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Actionable activating oncogenic ERBB2/HER2 transmembrane and juxtamembrane domain mutations

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We analyzed a family from India in which several members were diagnosed with stage IV NSCLC within six months of each other. The pattern of lung cancer in the family members across two generations indicated an inherited form of early-onset lung cancer. Interestingly all the affected members were non-smokers and were diagnosed with lung adenocarcinoma. We performed whole exome sequencing of DNA obtained from blood corresponding to three affected family members. We identified a germline heterozygous point mutation, G660D in ERBB2 gene. This mutation mapped to the transmembrane domain (TMD) of HER2. We then analyzed a mutation database representing 111,176 patient tumors for presence of the G660D mutation we observed in the familial case. Interestingly, we identified G660D HER2 TMD mutation to occur as a somatic alteration in multiple patient tumors. We also identified several recurrent juxtamembrane domain (JMD) mutations, including R678Q, E693K and Q709L. Using a saturation mutagenesis screen and testing of patient derived mutations we found that TMD and JMD mutations activate HER2. We found that the TMD and JMD mutations are poised to either improve the active dimer interface or stabilize an activating conformation. Further, we established the involvement of asymmetric kinase domain dimerization in the activation of G660D HER2 mutant. We tested anti-HER2 antibodies and small molecule kinase inhibitors against the HER2 mutants and found that they block their activity. Consistent with this, the G660D germline mutant lung cancer patient showed remarkable clinical response to HER2 inhibition. We estimate >6000 TMD/JMD mutant patients across multiple cancers are likely to benefit annually from targeted HER2 therapy.

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