ImageneSeq

Panel completo para el diagnóstico molecular

Reporte Clínico

Paciente: [redacted]

Imagene Health ID: Q587-O266-U217

Paciente

[redacted]

1966-4-18

Q587-O266-U217

Tipo de muestra: Sólida

Médico Tratante

[redacted]

Panel

Diagnóstico: Cáncer de pulmón de células no pequeñas

Fecha: 2022-11-03

Panel: ImageneSeq

Hallazgos Clínicamente Relevantes

Variantes con Clasificación I

Gen	Variante (Lecturas – Frec Alélica %)	Terapia blanco	Implicación clínica	Patogenicidad	Nivel de evidencia
KRAS	p.G12C c.34G>T (820 - 14)	Sotorasib Adagrasib	Sensibilidad	Patogénica	1A
		Afatinib Erlotinib Gefitinib	Resistencia	Patogénica	1A

Variantes con Clasificación II

Gen	Variante (Lecturas – Frec Alélica %)	Terapia blanco	Implicación clínica	Enfermedad relacionada	Patogenicidad	Nivel de evidencia
TP53	p.G105C c.313G>T (1646 - 24)		Diagnóstico	Síndrome de Li-Fraumeni	Patogénica	2C
RECQL4	p.R766fs*77 c.2296delC (1127 - 100)		Diagnóstico	Síndrome de Rothmund-Thomson	Probablemente Patogénica	2C
KMT2C	p.Y826* c.2447dupA (4744 - 50)		Pronóstico	Cáncer de pulmón	Patogénica	2C

Variantes con Clasificación III

Gen	Variante (Lecturas – Frec Alélica %)	Implicación clínica	Enfermedad relacionada	Patogenicidad	Nivel de evidencia
HNF1A	p.G292fs*25 c.872dupC (33 - 100)	Pronóstico	Cáncer de pulmón	Patogénica	3
KMT2B	p.R1021fs*14 c.3059dupG (310 - 100)	Pronóstico	Cáncer de pulmón	Probablemente Patogénica	3

Perfil Molecular para Inmunoterapia

Carga Mutacional del Tumor (TMB)	Terapia blanco	Nivel de evidencia	Estabilidad Microsatelital (MSI)
TMB-high 14 mut/mb	Pembrolizumab*, Nivolumab más Ipilimumab	1A	MSI-low

*Aprobado por la FDA para el tratamiento de pacientes con TMB > 10 mut/mb

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Resumen del Reporte ImageneSeq

La secuenciación masiva determinó variantes en los siguientes genes:

Variantes de clasificación I
Se identificó una variante en el gen *KRAS* (c.34G>T / p.G12C); *KRAS* es un oncogen frecuentemente mutado en numerosos tipos de cánceres, se cuenta con extensa evidencia de su rol en el desarrollo y progresión tumoral.

La variante p.G12C se encuentra 13% de los cánceres de pulmón de células no pequeñas (CPCNP), y ocasiona una ganancia de función del gen que activa la vía RAS resultando en proliferación celular y evasión de apoptosis, la variante p.G12C está relacionada con tabaquismo [336-339]. Las mutaciones en *KRAS* son de pobre pronóstico y han sido asociadas con respuesta reducida a terapia *EGFR* TKIs (Afatinib, Erlotinib, Geftinib), estas variantes no parecen afectar la eficacia de la quimioterapia [336]. A continuación se describen las terapias dirigidas con Sotorasib y Adagrasib para la variante p.G12C en CPCNP aprobadas por la FDA.

Sotorasib es un inhibidor selectivo de *KRAS* G12C, es recomendado por la NCCN para tratamiento del CPCNP avanzado o metastásico como terapia subsecuente en pacientes con la variante p.G12C, encontrada en el presente caso, con base en los resultados del ensayo clínico CodeBreaK100 (n=124) de fase II, 37.1% de los pacientes presentaron respuesta objetiva, de los cuales 3.2% tuvieron repuesta completa y 33.9% respuesta parcial, con supervivencia libre de progresión 6.8 meses y 12.5 meses mediana de supervivencia global [340].

De manera similar Adagrasib es otro inhibidor selectivo de *KRAS* G12C, recientemente aprobado por la FDA para tratamiento de CPCNP avanzado o metastásico con base en los resultados del ensayo clínico KRYSTAL-1 (n=112) de fase II en pacientes con la variante p.G12C que habían recibido previamente quimioterapia e inmunoterapia con una mediana de seguimiento de 15.6 meses, el 42.9% de los pacientes presentaron respuesta objetiva, la mediana de supervivencia libre de progresión fue de 6.5 meses y la supervivencia global fue 12.6 meses (CI 9.2 -19.2), los pacientes con metástasis cerebral mostraron una respuesta objetivo de 33% [341], cabe señalar que Adagrasib aún no se encuentra mencionado en las guías clínicas de NCCN.

Se han descrito diversos mecanismos de resistencia a la terapia con Sotorasib y Adagrasib entre ellos la mutación en lugares diferentes de *KRAS* y la activación de otras vías moleculares, se han detectado alteraciones genómicas adquiridas durante la terapia hasta en el 28% de los pacientes tratados con Sotorasib y 45% de los pacientes tratados con Adagrasib [342, 343].

Se detectó carga mutacional del tumor (TMB por sus siglas en ingles) de 14 mut/Mb, clasificada como alta (H-TMB), la H-TMB es un biomarcador para uso de inhibidores de checkpoints inmunológicos. A continuación se describen las terapias dirigidas con Pembrolizumab, Nivolumab, Durvalumab y Tremelimumab para H-TMB en CPCNP aprobadas por la FDA.

