Possible pathogenic hits (see excel file):

1. ***BRCA2*** c.8873_8874insAAGT ([redacted]*22): potential increase lifetime risk of breast cancer of 40-80% and ovarian cancer of 11-40%
2. ***BRCA2*** c.1536delT ([redacted]*11) / "likely pathogenic": potential increase lifetime risk of breast cancer of 40-80% and ovarian cancer of 11-40%

In males, if confirmed, consider testing female family members and be aware of potential increased risk of prostate cancer.

BRCA2 is a gene on 13q13.1 encoding a 10.4-kb transcript and composed of 27 exons. The gene product is a 380-kd protein made up of 3,418 amino acids. Like BRCA1, BRCA2 is a tumor suppressor gene whose mutations increased risk of breast, ovarian, and other cancers through loss of function. BRCA2 appears to be involved in the DNA repair process through protein interaction with the RAD51 protein, a key component in homologous recombination and double-strand break repair.

Pathogenic BRCA1 or BRCA2 mutations cause hereditary breast and ovarian cancer syndrome (HBOC), and, to a lesser extent, also increase risk for other cancers such as prostate cancer, pancreatic cancer, and melanoma. The lifetime risk for these cancers in individuals with a mutation in BRCA1 or BRCA2 is estimated to be:

The lifetime risk for these cancers in individuals with a mutation
in BRCA1 or BRCA2 is estimated to be:
• 40%-80% for breast cancer (vs a 12% baseline risk in the general population)
• 11%-40% for ovarian cancer (vs a 1-2% baseline risk in the general population)
• 1%-10% for male breast cancer (vs a 0.1% baseline risk in the general population)
• Up to 38% for prostate cancer (vs a 15-18% baseline risk in the general population)
• 1%-7% for pancreatic cancer (vs a 0.5% baseline risk in the general population)
• Patients with BRCA2 mutations may also be at an increased risk for melanoma

It is also well recognized that BRCA1 and BRCA2 mutations have incomplete penetrance and variable expressivity. So, there is wide variability in age of onset, tumor recurrence, and prognosis between patients with the same BRCA1 or BRCA2 mutation (even among those from the same family) and some patients harboring a pathogenic mutation may never develop breast cancer or other cancers.

Evidence:

- unable to locate variant specific literature in pubmed and not reported in clinvar / continue to monitor

- Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon) in a gene where loss of function (LOF) is a known mechanism of disease
- Located in a critical and well-established functional domain (Moderate)
- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project or 1000 Genomes (Moderate)

3. ***TTN*** c.40482C>A ([redacted]*)
4. ***TTN*** c.40484_40485insGTTCCTTC ([redacted]*)

5. ***TTN*** c.13283-37075_13283-37074insTTAATGTTGTTAATATTGTCAT ([redacted]*2)
6. ***TTN*** c.28352_28353insACTTCAATTT ([redacted]*4)

Although implicated in dilated cardiomyopathy, TTN is notorious for being a large gene containing many benign polymorphisms (some of which are bioinformatically predicted to be pathogenic). Unless positive family or personal history of cardiomyopathy, requires further evidence of pathogenicity.

7. ***ATM*** c.8107_8108insTATAAACATGATTGATA ([redacted]*2)
8. ***ATM*** c.8105T>A([redacted])

Although some rare cases of symptomatic het carriers have been reported, this is typically an early onset disease with autosomal recessive inheritance. May be of reproductive importance. Further data needed. Unlikely that both are pathogenic in an asymptomatic patient.

Causes classic ataxia-telangiectasia: primary features of classic A-T include progressive gait and truncal ataxia with onset between ages one and four years, progressively slurred speech, oculomotor apraxia (inability to follow an object across visual fields), choreoathetosis (writhing movements); oculocutaneous telangiectasia (usually evident by age 6 years); frequent infections (with accompanying evidence of serum and cellular immunodeficiencies); and hypersensitivity to ionizing radiation with increased susceptibility to cancer (usually leukemia or lymphoma).

Other features include premature aging with strands of gray hair and endocrine abnormalities, such as insulin-resistent diabetes mellitus.

The risk for malignancy in individuals with classic A-T is 38%. Leukemia and lymphoma account for about 85% of malignancies. Younger children tend to have acute lymphocytic leukemia (ALL) of T-cell origin and older children are likely to have an aggressive T-cell leukemia. Lymphomas are usually B-cell types. As individuals with classic A-T are living longer, other cancers and tumors, including ovarian cancer, breast cancer, gastric cancer, melanoma, leiomyomas, and sarcomas, have also been observed.

Evidence:
Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- Located in a critical and well-established functional domain (PKc_like) (Moderate)
- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project or 1000 Genomes (Moderate)

9. ***MRE11A*** c.87_88insTGATATTCAA ([redacted]*)

"Ataxia-telangiectasia-like" but autosomal recessive.

10. ***CFTR*** c.3756_3757insTCAATAAAAACCA ([redacted]*16)

    CFTR is the gene causing cystic fibrosis. Need to confirm pathogenicity but of primarily reproductive concern as this is autosomal recessive disease.

