IntelliPlex™ PIK3CA Mutation Kit

REF 82021 24 Reactions

RUO For Research Use Only

PlexBio Co., Ltd.
6F-1, No. 351, Yangguang St., Neihu Dist.
Taipei City, 11491, Taiwan
TEL: + 886-2-2627-5878
http://www.plexbio.com

IMPORTANT:
Read the instructions carefully prior to use

1. INTENDED USE

The IntelliPlex PIK3CA Mutation Kit, based on πCode™ technology and PlexBio's instrument platform, is an in vitro molecular assay intended for the qualitative identification of 17 single nucleotide changes on exons 9 and 20 of the PIK3CA gene using DNA samples derived from formalin-fixed paraffin-embedded (FFPE) tumor tissues from patients with colorectal cancer (CRC). This product is for research use only, and not for use in diagnostic procedures.

2. INTRODUCTION

The phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway plays an important role in cellular processes, such as proliferation, differentiation, survival, and migration. Alterations in the components of this signaling pathway, including gain-of-function mutations in the p110 catalytic subunit of PI3K, have been identified in a wide spectrum of human cancers. Mutations are often found in exon 9 and 20 leading to cell survival and proliferation. PIK3CA is thus a target for development of many anti-cancer drugs. It is thus critical to assess the mutation status of the PIK3CA gene. SelectAmp and πCode technology enable the multiplex, single-well detection of single nucleotide mutations of the PIK3CA gene from specimens containing large amounts of wild-type genomic DNA with significantly reduced sample requirement compared to conventional methods. The IntelliPlex PIK3CA Mutation Kit identifies 17 nucleotide changes on exons 9 and 20 of the PIK3CA gene (Table 1).

Table 1. Mutations Detected

Gene	Exon Codon	Amino Acid Change	Nucleotide Change	COSMIC ID
PIK3CA	Exon 9 Codon 542	p.E542K	c.1624G>A	760
		p.E542V	c.1625A>T	762
		p.E542G	c.1625A>G	761
	Exon 9 Codon 545	p.E545K	c.1633G>A	763
		p.E545Q	c.1633G>C	27133
		p.E545A	c.1634A>C	12458
		p.E545G	c.1634A>G	764
		p.E545D	c.1635G>T	765
		p.E545V	c.1634A>T	27155
	Exon 9 Codon 546	p.Q546E	c.1636C>G	6147
		p.Q546K	c.1636C>A	766
		p.Q546L	c.1637A>T	25041
		p.Q546P	c.1637A>C	767
		p.Q546R	c.1637A>G	12459
	Exon 20 Codon 1047	p.H1047Y	c.3139C>T	774
		p.H1047L	c.3140A>T	776
		p.H1047R	c.3140A>G	775

3. TECHNOLOGICAL PRINCIPLES

The **IntelliPlex PIK3CA Mutation Kit** utilizes two technologies, SelectAmp and πCode, to achieve high sensitivity multiplex mutation detection.

SelectAmp Technology

SelectAmp technology enables mutation-specific multiplex PCR amplification by blocking amplification of wild-type sequences with Locked Nucleic Acid (LNA). The subsequent selective PCR amplification of mutated sequences increases assay sensitivity and specificity.

πCode MicroDisc

πCode MicroDisc are manufactured to generate up to 16,000 distinct circular image patterns for multiplexing applications. Each πCode MicroDisc has a distinct circular image pattern, which corresponds to a specific capture

agent conjugated to the surface of the disc. πCode tagged with different capture agents are pooled, enabling specific detection of multiple analytes in a one-well reaction.

Detection Principle

The test is based on five processes listed as follows:

1. DNA extraction from specimens
2. Mutation-specific multiplex PCR amplification
3. Hybridization of PCR amplicons with mutation-specific probe tagged πCode in a one-well reaction
4. Fluorescent labeling with streptavidin-phycoerythrin
5. Image pattern decoding and fluorescent signal detection by the PlexBio™ 100 Fluorescent Analyzer

