

Characterization of the Clinical Phenotype of Biallelic *CHEK2* Carriers

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Abstract

Pathogenic heterozygous mutations in the *CHEK2* gene are associated with an approximate two-fold increased risk of female breast cancer, estimated to be 20-25% lifetime risk. As data is limited regarding the magnitude of cancer risk attributable to *CHEK2* mutations, testing negative for a familial *CHEK2* mutation does not eliminate familial risk factors and a discussion of potentially increased screening may be appropriate based on the family history of cancer. Additionally, limited data is available regarding breast cancer risk in the setting of homozygous or compound heterozygous *CHEK2* mutations. Our case series identified 23 *CHEK2* biallelic patients, including 6 *CHEK2* (c.1100delC) homozygotes and 17 *CHEK2* compound heterozygotes. Mutations in the compound heterozygotes included truncating mutations as well as low penetrant, pathogenic mutations. A subset of *CHEK2* compound heterozygotes exhibited a profoundly younger age of onset and appeared to have a greater than two-fold increased risk of breast cancer. As further data is needed to extrapolate lifetime risk of female breast cancer for *CHEK2* biallelic individuals, our results suggest that increased, earlier breast screening may be indicated for females who are identified to have two *CHEK2* mutations.

Background

The Checkpoint kinase 2 gene (*CHEK2*) has been described as a moderate risk female breast cancer gene. Current data suggests that women with monoallelic mutations in the *CHEK2* gene have an approximate 20-25% lifetime risk of developing breast cancer as compared to the United States general population risk of 12%. The National Comprehensive Cancer Network (NCCN) guidelines (version 1.2018) recommend that women who carry a monoallelic mutation in *CHEK2* can consider increased breast screening with annual mammography and breast magnetic resonance imaging beginning at age 40 or 10 years earlier than the earliest age of breast cancer diagnosis within the family. These recommendations may be altered based on additional family history information, such as earlier ages of diagnosis of breast cancer. However, limited data is available for women who carry biallelic *CHEK2* mutations and the application of current guidelines to these clinical scenarios is limited.

Adank M et al (2011) described 8/2554 females who were identified to carry biallelic *CHEK2* mutations within a Dutch cohort. All 8 cases were confirmed to be homozygous for the *CHEK2* (c.1100delC) Dutch founder mutation. They hypothesized a more than twofold increased risk of developing breast cancer for biallelic *CHEK2* (c.1100delC) females as compared to monoallelic *CHEK2* females. They tested and confirmed their hypothesis that biallelic *CHEK2* (c.1100delC) carriers exhibit more than an additive breast cancer risk, estimated to be approximately twice the risk of monoallelic *CHEK2* carriers. (p=0.044). Another study by Huijts PEA et al (2014) identified 6 biallelic *CHEK2* (c.1100delC) females affected with breast cancer from a Netherlands cohort with 3/6 patients developing a contralateral breast cancer. As both studies are exclusive to the *CHEK2* Dutch founder mutation, there is a need for additional data on biallelic carriers with other *CHEK2* mutations. Here we present two cases of biallelic carriers with mutations beyond c.1100delC.

Methods

Retrospective chart review was performed for females who underwent multi-gene panel genetic testing due to family and/or personal history of breast cancer between 2016 and 2017 through the Northwestern Medicine Cancer Genetics Program and Invitae Laboratories. Genetic testing results were reviewed and patients who were identified as biallelic *CHEK2* carriers were included.