Hay varios ensayos clínicos en CPCNP que evalúan la aplicabilidad de la alta carga mutacional como primera línea de tratamiento con Pembrolizumab, Nivolumab, Ipilimumab, Durvalumab y Tremelimumab versus quimioterapia (QT) basada en platino y aunque hay limitaciones metodológicas, la H-TMB e inmunoterapia está asociada con mejor respuesta: en un meta-análisis reciente de estas metodologías en CPCNP (n=3838), H-TMB e inmunoterapia se asoció a mejor repuesta objetiva RR: 1.37 y supervivencia libre de progresión HR: 0.69, sugiriendo un rol positivo de H-TMB como biomarcador de inmunoterapia [344], sin embargo todavía la NCCN no recomienda H-TMB como biomarcador de inmunoterapia por falta de suficiente información [336].

En el ensayo clínico fase III KEYNOTE-042 en CPCNP se analizó Pembrolizumab Vs quimioterapia basada en platino, fueron evaluables 793/1274 pacientes para TMB, encontrando una tasa de respuesta en pacientes con Pembrolizumab de 34.4% en el grupo H-TMB Vs 18.8% en el grupo L-TMB, la supervivencia libre de progresión fue HR 0.75 en H-TMB Vs 1.27 L-TMB, mediana de supervivencia global 21.9 meses en H-TMB Vs 12.0 meses en L-TMB, supervivencia global HR: 0.62 Vs 1.09, el punto de corte para TMB fue 175 mut/exoma [344, 345].

En el ensayo clínico fase III CheckMate 227 en CPCNP se analizó Nivolumab más Ipilimumab Vs quimioterapia, fueron evaluables 1004/1739 pacientes para TMB, la respuesta objetiva fue 45.3% en el grupo H-TMB Vs 26.9% grupo control QT, la supervivencia libre de progresión fue HR: 0.58 H-TMB Vs 1.07 L-TMB, la mediana de supervivencia libre de progresión fue 7.2 meses Vs 5.5 meses, supervivencia global HR: 0.68 Vs 0.75, el punto de corte para TMB fue 10 mut/Mb [344, 346].

En el ensayo clínico fase III MYSTIC en CPCNP se analizó Durvalumab más Tremelimumab Vs quimioterapia estándar, fueron evaluables 809/1118 pacientes con CPCNP, encontrando la respuesta objetiva en el grupo H-TMB fue 48.4% Vs 16.7% en L-TMB, la supervivencia libre de progresión fue HR: 0.53 en H-TMB Vs 1.55 en L-TMB, mediana de supervivencia global H-TMB 21.9 Vs 10 meses grupo control QT, supervivencia global HR: 0.49 H-TMB Vs1.16 grupo control QT, el punto de corte para TMB fue 20 mut/Mb y este estudio fue biopsia líquida a diferencia de los anteriores [344, 347].

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Variantes de clasificación 2

Se detectó una variante en el gen *TP53* (c. 313>T / p.G105C) el cual se relaciona con pérdida de función del gen. El gen *TP53* es el mas extensamente estudiado y está presente en un gran número de malignidades al verse alterado en aprox. 50% de las neoplasias; *TP53* regula el ciclo celular al detectar errores/daños en el DNA, induciendo reparación o apoptosis; el defecto en esta función lleva a división aberrante de células potencialmente oncogénicas [348]. Variantes con pérdida de función de *TP53* evaluado en estudios clínicos se ha asociado a relativo peor pronóstico y tendencia a resistencia a quimioterapia (en comparación con *TP53* silvestre) [348, 349]. Hay varios ensayos clínicos fase I en curso pero actualmente no se cuenta con terapia dirigida aprobada para cáncer de pulmón para *TP53*. Cabe señalar que se ha descrito cáncer de pulmón en pacientes con Síndrome Li-Fraumeni y mutaciones de línea germinal en *TP53* [359].

Se identificó una variante en el gen *KMT2C* (c.2447dupA / p.Y816*) resultando en perdida de función del gen. Este gen codifica para una histona metiltransferasa fuertemente relacionada en remodelación de la cromatina y regulación epigenética. Recientes reportes asociaron la pérdida de función de este gen en desarrollo de metástasis y en general, mal pronóstico [350, 351]. Se ha asociado mutaciones en el gen *KMT2C* a alta carga mutacional del tumor, y con mutaciones del gen *TP53*, en cuyo caso hay un posible efecto sinérgico para la alta carga mutacional del tumor, y puede ser utilizado como un posible predictor positivo de tratamiento con inmnunoterapia [352, 353].

Se identificó una deleción en el gen *RECQL4* (c.2296delC) causando un desplazamiento de marco y como consecuencia pérdida de función del gen. El gen codifica para una helicasa involucrada en replicación, recombinación y reparación del DNA, apuntándole como un oncogén y está relacionado con Síndrome Rothmund-Thomsom [354], sin embargo, cáncer de pulmón no hace parte del espectro de cánceres comunes en este síndrome. El gen *RECQL4* se ha identificado alterado en varios tipos de cáncer y relacionado con mal pronóstico (p.e. próstata) así como quimioresistencia a varios fármacos basados en platinos [355].

