The curious case of a woman with two BRCA1 mutations in trans.

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Since the identification of *BRCA1* twenty years ago there has not been a single unequivocal case of anyone (even in populations where there is a high frequency of founder mutations) harboring two *BRCA1* mutations in trans, suggesting that this is embryonically lethal. These findings have been substantiated by animal models where no viable offspring *Brca* null mice have been generated by crossing heterozygote carriers. It is known that Brca1 mice can be partially rescued by *Tp53* mutations, but they do not survive well. Recently one patient has been reported with a nonsense mutation on one *BRCA1* allele and a missense on the other. The patient in this study suffered from malignancy, intellectual disability and a number of other symptoms. The missense variant has not been extensively verified and as such can not verified as pathogenic at this time.

Here we report a woman, diagnosed with breast cancer during her fourth decade of life, who has been shown to harbour one nonsense mutation and a splice site mutation. Both changes results in the loss of wild-type *BRCA1*. The question raised by this finding is: How come this woman is alive and outside of her initial presentation is currently healthy? An in depth molecular analysis was performed which revealed the complexity of *BRCA1* expression and how this could only be achieved by close examination of other family members. The outcome of the study represents the most likely explanation for this extraordinary case.