

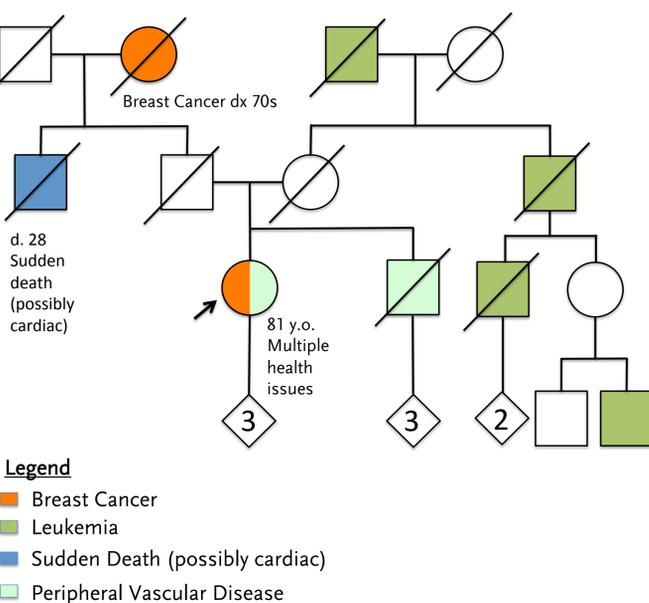
Introduction

Recent publications discuss targeted genetic testing for terminally ill patients whose histories are indicative of a genetic disorder, such as a hereditary cancer syndrome^{1,2}. Another study suggests that older adults have positive attitudes towards genetic testing at the end of life, for the benefit of family members and the community³.

Massively parallel sequencing allows for testing many genes at a similar cost to testing a single gene using traditional Sanger sequencing. Here, we present the case of a patient with a complex history that does not directly point to a specific genetic disorder.

The patient was seen at the end of life for genetic counseling in order to learn what genetic mutations she may pass on to her children. The patient banked DNA, and wanted to obtain as much genotype information as was reasonably obtainable in her lifetime. The patient's DNA was sequenced for >200 genes.

Pedigree



References

- Daniels MS, Burzawa JK, Brandt AC, Schmeler KM, Lu KH. A clinical perspective on genetic counseling and testing during end of life care for women with recurrent progressive ovarian cancer: opportunities and challenges. *Fam Cancer*. 2011 Jun; 10(2):193-7.
- Quillin JM, Bodurtha JN, Smith TJ. Genetics assessment at the end of life: suggestions for implementation in clinic and future research. *J Palliat Med*. 2008 Apr;11(3):451-8.
- Skirton H, Frazier LQ, Calvin AO, Cohen MZ. A legacy for the children--attitudes of older adults in the United Kingdom to genetic testing. *J Clin Nurs*. 2006 May;15(5):565-73.

Case Report

The patient was a terminally ill woman in her early 80s with no prior DNA testing.

Medical History:

- Hyperlipidemia, dx. mid 40s
- Hypertension, dx. mid 50s
- Spinal stenosis, dx. 60s (pain onset 20s)
- Breast cancer, dx. early 60s
- Peripheral artery disease, dx. 60s
- Pulmonary emboli, dx. 70s
- Stroke, dx. 70s
- Melanoma, dx. 80s

Family History:

As shown in pedigree, a family history of leukemia, breast cancer, sudden death, and peripheral artery disease.

DNA Testing:

Using next generation sequencing (Illumina MiSeq), the patient tested for >200 genes, including cardiac arrhythmias, hereditary cancer genes, clotting disorders, and multiple other inherited conditions.

