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Diagnostic Exome Sequencing provides diagnoses among patients with abnormal brain MRI findings

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Diagnostic exome sequencing (DES) is successful in solving the diagnostic odyssey for 30-40% of undiagnosed patients with a broad range of underlying Mendelian disorders. Among the first 500 reported DES families, 168 (34%) had a previous abnormal brain MRI. Positive findings were uncovered in 66 of these families (39%). Positive and likely positive alterations within clinically characterized genes were identified in 55 of the 168 families, for a molecular diagnostic rate of 33% among characterized genes. A novel gene finding was uncovered among 11 families (7%). The diagnostic rates among patients in this cohort are similar to the overall detection rates among all 500 referred patients (39% overall positive rate and 30% among characterized genes). Among the 66 positive findings, 43 (65%) were autosomal dominant, 12 (18%) were autosomal recessive, and 11 (17%) were X-linked molecular defects. The 66 positive patients with abnormal MRI findings were significantly less likely to have an autosomal recessive finding (18%) as compared to the entire positive cohort (51/163; 31%) (p=0.05). The most commonly observed MRI findings among the patients with positive findings were cerebellar hypoplasia, delayed myelination, cerebral atrophy, and agenesis of the corpus callosum. Several well-known molecular diagnoses were provided and/or confirmed including Leigh Syndrome, Genetic Prion Disease, and spinocerebellar ataxia. These data highlight the utility of DES in providing the most comprehensive molecular diagnosis given the diversity of genetic findings including 7% within novel genes.