Kawasaki disease (KD) is a multisystem vasculitis that predominantly targets the coronary arteries in children. Phenotypic similarities between KD and recurrent fever syndromes point to the potential role of inflammasome activation in KD. Mutations in NLRP3 are associated with recurrent fever/auto-inflammatory syndromes. We show that the KD-associated genetic polymorphism in Inositol-triphosphate 3-kinase C (ITPKC) (rs28493229) has important functional consequences, governing ITPKC protein levels and thereby intracellular calcium, which in turn regulates NLRP3 expression and production of IL-1β and IL-18. Analysis of transcript abundance, protein levels, and cellular response profiles from matched, serial biospecimens from a cohort of genotyped KD subjects points to the critical role of ITPKC in mediating NLRP3 inflammasome activation. Treatment failure in those with the ‘high-risk’ ITPKC-genotype was associated with the highest basal and stimulated intracellular calcium levels and with increased cellular production of IL-1β and IL-18 and higher circulating levels of both cytokines. Mechanistic studies using Itpkc-deficient mice in a disease model support the genomic, cellular and clinical findings in affected children. Our findings provide the mechanism behind the observed efficacy of rescue therapy with IL-1 blockade in recalcitrant KD, and identify that regulation of calcium mobilization is fundamental to the underlying immunobiology in KD.