Results

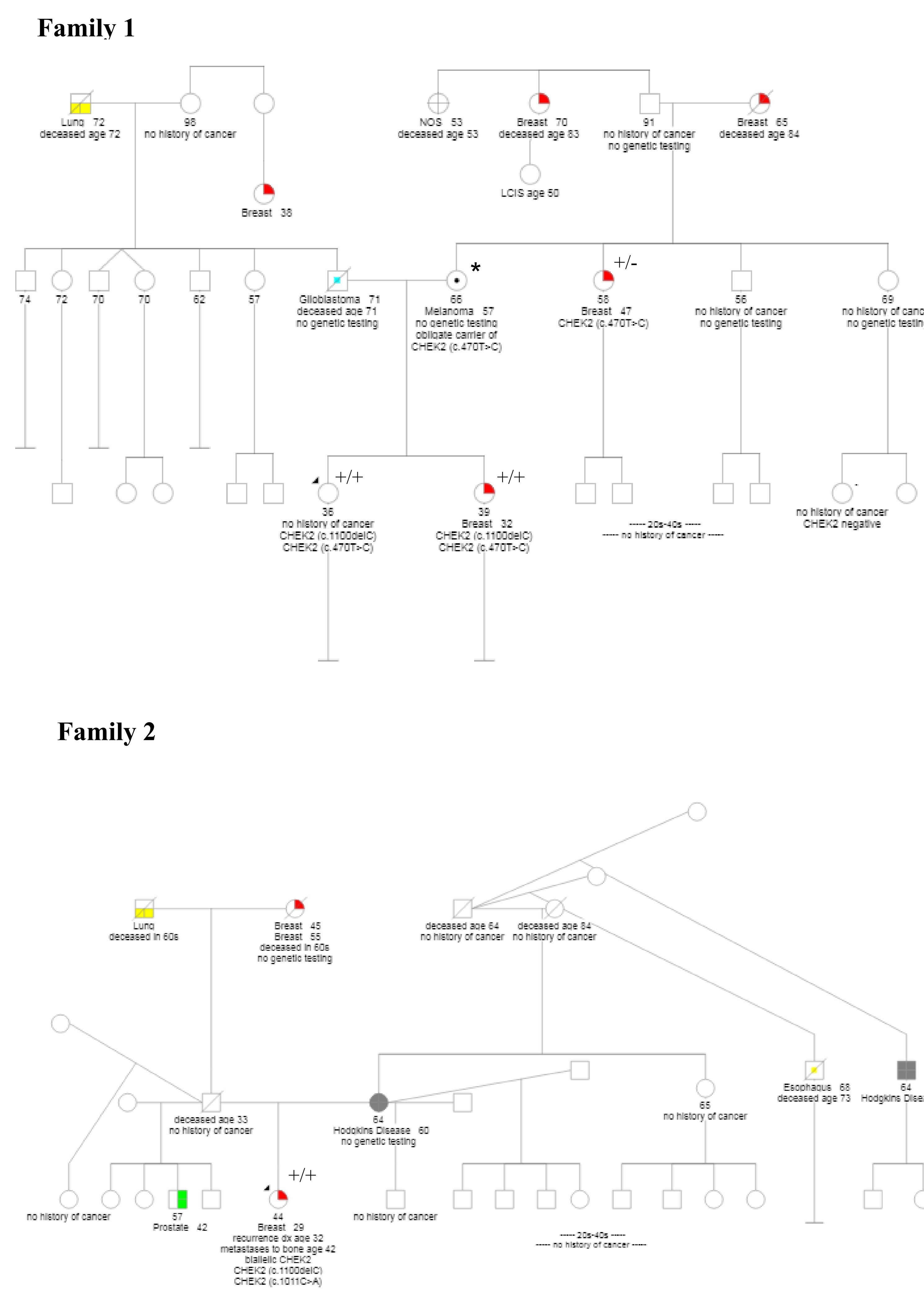
Our case series identified a total of 23 biallelic *CHEK2* patients. The cohort included 6 *CHEK2* (c.1100delC) homozygotes and 17 *CHEK2* compound heterozygotes, comprised of truncating mutations as well as low penetrant, pathogenic mutations. Detailed pedigree and clinical data was available for 2 patients and their families. These cases are described in Figure 1.

Family 1: The proband was referred due to a family history of breast cancer diagnosed in her sister at age 32. Her sister underwent genetic testing revealing biallelic *CHEK2* mutations (c.1100delC and c.470T>C). The proband's maternal aunt, diagnosed with breast cancer at age 47, underwent genetic testing revealing a monoallelic *CHEK2* (c.470T>C) mutation, making the proband's mother an obligate carrier of the monoallelic *CHEK2* (c.470T>C) mutation. It is unclear whether the biallelic *CHEK2* mutations are in cis or trans, but the presence of the single mutation the proband's maternal aunt suggests that the mutations are likely in trans.

Family 2: The proband was referred due to a personal history of young onset breast cancer diagnosed at age 29. Multi-gene panel testing revealed biallelic *CHEK2* mutations (c.1100delC and c.1011C>A). No cascade testing has been performed in this family to help clarify inheritance and/or to help assess whether the *CHEK2* mutations are in cis or trans.

Pedigree and clinical data for the remainder of our biallelic *CHEK2* cohort has not yet been ascertained.

Figure 1: Pedigrees of Biallelic *CHEK2* Females



Conclusions

Both cases of biallelic *CHEK2* mutations demonstrate affected females with an earlier age of onset breast cancer (average age 30.5 years). This is similar to Adank M et al (2011) findings; biallelic *CHEK2* (c.1100delC) carriers had an average age of onset for their first breast cancer at age 44 (range of 26-63). For other high risk breast cancer genes such as *BRCA1* and *BRCA2*, the average age of onset breast cancer is age 45 (95% CI 38-53). In comparison, studies have reported monoallelic *CHEK2* carriers to have an average age of onset of their first breast cancer at age 50 (95% CI 43-59).

Our case series is the largest cohort of biallelic *CHEK2* mutation carriers reported to date and includes compound heterozygotes. As current published studies do not include data pertaining to compound heterozygous *CHEK2* females, our data highlights the need for additional information to help characterize the phenotype of females with biallelic *CHEK2* mutations. Our two cases of *CHEK2* compound heterozygosity suggest a younger age of breast cancer onset as compared to women with monoallelic *CHEK2* mutations. If more evidence about biallelic *CHEK2* carriers is reported and confirms a younger-onset breast cancer phenotype, there will be a need to evaluate the possibility of changes to screening recommendations in this population.

References

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