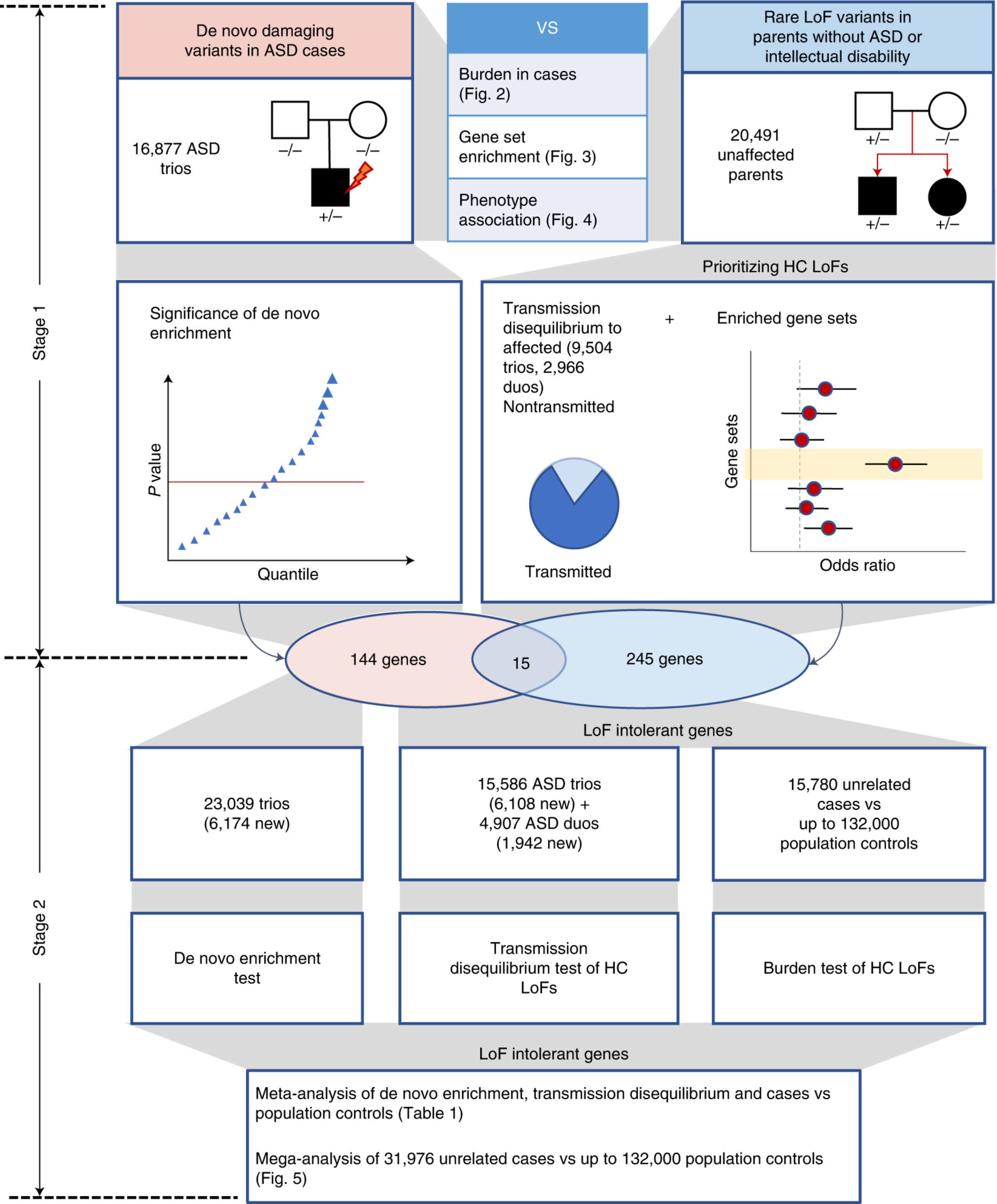
Stage 1
De novo damaging variants in ASD cases
16,877 ASD trios
–/–
–/–
+/–
VS
Burden in cases (Fig. 2)
Gene set enrichment (Fig. 3)
Phenotype association (Fig. 4)
Rare LoF variants in parents without ASD or intellectual disability
20,491 unaffected parents
+/–
–/–
+/–
+/–
Prioritizing HC LoFs
Significance of de novo enrichment
P value
Quantile
Transmission disequilibrium to affected (9,504 trios, 2,966 duos)
Nontransmitted
Transmitted
+
Enriched gene sets
Gene sets
Odds ratio
144 genes
15
245 genes
LoF intolerant genes
23,039 trios (6,174 new)
15,586 ASD trios (6,108 new) + 4,907 ASD duos (1,942 new)
15,780 unrelated cases vs up to 132,000 population controls
Stage 2
De novo enrichment test
Transmission disequilibrium test of HC LoFs
Burden test of HC LoFs
LoF intolerant genes
Meta-analysis of de novo enrichment, transmission disequilibrium and cases vs population controls (Table 1)
Mega-analysis of 31,976 unrelated cases vs up to 132,000 population controls (Fig. 5)