Reviewer's report

Title: Amplification of HER2 is a Marker for Global Genomic Instability

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Reviewer: Anne-Marie Cleton-Jansen

Reviewer's report:

This paper describes an evaluation of allelic imbalance in breast tumours in relation to Her2/neu gene amplification.

Major Compulsory Revisions

1. I am not a statistician, but the analysis of the confounding factors (ER and grade) in relation to AI and Her2 amplification seems not completely correct. Of course the fact that the authors address the possibility of confounding effects of other parameters is very good, but the AI itself is also a confounding factor, especially when occurring on the same chromosome. Furthermore, the analysis itself has not been described in detail. Presumably the samples in both groups (Her2amplified or Her2negative) were matched according to grade and ER status. Of course the groups will then become quite small, since the Her2amplified group contains only 41 cases. Concluding, I may be wrong and the statistics may be well performed, but from my view as a biologist it is not surprising that Her2 amplification associates with genomic instability, because Her2 is mostly amplified in grade III breast tumors, which have a higher degree of AI than low grade tumors.

2. The authors aim at identifying chromosomal changes that are common in Her2-amplified tumours. They indeed observe a higher incidence of allelic imbalance (AI) for microsatellite markers at 11q, 16q, 18q. However, these are quite commonly deleted regions in breast cancer, so how can these be specific for the 20% tumours with Her2 amplification? It might have been better to look at other regions that are less commonly deleted, to identify real specific loci for Her2. It may be a bit overstated to say that genes in these regions contribute to pathogenesis of Her2 positive tumors (page 9)

Minor Essential Revisions

1. It is not clear from the text or the tables how many tumors were successfully analyzed for AI on all loci, all 194 cases? Please clarify.

2. The color of the FISH signals in figure 1 should be clarified

3. In table 1 Menopausal should be followed by > 50 years

Level of interest: An article of importance in its field

Quality of written English: Acceptable
**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests