Discovery of candidate functional sequence variants

250K SNP microarray genotyping
- 386 family members from 26 extended and four 2-generation ASD families

Haplotype-sharing analysis
- 25 chromosomal regions identified

Custom sequence capture and Next-Gen DNA sequencing
- 25 chromosomal regions and additional regions/gene candidates from literatures (total 1,800 genes)

DNA Sequence alignment and variant detection
- In Silico functional variant annotation
  - 2,825 putative candidate functional sequence variants

Design custom microarray
- Successful probe design for 2,799 variants = 2,799 candidate variants

Custom microarray manufacturing
- Successful probe synthesis for 2,413 variants = 2,413 candidate variants

Array processing and analysis, case/control and discovery family samples

Sample QC, 3000 cases, 6000 controls
- Discard samples due to:
  - Poor DNA sample quality
  - Whole-chromosome abnormalities
  - Sample from duplicate enrollment
  - Samples from close relatives

SNP QC
- Discard non-polymorphic variants (false positives)

Principal component analysis
- Recalculate and correct for principal components
- Remove non-Caucasian samples to avoid errors due to population stratification

584 Sequence variants for association testing

Select single sample from multiplex families based on PCA
- 631 cases removed from multiplex families, 39 related controls removed

Final set of unrelated Caucasian samples: 1541 cases, 5785 controls.

Association testing/Segregation Analysis
- 11 SNPs with OR>1.5 (Table 3), 28 SNPs seen only in discovery families (Table 4)