Germline CDH1 deletions in hereditary diffuse gastric cancer families.

Germline CDH1 point or small frameshift mutations can be identified in 30-50% of hereditary diffuse gastric cancer (HDGC) families. We hypothesized that CDH1 genomic rearrangements would be found in HDGC and identified 160 families with either two gastric cancers in first-degree relatives and with at least one diffuse gastric cancer (DGC) diagnosed before age 50, or three or more DGC in close relatives diagnosed at any age. Sixty-seven carried germline CDH1 point or small frameshift mutations. We screened germline DNA from the 93 mutation negative probands for large genomic rearrangements by Multiplex Ligation-Dependent Probe Amplification. Potential deletions were validated by RT-PCR and breakpoints cloned using a combination of oligo-CGH-arrays and long-range-PCR. In-silico analysis of the CDH1 locus was used to determine a potential mechanism for these rearrangements. Six of 93 (6.5%) previously described mutation negative HDGC probands, from low GC incidence populations (UK and North America), carried genomic deletions (UK and North America). Two families carried an identical deletion spanning 193 593 bp, encompassing the full CDH3 sequence and CDH1 exons 1 and 2.
Other deletions affecting exons 1, 2, 15 and/or 16 were identified. The statistically significant over-representation of Alus around breakpoints indicates it as a likely mechanism for these deletions. When all mutations and deletions are considered, the overall frequency of CDH1 alterations in HDGC is approximately 46% (73/160). CDH1 large deletions occur in 4% of HDGC families by mechanisms involving mainly non-allelic homologous recombination in Alu repeat sequences. As the finding of pathogenic CDH1 mutations is useful for management of HDGC families, screening for deletions should be offered to at-risk families.