A geometric framework for the evaluation of rare variant tests of association

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The tidal wave of next-generation sequencing (NGS) data has arrived, but more questions than answers exist about how to best analyze NGS data to investigate the potential contribution of rare genetic variants on common human diseases. Numerous rare variant association testing methods have been proposed which all attempt to aggregate association signals across multiple variant sites in an effort to increase statistical power, since single variant association testing methods are extremely under-powered for rare single nucleotide variants. While emerging simulation methods suggest that some rare variant testing methods work better in certain genetic architectures than other methods, little concrete understanding of the tests is available. In this poster we propose a geometric framework which quickly classifies existing rare variant tests of association into two broad categories: length and joint tests. We demonstrate how genetic architecture (relative risk distribution, allele frequency distribution and number of variants) directly relates to the behavior of length and joint tests. We then illustrate further implications of the geometric framework including the impact of variant weighting strategies, population stratification and genotype uncertainty. We also describe how the geometric framework suggests numerous potential alternative rare variant association tests, and how they will behave. The geometric framework articulates the connection between disease architecture and test behavior, thus providing a clear set of next steps for applied and theoretical researchers.