Frequency of carriers for rare recessive Mendelian diseases in a Brazilian cohort of 320 patients

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Several metabolic disorders follow an autosomal recessive inheritance pattern. Epidemiological information on inherited disorders may be useful to guide health policies for metabolic diseases, but it is often inadequate, particularly in developing countries. We aimed to calculate the carrier frequencies of rare autosomal recessive metabolic diseases in a cohort of Brazilian patients using exome sequencing (ES). We reviewed the molecular findings of ES from 320 symptomatic patients who had carrier status for recessive diseases. Using the Hardy-Weinberg equation, we estimated metabolic disease frequencies \( (q^2) \) considering the respective carrier frequencies \( (2pq) \) observed in our study. We calculated the sensitivity of carrier screening tests based on lists of genes from five different clinical laboratories that offer them in Brazil. A total of 205 rare variants were reported in 138 different genes associated with metabolic diseases from 156 patients, which represents that almost half (48.8%) of the patients were carriers of at least one heterozygous pathogenic/likely pathogenic variant for rare metabolic disorders. We estimated that an average of 55.8% of the variants would not have been detected by carrier screening panels (average sensitivity of 44.2%). The combined frequencies of rare autosomal recessive metabolic diseases were estimated to be 10.96/10,000 (or ~0.1%). This study shows the potential research utility of ES to determine carrier status for rare metabolic diseases, which may be a possible strategy to evaluate the clinical and social burden of these conditions at the population level and guide the optimization of health policies and carrier screening panels.