

Background

The familial atypical multiple mole melanoma (FAMMM) syndrome, also known as melanoma-pancreatic cancer syndrome, is caused by pathogenic variants of CDKN2A and is associated with a 28-91% and a ~17% lifetime risk for melanoma and pancreatic cancer, respectively (Hampel *et al.*, 2014). In addition to a personal or family history of cancer, individuals may present with early onset of multiple (>50) atypical nevi. It has been suggested that other cancer types may be prevalent in CDKN2A-positive families including lung, breast, head and neck, CNS and others; however data supporting these associations are limited. In this case series we describe the clinical presentation of 27 CDKN2A mutation carriers, further delineating the spectrum of cancers reported in families with pathogenic CDKN2A variants.

Methods

Patients with a personal and/or family history of cancer were referred to Invitae for multigene panel genetic testing that included the CDKN2A gene. Cases were selected for further analysis if they had a Pathogenic or Likely Pathogenic (P/LP) variant in CDKN2A. Evaluation was limited to the p16 reading frame of CDKN2A. Variants were classified using a point-based system that closely adheres to the ACMG guidelines. De-identified personal and family histories provided by ordering clinicians were examined.

Results

27 cases from 22 unique families were identified with P/LP variants in CDKN2A: 21 affected with cancer and 6 unaffected carriers age 33-59 who were tested due to family history. 5 patients (3 cancer-affected) from 2 families were excluded from this analysis as they were found to also carry a P/LP variant in another hereditary cancer predisposition gene or were homozygous for CDKN2A.

From the 22 cases with only CDKN2A findings, 8 of the 18 affected patients (44%) had personal histories of melanoma. 4 of 18 (22%) presented with pancreatic cancer, two of whom also had melanoma. 2 of 18 (11%) presented with sarcoma and one additional patient had a first degree relative with sarcoma and breast cancer who was a known carrier of the familial variant. The remainder of affected carriers had histories of breast and uterine cancers respectively. 6 of 18 (33%) affected patients developed multiple primary cancers including four patients with multiple cutaneous melanomas and two with melanoma and pancreatic cancer. The range of age at first cancer diagnosis was 9-60 years and the average age was 37 years.

Results (cont.)

