Supporting Information

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Fig. S1. Electron densities around R577 of active FGFR1-3P and R577E of FGFR1-RE. (A) Electron density of active FGFR1-3P (3GQI) around the kinase insert region. Two kinase domains are shown in cyan and green ribbon representation. D519 of molecule E and R577' and Y583E' of molecule S are shown in stick presentation. AMP-PCP is shown in stick presentation, and the Mg ion is shown as a blue sphere. The $2F_o - F_c$ electron density map is shown in gray and contoured at 1.0σ . (*B*) An example $2F_o - F_c$ electron density map of FGFR1-RE is shown with two kinase domains in a ribbon diagram, and the side chains of R576 and R577E are shown in stick presentation and contoured at 1.0σ .



Fig. S2. Superpositions of all four molecules of FGFR1-RE. The four molecules of FGFR1-RE in the crystal lattice are superimposed and colored in gradient from green to light green.



Fig. S3. Superposition of FGFR1-RE dimer with FGFR1 kinase structure (1FGK). The R577E structure has four molecules in the asymmetric unit, arranged as two head-tail dimers. Inactive state structure of FGFR1 (e.g., 1FGK) was superposed onto the R577E mutant structure presented in this study. For all four molecules in the asymmetric unit there are significant clashes between the activation segment (between residues 652 and 663) and the N-terminal region of the α C-helix (residues 516–525) of the crystallographically related dimer molecule. The dimer of FGFR1-RE is colored in green and cyan, and the inactive FGFR1 kinase (1FGK) in magenta. The crystal form reported for R577E could not accommodate an inactive state FGFR1 kinase domain. We propose that this crystal form has trapped the kinase while it was sampling the active state conformation. General (A) and enlarged (B) views of the contact regions between FGFR1-RE and FGFR1 (1FGK) reveal clashes between the activation loop of FGFR1 (1FGK; magenta) and the β 3- α C loop of FGFR1-RE.



Fig. S4. Structure-based alignments of sequences from human FGFR1 and FGFR2 kinases and locations of loss-of-function mutations near helix α G. (A) The degree of residue conservation is shown with either blank (lowest), one dot, two dots, or a star (highest) for the four FGF receptors at the bottom of FGFR1 and FGFR2 sequences. The overall structure of FGFR1 is shown in gray ribbon, and the corresponding regions in the structure of sequences are indicated with arrows. Green colored residues are from molecule E (the enzyme), and the red colored residues are from molecule S (the substrate). (*B*) Locations of loss-of-function mutations in loops near the helix α G of FGFR1 and FGFR2 are shown in blue boxes. Amino acids from molecule E are shown in green, and amino acids from molecule S are in red. Helix α G is marked with the black box with the label on top of the sequences.