Variantes de Clasificación 3

Se identificó una variante en el gen *HNF1A* (c.872dupC) causando un desplazamiento de marco y proteína trunca con pérdida de función del gen. Estudios recientes apuntan que en cáncer de pulmón de células no pequeñas sobreexpresión del RNA antisentido (*HNF1A-AS1*) proveniente del gen en cuestión resulta en efectos oncogénicos (proliferación celular) en modelos de cáncer de pulmón [356]. Estudios siguen en curso para elucidar que mecanismos afectan y posibilidad de actuar como un blanco terapéutico o inducir sensibilidad a otras terapias (p.e. radioterapia) [357].

Se encontró una variante en el gen *KMT2B* (c.3059dupG) resultando en un desplazamiento de marco de lectura y proteína trunca, similar al *KMT2C*, es una histona metiltransferasa. Reportes indican que defectos en la función del gen lleva a reprogramación epigenética con efectos oncogénicos en CPCNP [358], hay escasa información referente a este gen, estudios siguen en curso.

Variantes descritas en guías clínicas no encontradas

No se encontraron variantes patogénicas en los genes *EGFR, ALK, ROS1, BRAF, NTRK, MET, RET, HER2.*

Recomendaciones

Se sugiere estudio de NGS en saliva y asesoramiento genético para descartar síndrome Li-Fraumeni y el síndrome de Rothmund-Thomson.

Limitantes del estudio

Este análisis no permite una diferenciación definitiva entre variantes somáticas y germinales, en caso de sospecha de cáncer hereditario se sugiere estudio de NGS en saliva y asesoramiento genético.

Desarrollo de Hallazgos Moleculares

KRAS

KRAS es un oncogen que codifica K-Ras, un miembro de la familia de proteínas de membrana Ras que se unen a GDP/GTP y que poseen actividad GTPasa. La activación de la señalización por Ras ocasiona crecimiento celular, diferenciación y supervivencia mediante la activación de la vía de cinasas Raf/MEK/ERK y la vía PI3K/Akt [209, 121]. El gen *KRAS* está frecuentemente mutado en varios tipos de cáncer, con alta incidencia en cáncer de páncreas, colorectal y pulmón [66, 85, 65].

TP53

El gen *TP53* codifica al supresor de tumor p53, una proteína involucrada en el checkpoint de daño al ADN del ciclo celular y ocasiona arresto al ciclo celular cuando detecta daño en el ADN. p53 puede activar genes de reparación de ADN o inducir apoptosis en presencia de daño al ADN [144]. La pérdida de p53 es común en cánceres agresivos avanzados [20]. Los portadores de mutaciones de línea germinal en *TP53* tienen el Síndrome de Li-Fraumeni, un síndrome de cáncer hereditario que resulta en múltiples tumores durante la adultez temprana, incluyendo cáncer de mama, tumores cerebrales y leucemias [221, 162, 238]. La expresión de p53 en células normales es baja, sin embargo, las alteraciones en *TP53*, incluyendo aquellas que resultan en pérdida de la función de supresor de tumor de p53, pueden ocasionar estabilización y expresión elevada de p5, particularmente en el núcleo. Varios estudios han demostrado que esto puede tener efectos oncogénicos [131, 123, 270, 191, 102].

KMT2C

KMT2C codifica la Histona-lisina-N-metiltransferasa 2C, también conocida como MLL-3, una enzima que es parte del complejo coactivador transcripcional y que está involucrada en la modificación de histonas y la regulación positiva de la transcripción [10, 140, 16]. MLL3 es un supresor de tumor involucrado en varios procesos celulares, incluyendo regulación de homeostasis y señalización de receptores de hormonas [10, 16, 126]. Las mutaciones que inactivan MLL3 y la regulación negativa de la expresión de MLL-3 se han reportado en varios tumores y se ha encontrado que participan en la tumorigénesis [289, 192, 122, 138, 31, 277].

RECQL4

El gen *RECQL4* codifica la ADN helicasa Q4 dependiente de ATP (RecQ4, RTS, proteína tipo RecQ 4). RecQ4 participa en la replicación del ADN, reparación del ADN y mantenimiento del ADN mitocondrial y telomérico [38, 39]. Las variantes patogénicas en RecQ4 resultan en disfunción telomérica y en alteraciones en la replicación y reparación del ADN nuclear y mitocondrial [39]. El mRNA de *RECQL4* y la expresión protéica de RecQ4 están incrementados en varios tipos de tumor comparado con tejido normal. Se sugiere que RecQ4 tiene participación en la proliferación celular y tumorigénesis en varios tipos de cáncer [161, 242, 63, 136, 11].

HNF1A

HNF1A (factor nuclear de hepatocito 1-alfa, o HNF-1-alfa) es un factor de transcripción involucrado en la regulación de múltiples genes [15, 208]. La proteína HNF-1-alfa, también conocida como TCF1, interactúa con otros reguladores de la transcripción como beta-catenina, miembros de la familia ATF2 y Smads para modular la activación transcripcional, e interactúa con TLE1 para reprimir la transcripción [135, 46, 80]. *HNF1A* actúa como supresor de tumor en varios tipos de cáncer, como cáncer de hígado, linfoma y neoplasias de células renales [142, 153, 198, 251].

KMT2B

KMT2B, también conocido como MLL4 o MLL2, codifica la proteína MLL-4, un miembro de la familia de histona metiltransferasas. MLL-4 regula tri-metilación de histona 3 lisia 4 (H3K4me3), una modificación central para la regulación de la transcripción [109, 7, 105, 50]. MLL-4 promueve el crecimiento de células de carcinoma de mama y colorrectal, además que está sobre-expresada en tejidos de estos tipos de carcinoma en comparación con tejido normal [182, 9, 240]. Además, las fusiones o reordenamientos que involucran a *KMT2B/MLL4* se han reportado en algunos carcinomas como el carcinoma hepatocelular, en donde es frecuente encontrar la integración de DNA del virus de hepatitis B (HBV) en KMT2B/MLL4 [245, 218, 189, 56, 183].