4. WARNINGS AND PRECAUTIONS

- For research use only. Not for use in diagnostic procedures.
- This assay kit should be only used by qualified laboratory personnel.
- Separate, dedicated rooms and equipment for pre- and post- PCR process with unidirectional manner to avoid any contaminations would be required.
- Pre-PCR process preparation should be operated in laminar flow hood to avoid contamination.
- Do not use a kit or reagent past its expiration date.
- Note that tumor samples are non-homogeneous and may also contain non-tumor sections from a same sample to cause false-negative results.
- Reagent Components have been diluted optimally. Further dilution of the component reagents is not recommended.
- Specimens should be handled as infectious material. Please follow universal precautions for safe use.
- Store assay kits and reagents according to the product label and instructions.
- Do not mix reagents from different lots.
- Dispose of unused reagents, specimens and waste according to applicable central/federal, state, and local regulations.
- Wear powderless gloves and do not touch and make any markings on the bottom of the plate at any time, as fingerprints and markings would interfere with decoding and signal acquisition.
- General laboratory precautions should be taken:
  - Do not pipette by mouth.
  - Wear protective clothing (e.g., disposable powderless gloves and laboratory coats) and eye protection.
  - Do not eat, drink or smoke in the laboratory.
  - Wash hands thoroughly after handling samples and reagents.
- The workspace, including racks and pipettes, should be thoroughly cleaned and wiped with 0.5% sodium hypochlorite solution followed by wiping with a 70% ethanol solution. A 1:10 dilution of household bleach will produce a 0.5% sodium hypochlorite solution.
- Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.
- Material Safety Data Sheets (MSDS) are available upon request from PlexBio Customer Service.

5. KIT COMPONENTS

The **IntelliPlex PIK3CA Mutation Kit** contains sufficient reagents for up to 24 tests. Kit components include:

1. PIK3CA KIT Reaction Mix
Ref. No.: 20205-R
Quantity & Volume: 1 vial, 240 µL/vial
Description: For PCR amplification
Contents: 36.4% MyFi 5X Reaction Buffer,
Magnesium chloride,
dNTPs and Enhancer,
3.6% MyFi DNA polymerase (Microbial)

2. PIK3CA KIT Primer Mix
Ref. No.: 20206-R
Quantity & Volume: 1 vial, 240 µL/vial
Description: For PCR amplification
Contents: <0.01% Forward Primer,
<0.01% Reverse Primer (biotin labeled),
<0.1% Locked Nucleic Acid

3. PIK3CA KIT πCode MicroDisc
Ref. No.: 20209-R
Quantity & Volume: 1 vial, 480 µL/vial
Description: For PCR amplicon capture
Contents: πCode MicroDisc, Glycerol
Phosphate buffered saline,
0.1% Albumin- from bovine (Biological),
<0.1% EDTA and <0.1% Sodium azide

4. PIK3CA KIT POS Control
Ref. No.: 20207-R
Quantity & Volume: 1 vial, 120 µL/vial
Description: Assay positive control
Contents: PIK3CA plasmid DNA (Microbial),
Tris-EDTA Buffer

5. NEG Control
Ref. No.: 20549-R
Quantity & Volume: 1 vial, 120 µL/vial

Description: Assay negative control
Contents: ddH_2O

6. **SA-PE Solution**
Ref. No.: 20302
Quantity & Volume: 1 bottle, 7 mL/bottle
Description: Streptavidin-phycoerythrin for fluorescent signal acquisition
Contents: Phosphate buffered saline,
0.5% Streptavidin-phycoerythrin,
1% Albumin- from bovine (Biological),
<0.1% Sodium azide

7. **Hy Buffer**
Ref. No.: 20547-R
Quantity & Volume: 1 bottle, 2.4 mL/bottle
Description: For hybridization
Contents: Saline-Sodium Phosphate-EDTA

8. **10X Wash Buffer**
Ref. No.: 20546-R
Quantity & Volume: 1 bottle, 50 mL/bottle
Description: For πCode washing
Contents: Phosphate buffered saline,
1% Tween-20 and <0.1% Sodium azide

NOTE: POS Control, NEG Control and Hy Buffer refer to positive control, negative control and hybridization buffer, respectively.

