Case Summary

Genes/Variants

KRAS

Actionable

Therapeutics

There are no recommended treatments for this case.

Clinical Trials

3 clinical trials recommended

Test Description

TEST!

testing duh

Author: Marc Bachmann

Variant Information

KRAS - https://app.molecularmatch.com/#sk/BJLizM0xz

Mutations in the RAS family of proteins are frequently observed across cancer types. The amino acid positions that account for the overwhelming majority of these mutations are G12, G13 and Q61. The different protein isoforms, despite their raw similarity, also behave very differently when expressed in non-native tissue types, likely due to differences in the C-terminal hyper-variable regions. Mis-regulation of isoform expression has been shown to be a driving event in cancer, as well as missense mutations at the three hotspots previously mentioned. While highly recurrent in cancer, attempts to target these RAS mutants with inhibitors have not been successful, and has not yet become common practice in the clinic.

Clinical Trials

Phase 2 Clinical Trial Treating Relapsed/Recurrent/Refractory Pediatric Solid Tumors With the Genomically-Targeted Agent Sorafenib in Combination With Irinotecan KRAS

Phase: 2
Drugs: Sorafenib, Irinotecan
Contact: (hayashi_r@wustl.edu) (314-454-6018)
Locations: United States - MO
https://app.molecularmatch.com/NCT02747537

A Phase II Trial of Trametinib With Docetaxel in Patients With KRAS Mutation Positive Non-small Cell Lung Cancer (NSCLC) and Progressive Disease Following One or Two Prior Systemic Therapies KRAS

Phase: 2
Drugs: Docetaxel, Trametinib
Locations: United States - AK, AR, CA, CO, CT, GA, HI, ID, IL, IN, IA, KS, KY, MA, MI, MN, MS, MO, MT, NE, NV, NH, NY, NC, ND, OH, OK, OR, PA, SC, SD, TN, TX, UT, WA, WI, WY
https://app.molecularmatch.com/NCT02642042

NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) - Phase 2 Subprotocol of Selumetinib (AZD6244 Hydrogen Sulfate) in Patients With Tumors Harboring Activating MAPK Pathway Mutations KRAS

Phase: 2
Drugs: Selumetinib
Locations: United States - AL, AZ, AR, CA, DE, FL, ID, IN, IA, LA, MS, MO, NV, NY, NC, OH, OK, OR, PA, SC, TN, TX, VA, WA, WV
https://app.molecularmatch.com/NCT03213691

Clinical Utility

The results for the following genes are negative. These results decrease the likelihood, but do not rule out a mutation in the genes listed:

DNA:

Hotspot genes: *ABL1, AKT1, ALK, AR, ARAF, BRAF, BTK, CBL, CDK4, CHEK2, CSF1R, CTNNB1, DDR2, DNMT3A, EGFR, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FGFR1, FGFR2, FGFR3, FLT3, FOXL2, GATA2, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, IFITM1, IFITM3, JAK1, JAK2, JAK3, KDR, KIT, KNSTRN, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MED12, MET, MLH1, MPL, MTOR, MYD88, NFE2L2, NPM1, NRAS, PAX5, PDGFRA, PIK3CA, PPP2R1A, PTPN11, RAC1, RAF1, RET, RHEB, RHOA, SF3B1, SMO, SPOP, SRC, STAT3, U2AF1, XPO1.*

CDS full gene: *ATM, BAP1, BRCA1, BRCA2, CDH1, CDKN2A, FBXW7, GATA3, MSH2, NF1, NF2, NOTCH1, PIK3R1, PTCH1, PTEN, RB1, SMAD4, SMARCB1, STK11, TET2, TP53, TSC1, TSC2, VHL, WT1.*

Copy gain: *ACVRL1, AKT1, APEX1, AR, ATP11B, BCL2L1, BCL9, BIRC2, BIRC3, CCND1, CCNE1, CD274, CD44, CDK4, CDK6, CSNK2A1, DCUN1D1, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, GAS6, IGF1R, IL6, KIT, KRAS, MCL1, MDM2, MDM4, MET, MYC, MYCL, MYCN, MYO18A, NKX2-1, NKX2-8, PDCD1LG2, PDGFRA, PIK3CA, PNP, PPARG, RPS6KB1, SOX2, TERT, TIAF1, ZNF217.*

RNA fusion: *ALK, RET, ROS1, NTRK1, ABL1, AKT3, AXL, BRAF, CDK4, EGFR, ERBB2, ERG, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, NTRK3, PDGFRA, PPARG, RAF1.*

Benign and unknown variants in the genes may have been identified, but have not been included in the report, except for those associated with possible drug metabolism or response to therapy.

