Author’s response to reviews

Title: Mutational analysis of BRCA1 and BRCA2 genes in women with familial breast cancer from different regions of Colombia

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Version: 1 Date: 12 Jun 2019

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Response to Reviewers.

Reviewer #1.

The main outcome of this study is a (very) rare occurrence of overtly deleterious (protein-truncating) mutations in BRCA1/2 genes in familial breast cancer patients. It has to be discussed in great detail.

What were the criteria for selection of the patients?

These criteria were added to manuscript. See Methods, lines 6-10, in blue.

Please provide characteristics of the patients in more detail.

The data collected from the patients were family history, age, type of cancer and bilaterality (see table 1, added to manuscript).

No data derived from the study of pathology as hormonal markers, TNM, or tumor stage were collected. The regional medical centers did not have this information available.

What BRCA1/2 alterations were detected in related countries and ethnic groups?
This information has been added to manuscript. See in discussion page 8, second paragraph lines 3 -9, in blue.

I disagree with relying on silico tools while estimating pathogenicity of missense mutations in BRCA1/2 genes: this is a very sensitive issue, one cannot claim cancer-predisposing role of missense BRCA1/2 variants in the absence of firm clinical evidences.

The table 1, added to the manuscript, shows a frequency of invasive ductal carcinoma of 88% in the sample collected. The high frequency found in our work is in accordance with data from the National Breast Cancer Foundation (https://www.nationalbreastcancer.org/invasive-ductal-carcinoma) where a diagnosis of this type of breast cancer is estimated between 70 - 80% of the cases.

It is also interesting to observe in this table that the average age for cancer diagnostic, in half of the patients, is less than 45 years.

Although important clinical data are lacking, the pathogenicity of these variants could be tested in future studies by segregation analysis or in vitro cell studies where the level of expression and alteration of the protein could be evaluated.

Reviewer #2.

Answer: All references were reviewed.