Carga de mutación tumoral alta

La carga de mutación tumoral alta (TMB, por sus siglas en inglés) alta indica la presencia de un número elevado de mutaciones somáticas no sinónimas en regiones codificantes del genoma de una célula tumoral, expresada en mutaciones por megabase (mut/Mb) de ADN de tumor secuenciado [290, 95, 168]. Altos niveles de TMB pueden estar asociadas con mantenimiento anormal del genoma debido a reparación por mismatch (MMR) del ADN defectuosa, inestabilidad microsatelital (MSI) alta, mutaciones en el dominio de exonucleasa de la ADN polimerasa eta (POLE) o mutaciones en los miembros de la familia APOBEC [5, 103]. Además, la TMB alta puede ocurrir como resultado de exposición a carcinógenos ambientales como el humo de tabaco y radiación ultravioleta [5, 27]. Mientras que la mayoría de los tumores con MSI alta también tienen TMB alta, sólo algunos tumores con TMB alta tienen MSI alta [29]. La TMB se correlaciona con la carga de neoantígenos en células tumorales. Se espera que una TMB alta resulte en un incremento en la presentación de neoantigenos por proteínas MHC en la superficie celular, incrementando la probabilidad de reconocimiento de células tumorales y citólisis por linfocitos que se infiltran en el tumor (TIL) [234, 258]. La TMB alta también puede ser un factor pronóstico asociado con mejor supervivencia del paciente [108, 110]. Hay evidencia clínica que asocia alta TMB con sensibilidad y respuesta a inhibidores de checkpoint inmunológico como nivolumab, ipilimumab, pembrolizumab y atezolizumab en algunos tipos de cáncer como cáncer de pulmón de células no pequeñas, melanoma, carcinoma urotelial y cáncer colorrectal [30, 78, 258, 214, 216, 70]. La TMB y la expresión de PD-L1 son biomarcadores con valor para predecir respuesta a inmunoterapia [286, 93, 213, 92].

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Q587-O266-U217

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Reporte de Patología

Médico Patólogo	Prueba realizada por	Revisión por	Diagnosticado por
[redacted]	Imagene Heatlh	Dr. Carlos González Dr. Herbert García	[redacted]

Control de Calidad de Patología

Imagene ID	Contenido tumoral	Conc (ng/µl)	Cantidad Total (ng)	Reporte de QC
Q587-O266-U217	40	5.786	260.37	2022-10-27

CARLOS ALBERTO GONZALEZ VILLARREAL
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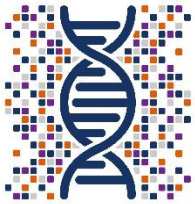
Certificado Consejo Mexicano de Genética 2017-2022
Posgrado Bioinformática Clínica

[redacted]

Q587-O266-U217



[redacted]

Estadísticas de Calidad de la Secuencia Genética

Imagene ID	Lecturas crudas (Gb)	Datos crudos (Gb)	Efectivos (%)	Tasa de error (%)	Q30 (%)	GC (%)
Q587-O266-U217	82.58	12.39	99.56	0.04	90.90	47.77

Estadísticas del Mapeo, Cobertura y Profundidad

Imagene Health ID:	Q587-O266-U217
Library Namex:	TDNA220043210-1A
Coverage of Target (%):	100.00
Average Sequencing Depth on Target:	1332.00
Duplication Rate:	53.92
Probe Capture Ratio (%):	65.02
Total Bases Num in BAM (Mb):	12332.57
Total Reads Num in BAM:	82440560
Mapping Reads Num:	82169929
Mapping Rate (%):	99.67
Mismatch Rate in Target Region (%):	0.4114
Mismatch Rate in All Effective Sequence (%):	0.9376
Target Region Size (bp):	2689765
Total Mapped Base Num after RmdUp (Mb):	6234.11
Average Read Length (bp):	149.59
Read Num On Target Before RmdUp:	63698614
Read Num On Target After RmdUp:	29354287
Base Num On Target After RmdUp (Mb):	3582.77
Site Num Covered On Target (bp): Base Covered On Target:	2689634
Fraction of Target Covered With At Least 10x(%):	99.96
Fraction of Target Covered With At Least 50x(%):	99.78
Fraction of Target Covered With At Least 200x(%):	98.63
Fraction of Target Covered With At Least 500x(%):	93.46
Fraction of Target Covered With At Least 1000x(%):	71.41
Fraction of Target Covered With At Least 1500x(%):	37.74
Fraction of Target Covered With At Least 2000x(%):	12.72

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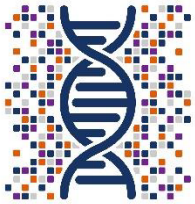
Q587-O266-U217



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Descripción Detallada de las Variantes

Variantes de Clasificación I

Cromo-soma	Cambio genómico	Gen	Cambio en Proteína	Cambio en Transcrito	ID de transcrito	Tipo de variante	Impacto en proteína	Frec. Alélica %	Lecturas	Nivel de evidencia	Patoge-nicidad
12	g.25398285C>A	*KRAS*	p.G12C	c.34G>T	NM_004985.5	SNV	missense	14	820	1A	Patogénica