The classification and interpretation of all variants identified in this assay reflects the current state of scientific understanding at the time this report was issued. In some instances, the classification and interpretation of such variants may change as new scientific information becomes available.

Variants are classified as per the ACMG Guidelines (Richards, Aziz et al. 2015).

The genes were also screened as per the ACMG guidelines for likely deleterious and pathogenic mutations in the relevant genes (Green, Berg et al. 2013, Directors 2015). Databases used for interpretation include COSMIC, Oncomine™, ClinVar, ExAC, dbSNP Build 83/147, *BRCA* Exchange, KConFAB, LOVD and IARC *TP53*.

Variant/Gene Publications

Khambata-Ford, Shirin, et al. "Analysis of potential predictive markers of cetuximab benefit in BMS099, a phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer." *J. Clin. Oncol.* (2010)
Publication: PUBMED

KRAS

Jänne, Pasi A, et al. "Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study." *Lancet Oncol.* (2013)
Publication: PUBMED

KRAS

Dingemans, Anne-Marie C, et al. "A phase II study of sorafenib in patients with platinum-pretreated, advanced (Stage IIIb or IV) non-small cell lung cancer with a KRAS mutation." *Clin. Cancer Res.* (2013)
Publication: PUBMED

KRAS

Medical Sign Off

Cautions

Clinical Correlation:

Test results should be interpreted in the context of clinical findings, family history and other laboratory data. Misinterpretation may occur if the information provided is inaccurate or incomplete. Incidental germline mutations are reported as per the ACMG recommendations.

Technical Limitations:

Rare mutations/polymorphisms exist that could lead to false negative or false positive results. If the results obtained do not match the clinical findings, additional testing should be considered. Negative results decrease the likelihood but do not rule out the mutations in the genes listed. We predict that some samples/individuals have a gene mutation that is not identified by the methods used in this panel.

Bone Marrow Transplants:

Bone marrow transplants from allogeneic donors will interfere with testing using germline samples. Contact the laboratory for instructions for testing patients who have received a bone marrow transplant.

In-Silico Analysis:

Multiple analytic techniques were used to assist in the interpretation of these results. If you run your own analysis, note that algorithms may have changed since this test and you may see different results.

Grantham score

The Grantham score attempts to predict the distance between two amino acids, in an evolutionary sense. A lower Grantham score reflects less evolutionary distance. A higher Grantham score reflects a greater evolutionary distance. Higher Grantham scores are considered more deleterious:

- The more distant two amino acids are, the less likely the amino acids are to be substituted with one another.
- The more distant two amino acids are, the more damaging is their substitution.

The distance scores published by Grantham range from 5 to 215. A substitution of isoleucine for leucine, or of leucine for isoleucine, has a score of 5 (and is predicted to be tolerated). A substitution cysteine for tryptophan, or of tryptophan for cysteine, has a score of 215. Any variation involving cysteine has a high or very high Grantham score (and is predicted to be deleterious).

SIFT score

A SIFT score predicts whether an amino acid substitution affects protein function.

The SIFT score ranges from 0.0 (deleterious) to 1.0 (tolerated). The score can be interpreted as follows:

- 0.0 to 0.05 -- Variants with scores in this range are considered deleterious. Variants with scores closer to 0.0 are more confidently predicted to be deleterious.
- 0.05 to 1.0 -- Variants with scores in this range are predicted to be tolerated (benign). Variants with scores very close to 1.0 are more confidently predicted to be tolerated.

PolyPhen-2 score

The PolyPhen-2 score predicts the possible impact of an amino acid substitution on the structure and function of a human protein. This score represents the probability that a substitution is damaging. Ion Reporter™ Software reports the pph2-prob PolyPhen-2 score.

The PolyPhen-2 score ranges from 0.0 (tolerated) to 1.0 (deleterious). Variants with scores of 0.0 are predicted to be benign. Values closer to 1.0 are more confidently predicted to be deleterious. The score can be interpreted as follows:

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- 0.0 to 0.15 -- Variants with scores in this range are predicted to be benign.
- 0.15 to 1.0 -- Variants with scores in this range are possibly damaging.
- 0.85 to 1.0 -- Variants with scores in this range are more confidently predicted to be damaging.

Reclassification policy:

At this time it is not standard practice for the laboratory to systematically review variants of uncertain significance and provide amended reports to ordering medical practitioners or patients. However, we encourage you to contact the laboratory on 1800 455 433 or by email patientcare@genomicsforlife.com.au at any time, should you be interested in learning how the status of a particular variant may have changed over time.