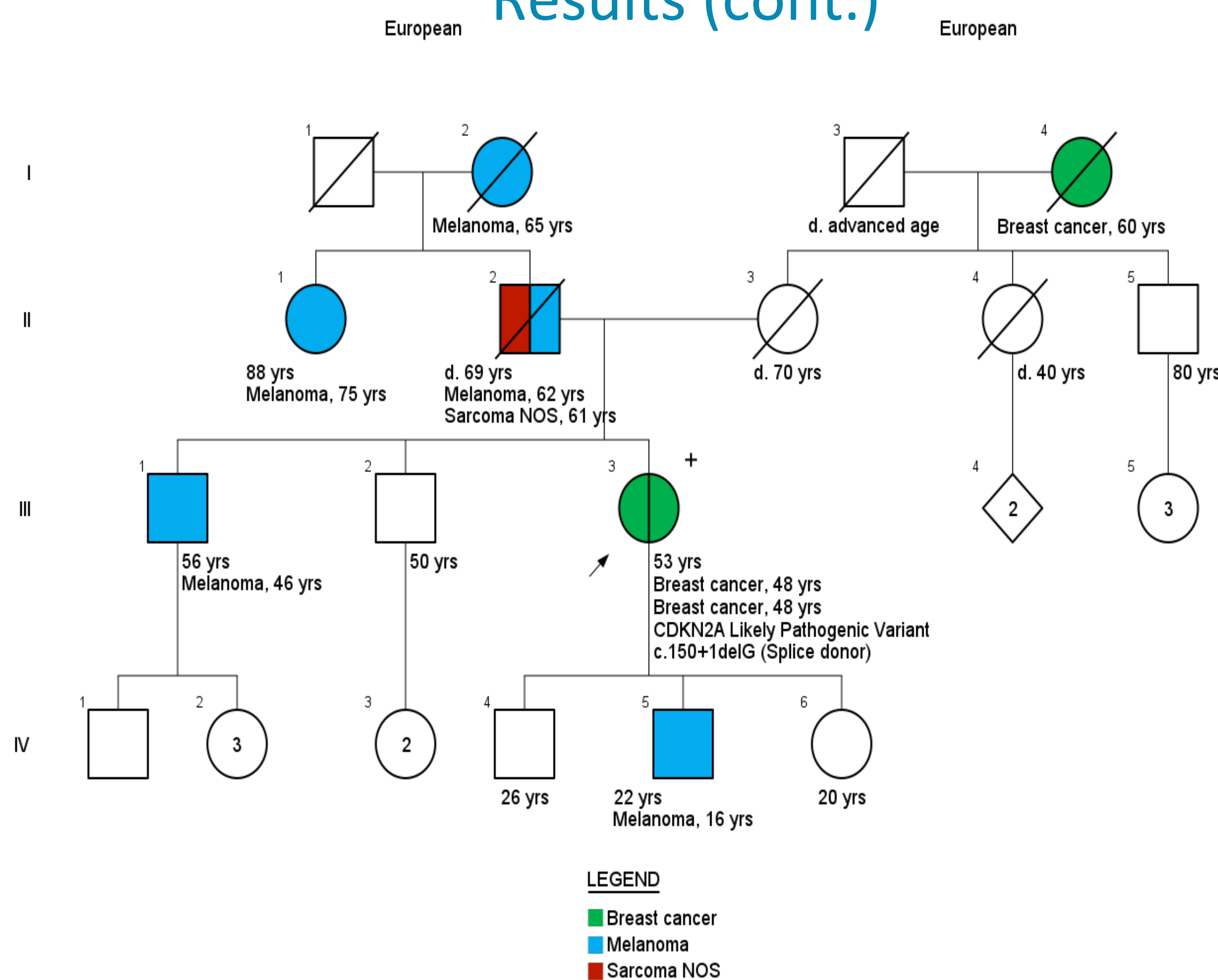


Figure 1. Female diagnosed with bilateral breast cancer at age 48 with family history of melanoma and sarcoma; CDKN2A Likely Pathogenic Variant detected by 25 gene Breast and Gynecologic Cancer Syndromes panel