6. MATERIALS AND EQUIPMENT REQUIRED BUT NOT SUPPLIED

Required products for compatibility with IntelliPlex kits:

- 96-well plate (Plexbio; Cat. No. 80025 or Greiner Bio-one; Cat. No. 655101)
- IntelliPlex™ 1000 πCode Processor (PlexBio; Cat. No. 80033)
- PlexBio 100 Fluorescent Analyzer (PlexBio; Cat. No. 80000)
- U Tray (PlexBio; Cat. No. 80023)
- V Tray (PlexBio; Cat. No. 80024)
- DeXipher™ RUO (Required: PlexBio; Cat. No. 80050)

Required components:

- Qubit™ Fluorometer with dedicated quantitative reagents (Invitrogen; any models) or equivalent
- Clean tubes for PCR reaction (Gunster; Cat. No. MB-P08A or equivalent)
- Dedicated micropipette
- Filter tips for micropipette
- ddH_2O for dilution of 10X Wash Buffer
- Nucleic acid sample purification kit compatible with downstream PCR amplification
- For FFPE samples: FFPE DNA extraction kit (Recommended: QIAamp DNA FFPE Tissue Kit, Qiagen; Cat. No. 56404 or equivalent)
- Vortex mixer
- Micro-centrifuge
- Thermocycler (Recommended: DigiPlex™ Thermocycler, PlexBio; Cat. No. 80018/ MiniAmp™ Thermal Cycler, Applied Biosystems™; Cat. No. A37834 or equivalent)
- Industrial Computer (Recommended: PlexBio; Cat. No. 80002)

7. STORAGE, STABILITY AND TRANSPORTATION

Storage

All kit components should be stored at 2-8°C.

Stability

Do not use any kit that has expired. All components are stable up to the expiration date on the label if handled and stored under the recommended conditions.

Transportation

The shipping temperature for the kit is 2-8°C. If the kit package or components are incomplete, please contact PlexBio customer service (service@plexbio.com).

8. INSTRUMENT AND SOFTWARE

Instrument

Please refer to the instrument user manual for complete operation instructions (Thermocycler, IntelliPlex 1000 πCode Processor and PlexBio 100 Fluorescent Analyzer).

Software Installation

The PIK3CA Mutation Kit has a designated Kit App and ENC file. The Kit App contains the πCode target assignments and the ENC file includes the lot number and expiration date. Please make sure you have the Kit App installed and the ENC file imported into DeXipher before your first assay run.

Kit App Installation

1. Log into www.plexbio.com and download the **PIK3CA Mutation Kit App**.
2. Click on the "Installer" in the APP folder and follow the instructions to complete Kit App installation.

NOTE:
The Kit App only needs to be installed once. Version updates will be notified by customer service.

ENC File Installation

1. Log into www.plexbio.com and download the **PIK3CA Mutation Kit** ENC file. Each kit lot number will have a unique ENC file, so you will need to download a new ENC file each time you purchase a kit with a different lot number. Make sure to select the ENC file with the lot number that corresponds to your RUO kit.
2. Save the ENC file to your computer.
3. Follow the PlexBio 100 Fluorescent Analyzer User Manual to import the ENC file.

9. SAMPLES

The **IntelliPlex PIK3CA Mutation Kit** supports a variety of samples, including the use of formalin-fixed paraffin embedded tissue (FFPET). The nucleic acid of all samples must be extracted with a purification procedure supporting downstream PCR amplification.

NOTE FOR USE OF FFPET:

- FFPET specimens may be stored ≤ 30°C for up to 12 months after the date of tissue collection and processing. The optimal tissue fixation time for test should be less than 72 hr.
- Only FFPET sections of 10-µm thickness containing at least 10% tumor content are to be used in the PIK3CA Mutation Test. Any specimen containing less than 10% tumor content should be macro-dissected prior to deparaffinization.
- Do not use stained FFPE specimens which could generate invalid and/or incorrect results.

Storage of Extracted DNA

Extracted DNA can be stored at 2°C to 8°C for immediate use (≤ 24 hours), or at -15°C to -25°C for long-term (> 24 hours) storage. Do not subject the extracted DNA to repeated freeze/thaw cycles.

10. BEFORE YOU START

1. Check that the Kit App has been installed and the lot specific ENC file has been imported to DeXipher.
2. Check that you have 20 µL of extracted DNA (0.5 ng/µL) ready for analysis.

11. ASSAY PROCEDURE

Warning:
Read the instructions carefully and follow every step of the assay protocol correctly.

