Table 1 Decision framework for method selection

Scenario / Input	Genetic architecture	Data condition	Recommended method	Common additional settings
Majority of variants are causal, with concordant effects	Concordant; moderate-to-high causal proportion (≥20–30%)	Moderate-to-large sample size; MAC ≥ 10–50	Burden (VT / weighted)	URV collapsing; ancestry-stratified frequencies; parallel reporting of SKAT-O
Effect directions unknown or mixed	Heterogeneous; sparse causal variants (≤10–15%)	Any	SKAT-O / MK-SKAT	Multi-weight / multi-kernel; Cauchy combination
Many non-causal or oppositely directed effects	Strong heterogeneity	Any	SKAT	Linear kernel + Beta weights; multiple masks
Extremely imbalanced case–control design	Any	Limited number of cases (e.g., >200 is more stable)	SKAT / SKAT-O	SPA or robust test variants; Firth comparison analysis
Small sample size (low MAC)	Any	Few cases (<200)	SKAT-O (with correction)	Permutation or approximate correction; stricter masks
Limited computational resources (initial screening)	Uncertain	Any	Burden / VT → SKAT-O confirmation	Stratified screening; fine examination of candidate sets