E-cadherin has a determinant role in tumour progression, acting as an invasion and metastasis suppressor. Germline mutations of E-cadherin gene (CDH1) occur in 30% of families with Hereditary Diffuse Gastric Cancer (HDGC); of these 23% are missense mutations. The CDH1 missense mutations described to date span the entire gene and some lead to significant functional consequences. In this study, we explored the hypothesis that mutations affecting different E-cadherin protein domains have distinct effects on cell motility. To accomplish our objective we characterized the effect of eleven HDGC CDH1 germline missense mutations (T118R, L214P, G239R, A298T, T340A, P373L, R749W, E757K, E781D, P799R and V832M) on cell motility. Further, we studied their effect on the activation of signalling pathways known to be relevant for cell motility such as the EGFR, Src kinase and MAPKs. CDH1 mutations localized on the extracellular and juxtamembrane domains, both affecting the integrity of the extracellular domain, led to increased cell motility accompanied by increased EGFR activation. Moreover, we observed that cells expressing extracellular mutants exhibit increased activation of Src kinase and p38 MAPK. Our results allowed the identification of the E-cadherin domains pivotal for cell motility, further demonstrated a genotype-phenotype correlation, and defined a subset of HDGC cases which may benefit from
EGFR inhibitors.

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