11.1 DNA Quantification

1. Quantify the extracted DNA using a Qubit Fluorometer with dedicated quantitative reagents (or equivalent) according to the manufacturer's protocol.
2. The DNA stock concentration should be ≥ 0.5 ng/µL to ensure optimal assay performance. Each PCR reaction uses 20 µL of a 0.5 ng/µL DNA stock (10 ng DNA input). DNA input amounts lower than 10 ng per reaction well are not recommended.

11.2 Multiplex PCR Amplification

1. Vortex to mix each sample before use.
2. Spin down and keep samples on ice.
3. Prepare the PCR Reaction:

For each PCR reaction:

PIC3KA Reaction Mix	10 µL
PIC3KA Primer Mix	10 µL
Sample/POS Control/NEG Control	20 µL
Total volume	40 µL

NOTE:

- The amount of Reaction Mix and Primer Mix required depends on the number of reactions.
- Both POS Control and NEG Control are required for test validity and report generation and must be included in each assay run.

4. Mix by tapping the tubes and spin down before placing the tubes on the thermocycler. Set up the PCR program conditions as below:

PCR Program Conditions*

Temp. (˚C)	Time	Cycles
95	5 min	-
95	20 sec	36
70	20 sec	
55	20 sec	
60	25 sec	
4	Hold	-

NOTE: *Ramp rate: 20% (PlexBio; Cat. No. 80018). 3°C/sec (ABI MiniAmp™; Cat. No. A37834).*

11.3 DNA Hybridization and SA-PE Reaction

1. **Prepare 1X Wash Buffer:** Transfer 50mL of the 10X Wash Buffer to the IntelliPlex 1000 πCode Processor 1L Wash Buffer bottle and add 450 ml ddH_2O. Mix by swirling.

NOTE: The prepared 1X Wash Buffer can be used for up to one week.

IntelliPlex 1000 πCode Processor Wash Buffer consumption:

Procedure	Wash Buffer Consumption (mL)
Self-test	50
DNA & RNA program (1 lane, up to 8 tests)	150
DNA & RNA program (3 lanes, up to 24 tests)	220

2. **Add 20 µL πCode MicroDisc to 96 well plate:** Mix by vortexing the **PIK3CA πCode MicroDisc** for 10 seconds, then, by pipetting, add 20 µL of the πCode to each well directly. Vortex the tube of πCode every four wells in between dispensing to ensure homogeneous suspension.

   NOTE: Each amplified PCR products (including samples, POS and NEG control) should be added into wells respectively in order of A1, B1…H1 and followed by A2, B2…H2 and so on.

3. **Add 100 µL of PIK3CA Hy Buffer** to each well.

4. Spin down the PCR products.

5. **Denature the PCR products** on the thermocycler by heating at 95˚C for 5 minutes, immediately cooled on ice/cooler or thermocycler to ensure the denatured status. Spin down before use. Use immediately (within 1 hour after denaturation).

   NOTE: Pay attention to the lid temperature of thermocycler while taking out the denatured PCR products.

6. **Add 10 µL of the denatured PCR products** to each well.

7. **Pipet the desired volume of SA-PE solution** into the SA-PE solution tank (V Tray). Please note that the dead volume of V Tray is **500 µL** for up to 6 selected lanes or **800 µL** if more than 6 lanes are selected. The minimum usage of SA-PE is **one lane (900 µL)**.

   Calculation Example:
   For a 3-lane reaction, the required SA-PE solution volume is at least:
   400 µL x 3 rows + 500 µL(dead volume)= 1.7 mL
   It is recommended to add extra solution volume into the V Tray to ensure sufficient dispensing volume.

   NOTE:

   Required SA-PE Solution by Lane(s):

Number of Processed Lane(s)	Required SA-PE Solution (µL)
1	900
2	1300
3	1700
4	2100
5	2500
6	2900
7	3600
8	4000
9	4400
10	4800
11	5200
12	5600

   - SA-PE solution should be kept in the dark.
   - **Do not** reuse the leftover SA-PE solution and V Tray tank. Replace a new V Tray with every assay run.