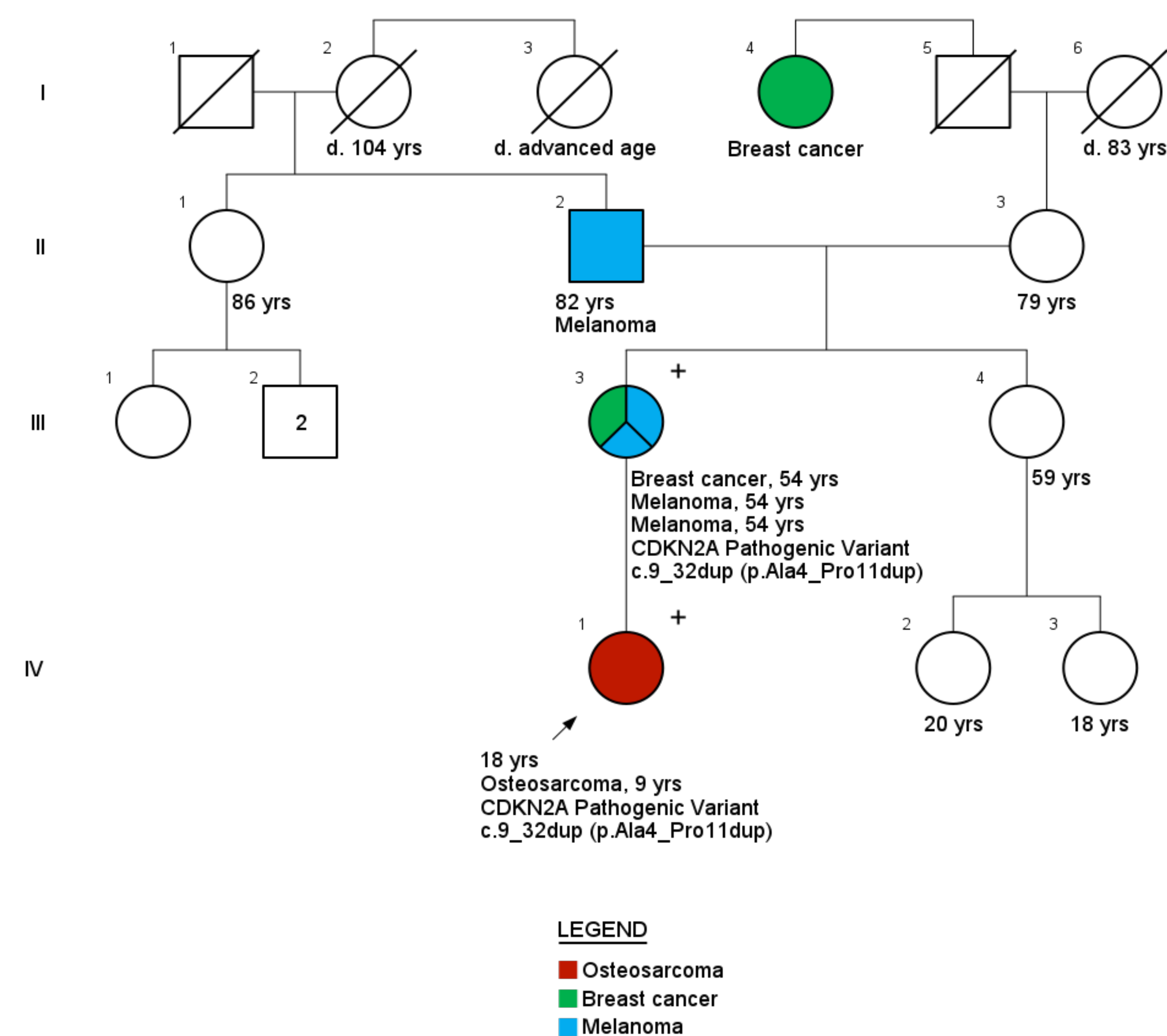


Figure 2. Female diagnosed with osteosarcoma at age 9; BRCA2 mutation detected by 34-gene Hereditary Cancer Syndromes panel.

Results (cont.)