    Evidence:
    Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
    - Located in a critical and well-established functional domain (ABC_ATPase; ABC_tran) (Moderate)
    - Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project or 1000 Genomes (Moderate)
    - need to check CFTR specific databases

11. ***SMPD1*** c.1826_1828delGCC ([redacted])

SMPD1 causes Niemann Pick disease a recessive lysosomal storage disorder. May be of reproductive importance. Not expected to affected hets.

At least 175 mutations in the SMPD1 gene have been found to cause Niemann-Pick disease types A and B. These types of Niemann-Pick disease are characterized by a buildup of fat within cells that leads to lung disease and enlargement of the liver and spleen (hepatosplenomegaly). Type A is more severe and is characterized by severe neurological impairment in early childhood.

SMPD1 gene mutations that cause complete loss of enzyme function tend to cause Niemann-Pick disease type A. In the Ashkenazi (eastern and central European) Jewish population, three mutations are responsible for about 90 percent of all Niemann-Pick disease type A cases. Mutations that lead to the production of an enzyme that retains some activity often cause Niemann-Pick disease type B. A reduction in enzyme activity within cells allows sphingomyelin to accumulate in cells. The accumulation of this lipid causes cells to malfunction and eventually die. Over time, cell loss impairs function of tissues and organs including the brain, lungs, spleen, and liver in people with Niemann-Pick disease types A and B.

12. ***RAG2*** c.614_613insTA ([redacted]*3)
13. ***RAG2*** c.616_615insATAAGA ([redacted])

    RAG2 is a causative gene for Omenn syndrome, an immunodeficiency syndrome. Highly unlikely that both of these are pathogenic in an asymptomatic individual. May be of reproductive value.

14. ***GFPT1***c.1613_1614insTGACTATGT ([redacted])

Potential pathogenic mutation for autosomal recessive congenital myasthenic syndrome (weakness with repetitive effort). Potential reproductive importance. Would need to (a) confirm, and (b) test partner for potential clinical utility in asymptomatic carrier.

Evidence:
Located in a critical and well-established functional domain (SIS) (Moderate)
- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project or 1000 Genomes (Moderate)
- Protein length change due to in-frame insertion/deletion in a non-repeat region (Moderate)

15. ***HESX1*** c.261_262insCATTATTGGGT ([redacted]*16)

This gene also causes another AR disorder lysosomal storage disorder (sphingomyelinase deficiency) and septo-optic dysplasia. Potentially of reproductive importance.

Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project or 1000 Genomes (Moderate)

16. ***CEP290*** c.38_39insATATATCTATTATTAT ([redacted]*6)

Causes Leber congenital amaurosis: an AR form of early blindness. Potentially of reproductive importance.

Leber congenital amaurosis is a severe retinal dystrophy, causing blindness or severe visual impairment at birth or during the first months of life. It is generally inherited in an autosomal recessive manner and is genetically heterogeneous.

17. ***DMD*** c.1001T>A ([redacted])

X-linked but unlikely to be pathogenic in asymptomatic adult.

Evidence:
located in a critical and well-established functional domain (SPEC) (Moderate)
- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project or 1000 Genomes (Moderate)
- Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease (Supporting)
- Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc) (Supporting)

18. ***ABCC9*** c.531_532insCTTTCATATT ([redacted]*32)

Potentially causing AD familial dilated cardiomyopathy – however this gene is not on the ACMG incidental findings list. General population screening data insufficient.

Evidence:
Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project or 1000 Genomes (Moderate)

19. ***DSG4*** c.1198G>A ([redacted])

May cause autosomal recessive localized hypotrichosis. Minimum clinical value (even repro).

Evidence:
Located in a critical and well-established functional domain (CA_like) (Moderate)
- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project or 1000 Genomes (Moderate)
- Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease (Supporting)
- Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc) (Supporting)

20. ***GARS*** c.873_874insAAGGCATAAGATATAAAGTATTAT ([redacted]*DIKYY)

May cause AD distal neuropathy or CMT. Further evidence needed. Not on ACMG incidental list. Population screening data lacking.

21. ***ANK2*** c.3679delA ([redacted]*13)
22. ***ANK2*** c.3662_3663insCT ([redacted]*6)
23. ***ANK2*** c.3667_3677delCCAATTACCAT ([redacted]*10)

May cause familial HCM; but population data lacking.

Evidence:
Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project or 1000 Genomes (Moderate)

24. ***CNGB3*** c.71_72insATATA ([redacted]*60)

Causes AR hereditary eye disease/early macular degenration. Possible repro significance.

Evidence:
Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project or 1000 Genomes (Moderate)

25. ***ATR*** c.2153_2154insATTAAATAAGTCATAATCAC ([redacted]*5)

Possible increased breast cancer risk but lacking population data.

Evidence:

Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)

- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project or 1000 Genomes (Moderate)

26. ***GABRG2*** c.523_524insGA ([redacted]*9)

Possible AD susceptibility to epilepsy. Not on ACMG incidental findings list.

Evidence:

Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)

- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project or 1000 Genomes (Moderate)