



eFigure 1. Distribution of variants across the 34 epidermal growth factor-like repeat (EGFR) domain of *NOTCH3*.

The EGFR cut-offs in figure 4 were chosen based on previous findings and this distribution. We initially started with the cut-off proposed by Rutten et al. (2019), i.e. EGFR 1-6 versus the rest. We also assessed, in a pre-specified hypothesis, variants in the ligand-binding domain (EGFRs 10-11) as these have been suggested to differ in clinical phenotype. We then further sub-divided the population based on the distribution of the variants across EGFR domains that are present in our patient cohort, shown in eFigure 1 (included below), to ensure a reasonable number of participants in each subgroup of figure 4.