8. **Run hybridization and wash:** This assay uses the **DNA/RNA program** in the **Molecular Assay** window of the IntelliPlex 1000 πCode Processor. Refer to the IntelliPlex 1000 πCode Processor operation manual and follow the instructions to set up the built-in assay program (Homepage/ Molecular Assay/ Well Selection/ DNA/RNA/ Confirm procedure conditions/ Start Running). The plate will be ready for decoding once the program is finished.

   NOTE:
   - IntelliPlex 1000 πCode Processor must be maintained properly and regularly.
   - **Do not** open the door when the instrument is in operation.
   - The kit contains sufficient reagents for 5 runs of tests (including POS and NEG controls) for a maximum of 24 tests. Please note that the included Wash Buffer is only sufficient for up to two independent runs. Additional Wash Buffer can be ordered from PlexBio (Ref. No: 80210).

11.4 Image Decoding and Fluorescent Detection

1. Follow the PlexBio 100 Fluorescent Analyzer User Manual to set up the read.

   NOTE:

- PlexBio 100 Fluorescent Analyzer must be calibrated regularly (once per month).
- Check that the correct ENC file has been imported.

2. Launch DeXipher to run the **Qualitative Assay**.
3. Mark the wells for sample, positive and negative controls.
4. Enter sample information and assay name. Place the plate into the device with the correct orientation as shown on the screen.
5. The raw data will be analyzed through the kit ENC to generate the mutation call report.

NOTE:

- A single run can include from 2 to 96 tests (including POS and NEG controls) per 96 well Microwell plate. When running more than 24 specimens, multiple IntelliPlex PIK3CA Mutation Kits of the same lot will be required.
- The procedure described above must be followed to detect ≥ 0.2~2.08% mutant sequences in a background of wild-type DNA for the PIK3CA mutations in Table 1.

12. DISCLAIMERS

Negative Test Result

A negative test result means that the targeted mutation was not detected by the kit. Experimental errors or other causes may lead to false negative results. Interpretation of the results should consider these possibilities.

Positive Test Result

A positive test result means that the targeted mutation was detected by the kit. Experimental errors or other causes may lead to false positive results. Interpretation of the results should consider these possibilities.

13. INTERPRETATION OF RESULTS

Table 2. Interpretation of Result

Test Result	Reported Result	Interpretation
Mutation Detected	Ex. E542K (Refer to Table 1 for details)	Targeted mutation detected
Mutation Not Detected	None	Targeted mutation not detected
Invalid Assay	Invalid	**Possible Causes:** 1. PCR Inhibition (presence of inhibitor in the sample) 2. Improper stored reagents 3. Low sample DNA input or quality 4. Low πCode Disc Count (the πCode tube was not vortexed before pipetting) 5. Reagent not added 6. Failed Blank πCode Control 7. Sample quality due to improper fixation process or storage condition

NOTE:

In case of heterogeneity of samples or multiple mutations, only the dominantly detected mutation is reported. “Mutation Detected” indicates that the signal for at least one mutation site is greater than the cutoff value of the corresponding target. When multiple mutations are detected in a sample, only the one that exhibits the highest signal is reported.

14. TROUBLESHOOTING

The troubleshooting listed below addresses possible problem causes and solutions provided during assay procedures.

Problem	Possible Cause	Recommendations
No Valid Assay Assigned	1. No plate inserted. 2. Plate inserted in wrong orientation. 3. No assay APP installed. 4. No ENC file imported. 5. Two or more lots of reagent used.	1. Confirm plate is inserted and repeat reading. 2. Confirm orientation of plate and repeat reading. 3. Install assay APP and repeat reading. 4. Import ENC file and repeat reading. 5. One reagent lot used at a time.
Positive Control Fail / Negative Control Fail	1. No POS Control or NEG Control added. 2. DNase contamination. 3. Assay did not work. 4. Cross contamination between samples. 5. Wrong PC/NC wells chose.	1. Ensure POS Control and NEG Control are added. 2. Ensure all operating procedures are followed correctly. Ensure work environment is free of DNase. 3. Make sure all the assay procedures are followed correctly. 4. Clean all surfaces and equipment. Operate pre-PCR and post-PCR in the dedicated area and separate the equipment for use. 5. Choose the correct PC/NC wells and repeat reading.