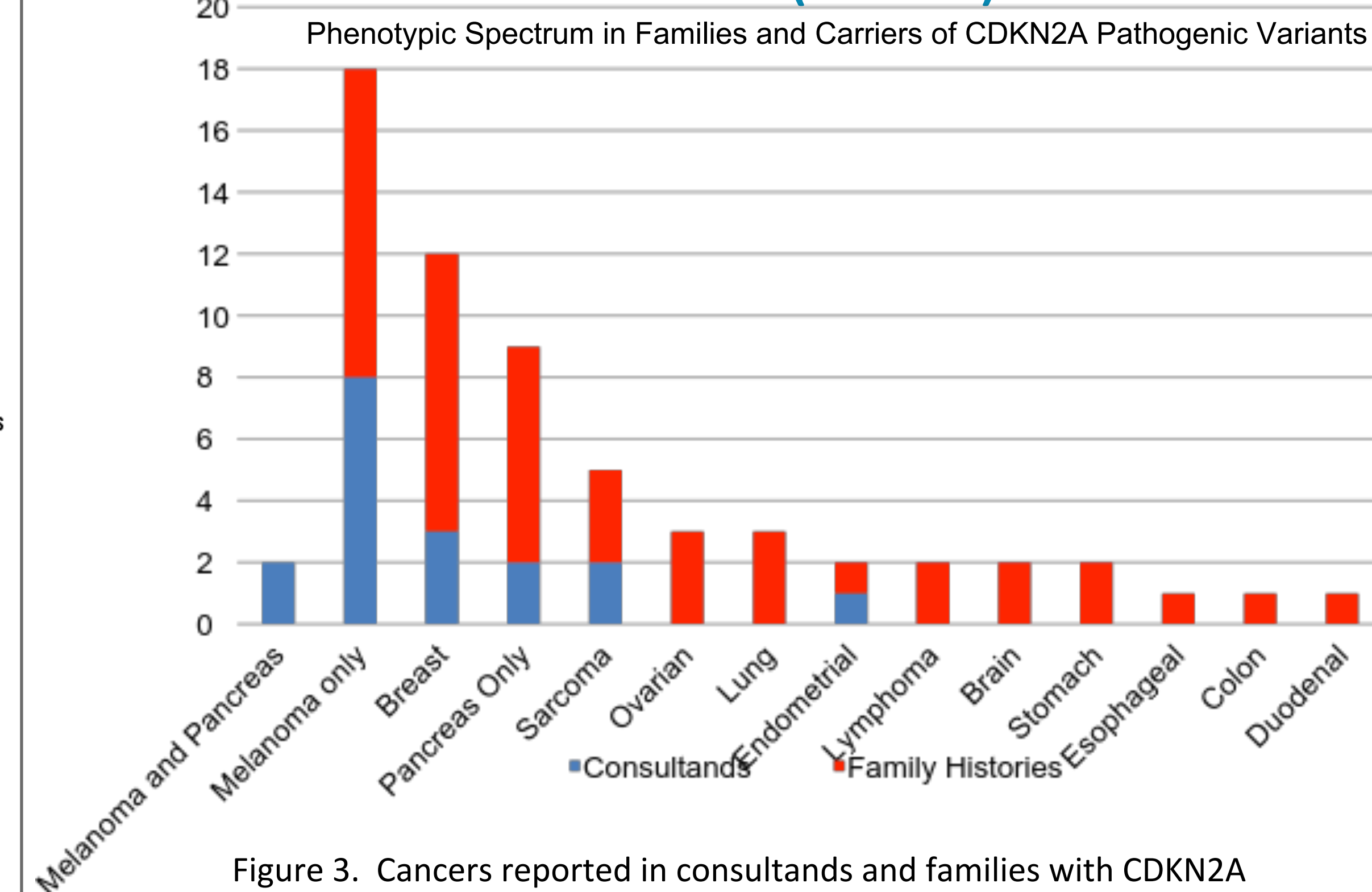


Figure 3. Cancers reported in consultants and families with CDKN2A Pathogenic and Likely Pathogenic Variants.

Family history information was available from 20 families. A family history of melanoma was reported in 10 of 20 (50%), breast cancer in 9 of 20 (45%), pancreatic cancer in 7 of 20 (35%), sarcoma, ovarian and lung in 3 of 20 (15%) respectively, and lymphoma, brain and stomach cancer each in 2 of 20 (10%). Reported family histories included uterine, duodenal, esophageal and colon cancers. We identified one patient, excluded from this series, with a history of pediatric-onset non-Hodgkin's lymphoma who was found to be homozygous for a pathogenic truncating variant in CDKN2A. The family history was significant for pancreatic cancer and consanguinity.

Conclusions

This patient series expands the phenotypic spectrum of CDKN2A, for example the observation of sarcoma in several affected families. Sarcoma is a rare cancer accounting for approximately 1% of all cancer diagnoses, and is associated with significant morbidity and high mortality.

In addition to sarcoma, these families presented with other features beyond the well described risks for melanoma and pancreatic cancers, including lung, breast and ovarian cancers, early-onset disease and multiple primary cancers. These features are reminiscent of some of the well-defined cancer predisposition syndromes and emphasize the value of multiple gene panel testing even when there is clinical suspicion for specific syndromes. These observations suggest the need for further studies into the role of CDKN2A in sarcoma, and underscores the value of expanded multi-gene panel testing in families with complex presentations.