Variantes de Clasificación II

Cromo-soma	Cambio genómico	Gen	Cambio en Proteína	Cambio en Transcrito	ID de transcrito	Tipo de variante	Impacto en proteína	Frec. Alélica %	Lecturas	Nivel de evidencia	Patoge-nicidad
17	g.7579374C>A	*TP53*	p.G105C	c.313G>T	NM_000546.6	SNV	missense	24	1646	2C	Patogénica
8	g.145738769delG	*RECQL4*	p.R766fs*77	c.2296delC	NM_004260.4	Deletion	frameshift	100	1127	2C	Probablemente Patogénica
7	g.151945072_151945073insT	*KMT2C*	p.Y816*	c.2447dupA	NM 170606.3	Insertion	frameshift	50	4744	2C	Patogénica

Variantes de Clasificación III

Cromo-soma	Cambio genómico	Gen	Cambio en Proteína	Cambio en Transcrito	ID de transcrito	Tipo de variante	Impacto en proteína	Frec. Alélica %	Lecturas	Nivel de evidencia	Patoge-nicidad
1	g.11186866A>C	*MTOR*		c.6352-13T>G	NM_004958.4	SNV		50	1382	3	Significado incierto
1	g.162725003A>G	*DDR2*	p.I159V	c.475A>G	NM_001014796.3	SNV	missense	50	1580	3	Significado incierto
11	g.76257147G>T	*EMSY*	p.V1194L	c.3580G>T	NM_020193.5	SNV	missense	9.44	1758	3	Significado incierto
1	g.204506566C>T	*MDM4*	p.Q118*	c.352C>T	NM_002393.5	SNV	stop gain	4.15	1372	3	Significado incierto
1	g.206647743G>A	*IKBKE*	p.V53M	c.157G>A	NM_014002.4	SNV	missense	38	2265	3	Significado incierto
12	g.121432116121432117insC	*HNF1A*	p.P289fs*28	c.863_864insC	NM_000545.8	Insertion	frameshift	3.12	1251	3	Significado incierto
12	g.121432125_121432126insC	*HNF1A*	p.G292fs*25	c.872dupC	NM_000545.8	Insertion	frameshift	100	33	3	Patogénica
13	g.29001398G>T	*FLT1*	p.P445Q	c.1334C>A	NM_002019.4	SNV	missense	21	1375	3	Significado incierto
17	g.38487598C>G	*RARA*	p.T43S	c.128C>G	NM_000964.4	SNV	missense	50	360	3	Significado incierto
19	g.36214633_36214634insG	*KMT2B*	p.R1021fs*14	c.3059dupG	NM_014727.3	Insertion	frameshift	100	310	3	Probablemente Patogénica
22	g.22221726_22221728delGCC	*MAPK1*	p.A7del	c.20_22delCGG	NM_002745.5	Deletion	in-frame	50	134	3	Significado incierto
22	g.23653975_23653976insCCGG	*BCR*	p.V1094fs*17	c.3275_3278dupCCGG	NM_004327.4	Insertion	frameshift	18	2206	3	Significado incierto
2	g.225360697A>T	*CUL3*		c.1708-14T>A	NM_003590.5	SNV		50	887	3	Significado incierto
2	g.47705515C>A	*MSH2*	p.T772K	c.2315C>A	NM_000251.3	SNV	missense	50	1639	3	Significado incierto
3	g.52584433_52584434insCCT	*PBRM1*		c.4576+5_4576G	NM_018313.5	Insertion		50	1093	3	Significado incierto

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4	g.1061563 8 4G>A	*TET2*	p.G429R	c.1285G>A	NM_00112 7208.3	SNV	missense	50	1084	3	Significado incierto
4	g.18752151 4T>G	*FAT1*	p.I3881L	c.11641A>C	NM_00524 5.4	SNV	missense	50	1429	3	Significado incierto
4	g.20469430 G>A	*SLIT2*	p.V151I	c.451G>A	NM_00478 7.4	SNV	missense	5.83	463	3	Significado incierto
5	g.56177872_ 56177874 delACA	*MAP3K1*	p.T949del	c.2845_28 47delACA	NM_00592 1.2	Deletion	in-frame	50	1060	3	Significado incierto
6	g.32188401C >A	*NOTCH4*	p.D314Y	c.940G>T	NM_00455 7.4	SNV	missense	43	1050	3	Significado incierto
6	g.33288355_ 33288356i nsAGT	*DAXX*	p.L352dup	c.1054_105 6dupCTA	NM_00114 1969.2	Insertion	in-frame	50	1978	3	Significado incierto
7	g.1519455 71T>A	*KMT2C*	p.T650S	c.1948A>T	NM_17060 6.3	SNV	missense	11	839	3	Significado incierto
7	g.4172984 3C>T	*INHBA*	p.R229Q	c.686G>A	NM_00219 2.4	SNV	missense	49	902	3	Significado incierto
7	g.504680 80C>A	*IKZF1*	p.R439S	c.1315C>A	NM_00606 0.6	SNV	missense	11	1883	3	Significado incierto
8	g.930749 76T>C	*RUNX1T1*		c.- 24+32280A >G	NM_17563 5.3	SNV		50	1503	3	Significado incierto
X	g.1006136 41C>A	*BTK*	p.G313V	c.938G>T	NM_00006 1.3	SNV	missense	19	1611	3	Significado incierto
X	g.1321275 C>A	*CRLF2*	p.W160C	c.480G>T	NM_02214 8.4	SNV	missense	23	1778	3	Significado incierto
X	g.667651 61A>T	*AR*	p.Q58L	c.173A>T	NM_00004 4.6	SNV	missense	5.33	338	3	Significado incierto

