عنوان مقاله:

Genetic epidemiology of rare autosomal recessive disorders investigated through consanguineous marriages: the Homozygosity Index approach

محل انتشار:

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خلاصه مقاله:

The theoretical foundations to predict the frequency of alleles associated withrare autosomal recessive (RAR) disorders through the study of consanguineosmarriages were established in the pre-molecular era by the Swedish geneticstDahlberg, who first noticed in 1943 that the proportion of consanguineousparents of children affected with any of such disorders (C') is inverselyproportional to the frequency of the mutated gene in the general population(q). In Italy we were then able to calculate q for PKU, Friedreich ataxia and CFeven before the cloning of the respective genes thanks to the Vatican Archive of consanguineous marriages, created by Cavalli-Sforza and coworkers, whichdocuments the variations in time and space of consanguineous marriages inthe general population broken down for the different Italian regions andprovinces for five years periods during almost 400 years (1600–1964). Theprobability that a child of consanguineous parents carries two copies of thesame allele identical by descent (IBD) is called autozygosity (=homozygosityby IBD). Then if one knows precisely the frequency of consanguineousmarriages in the general population for any given time period and populationsubgroup (C) from the Vatican Archive and the proportion of consanguineousparents of children affected with a given RAR disorder (C'), q can be accuratelycalculated following Dahlberg's approach.Today a new epidemiological approach makes it possible to estimate q for aRAR disorder if you know the mutational spectrum, the proportion of trulyhomozygous patients determined by mutation analysis (HomozygosityIndex : HI) and the inbreeding coefficient estimate (F) in a sample of affectedindividuals as we did for PKU and Mediterranean Fever in Lebanon andTurkey, and for Wilson disease in Sardinia. More recently we appliedsuccessfully the HI method to the study of Congenital Adrenal Hyperplasia(CAH) in mainland Italy and Sardinia (Clin. Genetics, 93, 223-227, 2018).A few interesting conclusions can be drawn from these papers regarding somecost-effective choices in planning population screenings and public health policies in particular for the most important neurogenetic disorders. First ofall, genetic epidemiology based on consanguinity can make effective use ofgenomic data from the literature to calculate the inbreeding coefficient (F)which makes the HI approach easier and more precise. Secondly it shows thatthis genetically based epidemiological approach overcomes the pitfalls ofbiochemically based screenings. In conclusion the HI approach (made possibleby available molecular ... data of

کلمات کلیدی:

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