The genes tested include:
AARS, ACTC1, ACTN2, AH11, AKAP9, ALDH7A1, ANK2, APC, ARL13B, ARL6, ASPA, AT1L1, B9D1, B9D2, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, BLM, BMPR1A, BRAF, BRCA2, BRIPI, BSCL2, CACNA1C, CACNA2D1, CACNB2, CAV3, CBL, CC2D2A, CCDC39, CCDC40, CDH1, CDK4, CDKN2A, CEP290, CFTR, CHD7, CHEK2, CSRP3, CYP7B1, DNAAF1, DNAAF2, DNAH11, DNAH5, DNAI1, DNAI2, DNALI1, DNLM2, DYNC2H1, EGR2, F2, F5, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCI, FANCL, FGD4, FGF1, FIG4, FOXH1, GABRG2, GARS, GDAP1, GDF1, GJB1, GLIS2, GPD1L, HAMP, HEXA, HFE, HFE2, HRAS, HSPB1, HSPB8, HSPD1, IFT80, IKBKAP, INPP5E, INVS, IQCB1, JPH2, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNQ1, KCNQ2, KCNQ3, KIAA0196, KIF1B, KIF5A, KRAS, LTCAM, LIG4, LITAF, LMNA, MAP2K1, MAP2K2, MED12, MED25, MEN1, MET, MFN2, MKK5, MKS1, MLH1, MPZ, MSH2, MSH6, MTRR2, MUTYH, MYBPC3, MYH7, MYL2, MYL3, MYOZ2, MYPN, NBN, NDRG1, NEFL, NEK8, NEXN, NODAL, NPHP1, NPHP3, NPHP4, NRAS, OFD1, PALB2, PALLD, PKD2, PKHD1, PLP1, PMP22, PROC, PROK2, PROKR2, PROS1, PRPS1, PRX, PTC1, PTEN, PTPN11, RAB7A, RAD51C, RAF1, RET, RRGRI1, RSPH4A, RSPH9, SBF2, SCN1A, SCN1B, SCN2A, SCN3B, SCN4B, SCN5A, SEMA3E, SERPINC1, SH3TC2, SHOC2, SLC16A2, SLC40A1, SLX4, SMAD4, SNTA1, SOS1, SOX9, SPAST, SPG11, SPG20, SPG21, SPG7, SPINK1, SPRED1, STK11, TCAP, TCTN1, TCTN2, TFR2, TMEM216, TMEM67, TNNC1, TNNI3, TNNT2, TP53, TPM1, TRIM32, TRPV4, TTC21B, TTC8, TTN, UPF3B, VHL, WDRPCP, XPNPEP3, YARS, ZFYVE26, ZFYVE27, ZIC3

* The assay performed did not test for deletions/duplications.

Test Results

A homozygous mutation for HFE-related hereditary hemochromatosis was found. The results prompted an additional hemochromatosis evaluation, which was negative.

No pathogenic mutations were identified any of the other genes tested.

Discussion

The patient had been affected with multiple life changing diseases through out the last several decades of her life. She had been concerned for some time about her children struggling with the same fate. No clear etiology had explained her multiple emboli/strokes, peripheral vascular disease, and hyper-tension. She also sought information about breast cancer and melanoma inheritance risks, sudden cardiac death, and hyperlipidemia. The broad range of diseases involved had previously made the desire for genetic testing cost prohibitive and too selective. The advent of massively parallel sequencing of hundreds of genes at a flat fee allowed for reconsideration of diagnostic and carrier genetic testing.

Informed consent was obtained after thorough discussion of possible outcomes including the high probability of identifying variants of uncertain significance (VUS's). The patient had little concern over VUS's, as she knew her offspring had decades to participate in the reclassification of them. The patient also understood that there are limitations to this testing: this test assessed some but not all known genes and mutations that cause hereditary cancer, sudden cardiac death and pulmonary embolism. She understood that this test did not test for genes conferring a risk of her other conditions (ex. hyperlipidemia genes).

Although no clear explanation for her diagnoses was identified, multiple significant disease alleles were found to be normal, thus conferring a lower relative risk of inherited cancer and sudden cardiac death (hyperlipidemia was not assessed). She felt great peace in leaving her offspring as much genotype information as was reasonably obtainable in her lifetime and banked DNA for further study.

Conclusion

The testing provided relevant information to the patient's children about the risk of Hemochromatosis and the reduced relative risk of inherited arrhythmias, clotting disorders, and cancer predisposition.

Broad genetic testing can be used as a supplement to DNA banking in a patient with a complex personal and family history.