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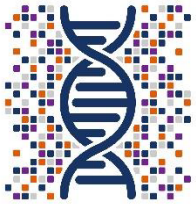

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Listado Genético

ABCB1	CCNE1	DNMT3A	GATA3	MAP2K4	PIK3R1	SMAD3
ABCC1	CD19	DOT1L	GATA4	MAP3K1	PIK3R2	SMAD4
ABCC2	CD22	DPYD	GATA6	MAP4K1	PKC/PRRT2	SMARCA1
ABCC3	CD274	DYNC2H1	GGH	MAPK1	PKC?	SMARCA4
ABCC4	CD33	E2F1	GID4	MAPK14	PKC?/PRKCE	SMARCB1
ABCC6	CD52	EGF	GLI1	MAPK8	PLCG2	SMARCD1
ABCG2	CD74	EGFR	GLI2	MAPK9	PLK1	SMO
ABL1	CD79A	EML4	GNA11	MAX	PMS1	SNAI1
ABL2	CD79B	ENOSF1	GNA13	MCL1	PMS2	SNAI2
ACTG1	CDA	EP300	GNAQ	MDM2	POLD1	SNCAIP
ACVR1B	CDC25C	EPCAM	GNAS	MDM4	POLE	SOCS1
ACVR2A	CDC42	EPHA3	GOPC	MED12	PPARG	SOD2
AIP	CDC73	EPHA5	GPC3	MEF2B	PPP2R1A	SOX10
AKT1	CDH1	EPHA7	GPR124	MEN1	PPP2R5B	SOX17
AKT2	CDK1	EPHB1	GRB2	MET	PRDM1	SOX2
AKT3	CDK12	EPHX1	GRIN2A	MITF	PREX2	SOX9
ALK	CDK2	ERBB2	GRM3	MLH1	PRF1	SPEN
AMER1	CDK4	ERBB3	GSK3B	MMP12	PRKAR1A	SPINK1
APC	CDK5	ERBB4	GSTA1	MMP14	PRKCI	SPOP
AR	CDK6	ERCC1	GSTM3	MMP9	PRKDC	SPTA1
ARAF	CDK7	ERCC2	GSTP1	MPL	PRSS1	SRC
ARFRP1	CDK8	ERCC3	H3F3A	MRE11A	PRSS8	STAG2
ARID1A	CDK9	ERCC4	HDAC1	MSH2	PTCH1	STAT3
ARID1B	CDKN1A	ERCC5	HDAC2	MSH3	PTCH2	STAT4
ARID2	CDKN1B	ERG	HDAC3	MSH6	PTEN	STK11
ASXL1	CDKN1C	ERRFI1	HDAC4	MTHFR	PTK2	STK4
ATIC	CDKN2A	ESR1/ER	HDAC6	MTOR	PTPN11	SUFU
ATM	CDKN2B	ETV1	HDAC8	MTR	QKI	SYK
ATR	CDKN2C	ETV4	HGF	MUTYH	RAC1	TAF1
ATRX	CEBPA	ETV5	HIF-1/HIF1A	MYB	RAC2	TBX3
AURKA	CEP57	ETV6	HNF1A	MYC	RAD50	TCF7L2
AURKB	CHD2	EWSR1	HOXB13	MYCL	RAD51	TEK
AXIN1	CHD3	EXT1	HRAS	MYCN	RAD51C	TERT
AXIN2	CHD4	EXT2	HSD3B1	MYD88	RAD51D	TET2
AXL	CHEK1	EZH2	HSP90AA1/HSP9(	MYO1B	RAF1	TGFBR1
BAP1	CHEK2	FAM46C	IDH1	NAT1	RANBP2	TGFBR2
BARD1	CIC	FANCA	IDH2	NAT2	RARA	TLR4
BAX	CNTNAP1	FANCB	IGF-1	NBN	RARB	TMEM127
BCL10	CNTNAP2	FANCC	IGF1R/IGFR	NCOR1	RASSF1	TMPRSS2
BCL11A	COL22A1	FANCD2	IGF2	NF1	RASSF8	TNF/TNF-alpha
BCL2	COMT	FANCE	IGF2R	NF2	RB1	TNFAIP3

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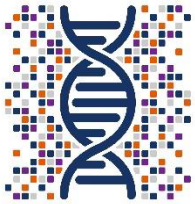