Problem	Possible Cause	Recommendations
πCode MicroDiscs Count Fail	DeXipher is unable to detect sufficient πCode MicroDiscs numbers for mutation determination.	
	1. πCode MicroDiscs are not proper dispersed in the well.	1. Re-disperse the microplate using IntelliPlex 1000 Processor and repeat reading.
	2. Not enough πCode MicroDiscs added to well.	2. Ensure πCode MicroDiscs are well-mixed with proper amount added.
	3. Microbes exist in buffers.	3. Use freshly prepared wash buffer and ddH_2O for hybridization to reduce πCode MicroDiscs loss rate.
	4. Instruments error or malfunction.	4. Contact PlexBio Customer Service.
SA-PE Monitor Control Fail	Performance of SA-PE is assessed by the SAPE Monitor Control.	
	1. No SA-PE was added or insufficient SA-PE solution for dispensing.	1. Make sure all the assay procedures are followed correctly. Calculate sufficient SA-PE solution volume for dispensing. Repeat test.
	2. SA-PE solution inactivation.	2. Ensure correct storage condition and minimize the light exposure. Do not use SA-PE past its expiration date.
	3. Incorrect tested lanes of microplate selected for SA-PE solution dispensing.	3. Repeat assay and make sure rows selected correctly.

Problem	Possible Cause	Recommendations
Blank Control Fail	"Background" is determined by measuring MFI of an internal control that should not give a signal.	
	1. Wrong hybridization conditions.	1. Check correct hybridization program is selected.
	2. Residues of SA-PE solution in wells after hybridization.	2. Ensure all buffers (Wash buffer and ddH_2O) on IntelliPlex 1000 Processor are fresh-made and sufficient for washing procedures.
	3. PlexBio 100 Fluorescent Analyzer is not calibrated.	3. Perform calibration on PlexBio 100 Fluorescent Analyzer.
	4. Markings on plates.	4. Do not make any marking on plate.
Internal Control Fail	Internal Control monitors all steps in the procedure and must be positive.	
	1. PCR inhibition exists.	1. Follow instructions of sample extraction carefully. Ensure required temperature ranges and centrifugation needs are complied. Ensure complete removal of ethanol.
	2. PCR procedures are not performed correctly.	2. Make sure all PCR procedures are followed correctly. Do not to use expired materials or mixed lots of reagents. Ensure storage conditions are correct.
	3. DNase contamination.	3. Ensure all the operating procedures are followed correctly. Ensure work environment is free of DNase.
	4. Hybridization did not work.	4. Make sure all the assay procedures are followed correctly. Ensure samples are freshly heat-denatured.

Problem	Possible Cause	Recommendations
Reference Gene Fail	Reference Gene monitors quality of tested sample and must be positive.	
	1. No Sample added or absence of human-derived DNA.	1. Ensure human-derived DNA samples are added. Do not use artificial DNA as samples which may generate invalid results.
	2. Insufficient sample input for assays or poor sample quality.	2. Quantify samples and check the sample input and quality. If still remains failed, ensure the collected samples meet specimen requirements. Retest with new samples if needed.
	3. PCR inhibition exists.	3. Follow sample extraction instructions carefully. Ensure required temperature ranges and centrifugation needs are complied. Ensure complete removal of ethanol.
	4. PCR procedures are not performed correctly.	4. Make sure all PCR procedures are followed correctly. Do not to use expired materials or mixed lots of reagents. Ensure storage conditions are correct.

15. SYMBOLS

Symbol	Explanation	Symbol	Explanation
RUO	For research use only	REF	Catalog number
LOT	Batch number		Consult instructions for use
	Manufacturer		Use by Date
	Temperature limitation		Caution
	Contains sufficient for <n> tests		Date of Manufacture

Notice to User

The use of this product and the associated PlexBio instrumentation is covered by one or more issued (US10302640B2, US10436778B2, US10436776B2, US9063044B2, US10019815B2) and pending US and foreign patents owned by PlexBio Co., Ltd. The purchase of this product includes nontransferable rights to use this amount of the product to practice the methods described therein. No general patent or other license of any kind other than this specific right of use from purchase is granted. Further information on purchasing licenses for other applications can be obtained from PlexBio Co., Ltd. 6F-1, No. 351, Yangguang St., Neihu District, Taipei City 11491, Taiwan.

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