Clinical and molecular characteristics of NF1 mutations identified on hereditary cancer multi-gene panels.

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**Background:** Somatic mutations to the *NF1* gene have been shown to play a role in several tumor types. Evaluation of patients with Neurofibromatosis type 1 (NF1) has led to the longstanding clinical observation of a high rate of somatic mosaicism in *NF1*. We explored the clinical and genetic features of patients with *NF1* mutations identified through cancer susceptibility testing. **Methods:** Results from a cohort of 118,768 patients who underwent multigene panel testing (MGPT) were queried to identify probands with a *NF1* pathogenic/likely pathogenic variant. Next generation sequencing was performed on panels of 2-67 hereditary cancer genes. Review of test requisition forms and available clinical history/pedigree was performed. NF1 cases were defined by concordance with NIH criteria. Additionally, we used a biphasic distribution to define a cutoff, dividing non-NF cases into normal and low variant allele frequency (VAF). **Results:** 158 total patients were identified; 89 patients had a reported clinical diagnosis of NF1; 69 had a mutation in *NF1* but not reported as having NF1. Of the latter category, 2 Patients reported as having NF1 were diagnosed with cancer earlier (45.5 vs 54.8 years, p = 6.9 x 10^-5), without statistically significant difference in number or cancer type. However, sarcoma (p = 0.20), and ER+ breast cancer (OR 2.64, p = 0.08) approached significance as more common in patients with NF1. Patients with low VAF were diagnosed with cancer earlier (49.7 vs 58.9 yrs, p = 0.02). Mutations in other cancer susceptibility genes were present in 4.4% of clinical NF1 and 11.5% of *NF1* mutation only cases; 75% of the latter category patients met NCCN 2016 family history guidelines for BRCA testing. **Conclusions:** Low VAF of the *NF1* gene could result from somatic mosaicism, circulating tumor, or clonal hematopoiesis of indeterminant potential (CHIP). Our data show that patients with low VAF are diagnosed with cancer earlier, meaning that the observed low VAF is unlikely to be associated with CHIP, and more likely due to true somatic mosaicism. Additionally, our data suggests that the marginal utility of MPGT in breast cancer patients with clinically diagnosed NF may be low.