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BCL2L1	*COPS3*	*FANCF*	*IKBKB*	*NFE2L2*	*RBM10*	*TNFRSF11A*
BCL2L2	*CREBBP*	*FANCG*	*IKBKE*	*NFKBIA*	*RECQL4*	*TNFRSF14*
BCL6	*CRKL*	*FANCI*	*IKZF1*	*NKX2-1*	*REL*	*TNFSF11*
BCOR	*CRLF2*	*FANCL*	*IL7R*	*NOTCH1*	*RET*	*TOP1*
BCORL1	*CSF1R*	*FANCM*	*INHBA*	*NOTCH2*	*RHBDF2*	*TOP2A*
BCR	*CSMD1*	*FAS*	*INPP4B*	*NOTCH3*	*RHEB*	*TP53*
BIRC5	*CSMD3*	*FAT1*	*IRF2*	*NOTCH4*	*RHOA*	*TPMT*
BLCAP	*CTCF*	*FBXW7*	*IRF4*	*NPM1*	*RICTOR*	*TSC1*
BLK	*CTLA4*	*FCGR3A*	*IRS2*	*NRAS*	*RNF43*	*TSC2*
BLM	*CTNNA1*	*FGF10*	*ITK*	*NRG1*	*ROCK1*	*TSHR*
BMPR1A	*CTNNB1*	*FGF14*	*JAK1*	*NSD1*	*ROS1*	*TUBA1A*
BRAF	*CUL3*	*FGF19*	*JAK2*	*NTRK1*	*RPS6KA1*	*TUBB*
BRCA1	*CXCL10*	*FGF23*	*JAK3*	*NTRK2*	*RPS6KB1*	*TUBD1*
BRCA2	*CXCL8*	*FGF3*	*JUN*	*NTRK3*	*RPTOR*	*TUBE1*
BRD3	*CXCR4*	*FGF4*	*KAT6A*	*NUP93*	*RRM1*	*TWIST1*
BRD4	*CYLD*	*FGF6*	*KDM5A*	*OPRM1*	*RUNX1/AML1*	*TYMS/TS*
BRIP1	*CYP19A1*	*FGFR1*	*KDM5C*	*PAK1*	*RUNX1T1*	*U2AF1*
BTG1	*CYP1A1*	*FGFR2*	*KDM6A*	*PAK3*	*RUNX2*	*UGT1A1*
BTK	*CYP1A2*	*FGFR3*	*KDR/VEGFR*	*PALB2*	*SATB2*	*UGT1A9*
BUB1	*CYP1B1*	*FGFR4*	*KEAP1*	*PARK2*	*SBDS*	*UMPS*
BUB1B	*CYP2A6*	*FH*	*KEL*	*PARP1*	*SDHA*	*VEGFA*
BUB3	*CYP2B6*	*FLCN*	*KIAA0427*	*PARP2*	*SDHAF2*	*VEGFB*
C11orf30	*CYP2C19*	*FLT1*	*KIT*	*PARP3*	*SDHB*	*VHL*
C17orf108	*CYP2C8*	*FLT3*	*KLHL6*	*PARP4*	*SDHC*	*WEE1*
C8orf34	*CYP2C9*	*FLT4*	*KMT2A/MLL*	*PAX5*	*SDHD*	*WISP3*
CAMK2G	*CYP2D6*	*FOLR3*	*KMT2B*	*PBRM1*	*SETD2*	*WNT1*
CAMKK2	*CYP2E1*	*FOXA1*	*KMT2C/MLL3*	*PDCD1*	*SF3B1*	*WNT5A*
CARD11	*CYP3A4*	*FOXA2*	*KMT2D/MLL2*	*PDCD1LG2*	*SHH/Hedgehog*	*WNT6*
CASP7	*CYP3A5*	*FOXL2*	*KRAS*	*PDGFRA*	*SLC10A2*	*WRN*
CASP8	*CYP4B1*	*FOXO1*	*LMO1*	*PDGFRB*	*SLC16A7*	*WT1*
CBFB	*DAXX*	*FOXP1*	*LRP1B*	*PDK1*	*SLC19A1*	*XIAP*
CBL	*DDB2*	*FRS2*	*LRRK2*	*PEG3*	*SLC22A16*	*XPA*
CBR1	*DDR2*	*FUBP1*	*LYN*	*PHOX2B*	*SLC28A3*	*XPC*
CBR3	*DHFR*	*FYN*	*LZTR1*	*PIK3C2B*	*SLCO1B3*	*XPO1*
CCND1	*DICER1*	*GABRA6*	*MAGI2*	*PIK3CA*	*SLIT2*	*XRCC1*
CCND2	*DIRAS3*	*GATA1*	*MAP2K1/MEK1*	*PIK3CB*	*SLX4*	*YES1*
CCND3	*DIS3L2*	*GATA2*	*MAP2K2*	*PIK3CG*	*SMAD2*	*ZBTB2*
ZNF217	*ZNF703*					

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Listado Genético de Fusiones Analizadas

ALK	*BCR*	*BRAF*	*BRD4*	*ETV1*	*ETV4*	*ETV5*
ETV6	*EWSR1*	*FGFR1*	*FGFR3*	*JAK2*	*KMT2A*	*MYB*
NTRK1	*NTRK2*	*NTRK3*	*PPARG*	*RAF1*	*RET*	*ROS1*
TMPRSS2						

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Documentación del reporte

ASCO, AMP y CAP proponen clasificar las variantes genéticas en cuatro categorías basado en su impacto clínico (J Mol Diagn. 2017;19(1):4-23):

Categorías de variantes genéticas somáticas basada en la implicación clínica:

Clasificación I: Variantes con significancia clínico fuerte:

Nivel A Significancia Terapéutica:
Variantes que predicen respuesta o resistencia a terapias aprobadas por FDA o incluidas en guías profesionales para tumores específicos. Por ejemplo, BRAFV 600E predice respuesta a Vemurafenib en Melanoma.

Nivel A Significancia Diagnóstica/Pronóstica:
Variantes incluidas en guías profesionales como biomarcadores de diagnóstico o pronóstico para tumores específicos. Por ejemplo, la fusión PML-RARA es patognomónica de Leucemia Promielocítica y también es asociada con buen pronóstico.

Nivel B Significancia Terapéutica:
Variantes que predicen respuesta o resistencia a terapia basada en estudios con alto poder estadístico con consenso de expertos o estudios pequeños que repetidamente confirman o reproducen resultados en diferentes grupos.
Por ejemplo, múltiples estudios muestran que mutaciones en genes RAS o amplificación en gen BRAF reactiva la vía proteína quinasa resultando en resistencia a la terapia inhibidora BRAF en melanoma.

