# Novel large rearrangement of RAD51D in an ovarian and breast cancer family

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## Introduction

Several recent studies have established RAD51D as an important ovarian cancer predisposition gene. The lifetime risk of ovarian cancer in carriers of a pathogenic RAD51D variant is approximately 7–12%, and updated management guidelines recommend consideration of risk-reducing salpingo-oophorectomy in at-risk individuals [1–3].

The majority of RAD51D pathogenic variants described thus far are nucleotide substitutions and deletions/insertions of a few bases—such as nonsense substitutions, frameshift indels, and consensus splice site substitutions—leading to a premature stop codon. To date, no gross genomic deletions have been reported in the literature. Herein, we report a novel gross deletion involving RAD51D exons 9 and 10 in an individual with ovarian cancer and a family history of breast and ovarian cancer.

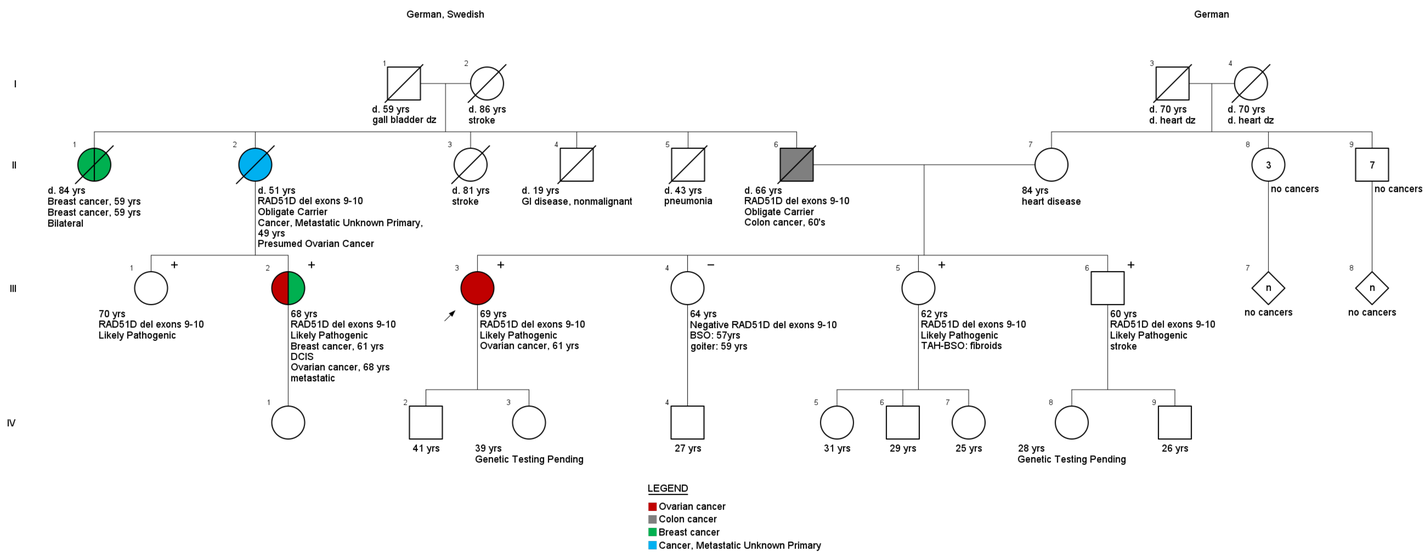
## Case Report

The proband is a 62-year-old woman diagnosed with epithelial ovarian cancer at age 61 who underwent germline sequencing and deletion/duplication analysis of 23 genes associated with increased risk for breast or gynecologic cancers. Also included were 12 genes with preliminary evidence of an association. A gross deletion of the genomic region encompassing exons 9 and 10 of the RAD51D gene was identified. No reportable variants were found in the remaining tested genes.

The proband's paternal cousin, subsequently confirmed to carry this deletion, was diagnosed with ductal carcinoma in situ at age 61 and ovarian cancer at age 68. The proband's paternal aunt (deceased at age 51) was an obligate carrier of the deletion reportedly diagnosed with an abdominal cancer, presumed to be ovarian, at age 49.

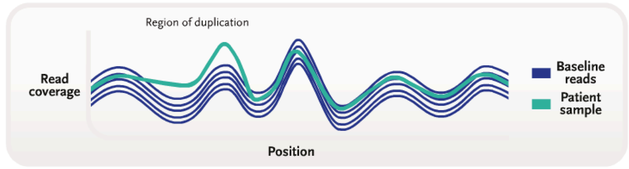
Additionally, the proband's 63 year old sister carries this deletion and is unaffected, but underwent total abdominal hysterectomy bilateral salpingo-oophorectomy (TAH-BSO) in her early thirties. Another sister, age 64 and unaffected, was tested and negative for the deletion. Additional family history includes another paternal aunt diagnosed with breast cancer at age 59. This aunt has not yet been tested for the familial deletion in RAD51D.

**Pedigree:**




## Methods

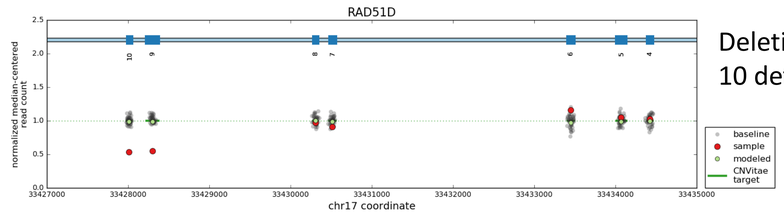
Copy number analysis was performed by a validated algorithm, CNVitae, to detect deletions and duplications with next–generation sequencing (NGS) [4]. The algorithm calls exonic deletions and duplications by calculating the statistical likelihood of each copy number state through comparison of the depth of sequence coverage at targeted exons to depth measured from data of a set of baseline samples.



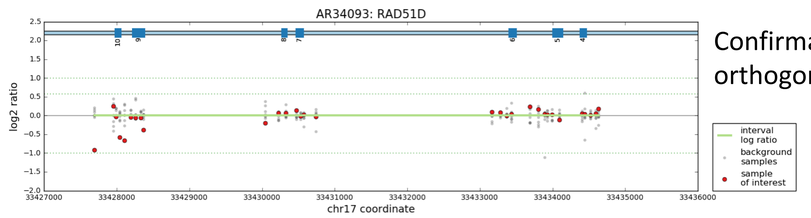

Read-depth approach to exon level copy number analysis by NGS. Example of a duplication.

## Analysis and Findings

A deletion of RAD51D exons 9-10 was detected with CNVitae and confirmed with an orthogonal array comparative genomic hybridization (aCGH) assay.




Deletion of RAD51D exons 9-10 detected by CNVitae




Confirmation with an orthogonal method (aCGH)

## Discussion

- This is the first report of a gross deletion involving exons 9 and 10 of RAD51D in a family with a substantial history of ovarian and breast cancers.
- Gross deletions may be difficult to detect with standard methodologies. CNVitae uses an NGS-based deletion/duplication method, which ensured detection of the RAD51D deletion in this family.
- Although the most frequent mutations encountered in hereditary cancer genes are small indels or single-base substitutions that result in premature stop codons, large genomic rearrangements have been identified in HBOC families and account for a small but significant proportion of cases in several populations [5-6]. Our findings support the inclusion of RAD51D in the list of genes in which gross deletions/duplications are considered for hereditary cancer risk.

## References

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