	752	0	0	4,78
HLA-DRB1	DRB1*14:54G	2	519	0	0	3,24
HLA-DRB1	DRB1*12:03:03	3	33	0	0	0
HLA-DRB1	DRB1*14:99	4	27	0	0	0

XI. Interpretation of Results

a) Typing result
The HLA typing result is automatically analyzed by analysis software (HLA NGT) and the results are displayed.

* Database: International Immunogenetics Information System (IMGT) Release version 3.31.0

b) How to determine the result at the individual Read level
HLA type confirmed from Reads with respect to the individual samples is automatically generated using an algorithm in the analysis software and its criteria are as described below.

A. Hetero Type

- Read Types from Exon 2 are ranked in the order of Depth, from highest to lowest (E2 Seq) and a combination of types with high Depth at each Exon determines the Allele 1 and Allele 2 Types.

HLA Locus	Allele Type	E2Seq	Depth	E3Seq	Depth	Freq.
HLA-DRB1	DRB1*12:01:01G	1	752	0	0	4,78
HLA-DRB1	DRB1*14:54G	2	519	0	0	3,24
HLA-DRB1	DRB1*12:03:03	3	33	0	0	0
HLA-DRB1	DRB1*14:99	4	27	0	0	0
HLA-DRB1	DRB1*14:04	5	23	0	0	0,06
HLA-DRB1	DRB1*14:172	6	3	0	0	0
HLA-DRB1	DRB1*14:129	7	3	0	0	0
HLA-DRB1	DRB1*14:01:02	8	3	0	0	0
HLA-DRB1	DRB1*04:05:01G	9	2	0	0	10,1
HLA-DRB1	DRB1*14:139	10	2	0	0	0
HLA-DRB1	DRB1*14:162	11	2	0	0	0

B. Homo Type

- Although Read Types from Exon 2 are ranked in the order of Depth, from highest to lowest (E2 Seq), when the Depth of an Allele Type at Exon 2 is less than cut-off, it is determined as Homozygous with the remaining Allele type.
- Even though determined as Homozygous, HLA Type may be present in both Allele 1 and Allele 2, which is similar to the Hetero result, in Excel Export. However, this may indicate that noise of partial NGS depth is not read properly. The result should be determined by checking whether Depth exceeds cut-off in reference to the criteria set forth in 'A' and 'B' clauses.

HLA Locus	Allele Type	E2Seq	Depth	E3Seq	Depth	Freq.
HLA-DRB1	DRB1*01:01:01G	1	1008	0	0	5.79
HLA-DRB1	DRB1*01:70	2	8	0	0	0
HLA-DRB1	DRB1*01:36	3	6	0	0	0
HLA-DRB1	DRB1*15:01:01G	4	5	0	0	7.96
HLA-DRB1	DRB1*01:79	5	4	0	0	0
HLA-DRB1	DRB1*01:29:01	6	3	0	0	0
HLA-DRB1	DRB1*01:60	7	3	0	0	0
HLA-DRB1	DRB1*01:01:02	8	3	0	0	0
HLA-DRB1	DRB1*01:19	9	3	0	0	0
HLA-DRB1	DRB1*01:01:03	10	2	0	0	0

XII. Limitations

- The Ezplex® HLA-DRB1 NGS typing Kit has been validated for use with whole blood samples run on the Illumina MiSeqDx Instrument.
- The procedures in this manual must be followed, as described. Any deviations may result in assay failure or cause erroneous results.
- Good laboratory practice is required to ensure the performance of the kit, with care required to prevent contamination of the kit components. Components should be monitored for contamination and any components thought to have become contaminated should be discarded as standard laboratory waste in a sealed pouch or zip-lock plastic bag.
- All samples should be handled as if they are infectious following proper biosafety precautions.
- Interpretation of results must account for the possibility of false negative and false positive results.
- False negative results may be caused by:
  - Unsuitable collection, handling and/or storage of samples.
  - Failure to follow procedures in this manual.
  - Use of unauthorized extraction kit or PCR platform.
- False positive results may be caused by:
  - Unsuitable handling of samples containing high concentration of nucleic acid (DNA).
  - Unsuitable handling of amplified product.
- All results should be interpreted by a health care professional in the context of patient medical history and clinical symptoms.

XIII. Performance Evaluation

A. Analytical Sensitivity (Limit of Detection)

Reference material DNA of HLA-DRB1 Locus was used for dilution in 4 stages and the test was repeated two times for each dilution. The concentration showing a 100% positive rate was 0.547 ng/mL, with a limit of detection 1ng/ml.

Locus	Limit of Detection (ng)
DRB1	1 ng

B. Analytical Accuracy

Using UCLA specimens with identified genotypes, the test was conducted once and confirmed whether they matched the identified genotypes.

Locus	Accuracy (95% CI)
DRB1	100 % (95% CI, 93.6 – 100 %)

C. Analytical Precision

1. Analytical Precision (Reproducibility)

Using the UCLA reference material for HLA, two investigators used one Lot and repeated the test 10 times in different locations for 5 non-consecutive days. The detection results were same across the tests and it was confirmed that results did not differ between investigators and between locations.

2. Analytical Precision (Repeatability)

Using the UCLA reference material for HLA, one investigator tested a total of 10 times repeatedly 5 days using 3 different lots. The detection results were same across the tests and it was confirmed that results did not differ within a test, between tests, between dates and between Lot.

D. Analytical Specificity (Interference)

The interference materials were prepared with 6 materials of endogenous - EDTA (1.8mg/mL), Ethanol (5%), Albumin (0.24g/mL), Hemoglobin (0.2g/mL) - those were tested three times with the UCLA DNA Reference Panels. As a result of the testing, no interference was detected in all cases.

E. Clinical Evaluation

The clinical efficacy was evaluated using a whole blood sample with HLA type confirmed using an approved product (control group), and it satisfied more than 93.4% of the performance criteria.

Locus	Positive Agreement (%)	95%CI
DRB1	100%	98.8 ~ 100%

XIV. References

1. Marsh SGE, Parham P, Barber LD, The HLA Facts Book. Academic Press 2000: 84-91.
2. Rodey Glenn E. HLA Beyond Tears. De Novo, Inc. 2000; 213

XV. Symbols and Information

Symbol	Meaning	Symbol	Meaning
	Storage Temperature		In-Vitro Diagnostic Medical Devices
	Expiration date		Product User Manual
	Catalogue Number		Manufacturer
	Lot Number		Contents sufficient for <n> tests

1

XVI. Technical Support

For Technical Support, please contact our Genetree Technical Support team. Before contacting Genetree Technical Support collect the following information

- Product name
- Lot number
- Software version

- Email for Technical Support: **technicalsupport@smlgenetree.com_**
- Email for Customer Support: **customersupport@smlgenetree.com**
- Tel: +82-2-2057-7900
- Fax: +82-70-7425-3950
- Mailing address: 225 Baumoe-ro, Seocho-gu, Seoul, 06740
- Republic of Korea
- Website: http://www.smlgenetree.com
  http://www.genetree.co.kr

SML Genetree Co. Ltd.
255 Baumoe-ro, Seocho-gu,
Seoul, 06740, Republic of Korea

SML Genetree Sciences, Inc.
400 Concar Drive, Suite 03-160
San Mateo, CA 94402