Nivel B Significancia Diagnóstica/Pronóstica:
Variantes diagnósticas o pronósticas basadas en estudios con alto poder estadístico con consenso de expertos o estudios pequeños que repetidamente confirman o reproducen resultados en diferentes grupos. Por ejemplo, mutaciones activantes KIT (D816V) que están presentes en casi todos los adultos (93%) con formas agresivas e indolentes de mastocitosis.

Clasificación II: Variantes con significancia clínica potencial:
Nivel C Significancia Terapéutica:
Variantes que predicen respuesta a terapias aprobadas por FDA incluidas en guías profesionales para un tumor diferente o terapias dirigidas en investigación mediante ensayos clínicos. Por ejemplo, pacientes con FLT3 en leucemia mieloide aguda está en estudio fase II/III para inhibidores FLT3 en ClinicalTrials.gov.

Nivel D Significancia Terapéutica:
Variantes que han sido asociadas con terapias dirigidas en estudios preclínicos. Por ejemplo, el fármaco RG7112 ha mostrado que inhibe a p53 no mutado (silvestre) de los tumores sólidos en estudios preclínicos y de fase I.

Clasificación III: Variantes de significado clínico incierto:

Variantes reportadas en el mismo o diferente tipo de cáncer sin significado clínico conocido y variantes en genes que no hayan sido reportadas en cualquier cáncer, estas variantes no deben haber sido reportadas con una frecuencia alélica significante en la población general como las encontradas en la base de datos del como el proyecto de los 1000 genomas, entre otras. El tipo de mutación, la función del gen debe ser considerado al evaluar estas variantes, el análisis in silico debe ser tomada como referencia, pero no es el único parámetro para evaluar.

Clasificación IV: Variantes Benignas o Probablemente Benignas:

Variantes con frecuencia alélica significativa en población general o en grupos específicos, no existe evidencia de asociación con cáncer. Usualmente variantes con frecuencia alélica de 50% o 100%, la mayoría de ellas son variantes germinales raras.

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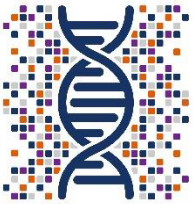

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Metodología del estudio genético de próxima-generación ImageneSeq+.

Con la plataforma NovaSeq 6000 somos capaces de secuenciar 48 genomas humanos completos y producir 6Tb de datos por corrida única en cuestión de 40 horas. 800Gb de datos crudos por hilera, 3.2Tb de datos por Flowcell, y 2 x 150 pb en longitud de lectura. 800M de lecturas crudas por Flowcell y longitud de lecturas 2 x 250 pb & 2 x 50 pb. Nuestro ImageneSeq+, es el panel genético más completo para el análisis de tumores sólidos que existe en el país, analizando más de 480 relacionados al cáncer, incluidas los introns de 43 genes para los cuatro tipos de anomalías genómicas: SNV, InDel, CNV y fusión. Además, incluimos el cálculo de inestabilidad microsatelital (MSI) como estable (MSI-L) o inestable (MSI-H) y carga mutacional del tumor (TMB) medida en mutaciones/Megabase como alta (TMB-H) o baja (TMB-L) que puede ayudar a guiar inmunoterapia en cáncer. Para aquellas muestras originadas de sangre completa o plasma se procede a aislar el material genético utilizando el protocolo MagMax Cell Free DNA. Ya una vez obtenido el material genético se procede a la preparación de clusters y librería utilizando el kit de KAPA para ADN. ImageneSeq+ fue creado utilizando todos aquellos genes que, de acuerdo con la Red Nacional Integral de Cáncer (NCCN, por sus siglas en inglés) de los Estados Unidos, están directamente relacionados en la enfermedad del cáncer y en base a la literatura médica más reciente. Todos los exámenes genéticos hechos por Imagene Health son realizados en laboratorios acreditados por CLIA, CAP y analizados en casa por médicos genetistas, biólogos moleculares y biotecnólogos.

Bioinformática del estudio genético de próxima-generación ImageneSeq+

Asimismo, el desarrollo de software de bioinformática para analizar, interpretar y reportar datos biológicos cuenta con certificación ISO 9001:2015, y nuestros reportes utilizan las recomendaciones de la Sociedad Americana de Oncólogos Clínicos (ASCO, por sus siglas en inglés) para la clasificación de las variantes genéticas identificadas. Se reciben los archivos de secuenciación en su totalidad por parte del laboratorio de referencia como los son BCL2FASTQ mediante multiplexado con CASAVA 1.8.2. Se procede al mapeo y realineamiento con Burrows-Wheeler Aligner, y preprocesamiento, incluido el marcado de lecturas duplicadas, realineaciones indel y recalibración de la base con Picard y GATK. Las mutaciones se filtraron en busca de apoyo mediante al menos 30 lecturas y un 3% de frecuencia alélica variante (VAF), y luego se anotaron mediante Annovar y SnpEff. TMB se calculó como el número total de SNV e indels dividido por Mb de ADN secuenciado. La interpretación clínica de las mutaciones detectadas en esos genes se realiza de acuerdo con la base de conocimientos integral de oncología interna de Qiagen construida en base a recursos públicos que incluyen GeneCards, CKB, OncoKB, COSMIC, ClinVar PMC, Drugs@FDA, Drug Information Portal (NIH), Selleck, PharmGKB, DGIdb, DRUGBANK, Drugs.com, ClinicalTrials.gov, ICTRP, ChiCTR, KEGG y señalización celular.

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