

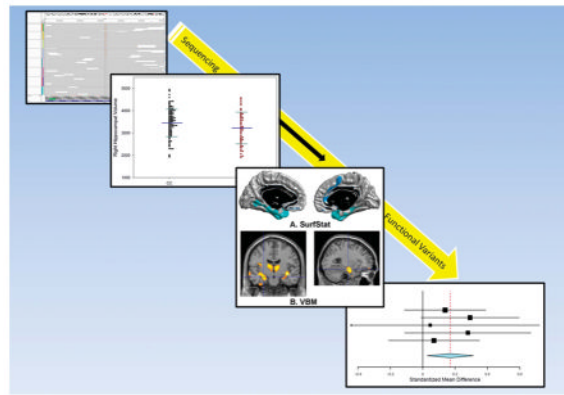
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Identification of functional variants from whole-exome sequencing, combined with neuroimaging genetics

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The image illustrates the schematic view for discovery of functional variants from whole-exome sequencing. We report on a novel strategy combining whole-exome sequencing and neuroimaging genetics to identify functional variants associated with the rate of hippocampal volume loss in mild cognitive impairment. Whole-exome sequencing was performed on a modest sample using an extreme trait design by selecting individuals at the extremes of the distribution of 2-year longitudinal change in hippocampal volume. To further investigate and extend the exome findings in a larger sample, we conducted quantitative trait analysis, including whole-brain search, combined with genotype imputation. Finally, meta-analysis was performed to validate the exome findings across five independent cross-sectional cohorts. Combining next-generation sequencing and quantitative imaging phenotypes holds promise for the discovery of variants involved in neurodegeneration and other brain disorders. For more information on this topic, please refer to the article by Nho *et al.* on pages 781–787.