Keratoconus is a chronic progressive disorder characterized by corneal deformation. It usually affects adolescents and young adults, reducing vision and decreasing the quality of life. To map its genetic architecture, we conducted a multi-trait genome-wide association study integrating corneal endophenotypes and case-control cohorts. Our stepwise approach began by selecting and analyzing four key endophenotypes of keratoconus in 16,464 participants. Second, we performed a multi-trait analysis using the selected endophenotypes, identifying 80 loci significantly associated with one endophenotype or more. Among these loci, 25 (5 novel) were significantly associated with keratoconus (Bonferroni-corrected $P \leq 6.3 \times 10^{-4}$). Third, a case-control meta-analysis (6,372 cases; 593,541 controls) revealed that 51 loci (8 novel) were significantly associated with keratoconus ($P \leq 5.0 \times 10^{-8}$). The gene-set analysis implicated extracellular matrix integrity, glucosylceramidase regulation and cell-differentiation pathways. Our integrated approach enhanced locus detection and strengthened biological insights, paving the way for improved genetic risk profiling and for identifying precise genetic targets.