MUTATIONAL LOAD IN EUROPEANS

Next-generation sequencing of human genomes has revealed millions of genetic variants and from sequencing parent-child trios we know how many de novo variants arise in the offspring (Nature Genetics). Some of these variants have been annotated as deleterious, i.e. causing disease. This latter group of variants constitutes the mutational load. Several studies have attempted to define this load in specific populations. The results may differ based on the different parameters used in the study, i.e. algorithms, statistics, sets of investigated genes and sequencing approaches (exon sequencing or direct genomic sequencing). Furthermore, differences in allele frequency between populations may have been caused by a genetic drift (e.g. population bottleneck, founder effect).

Fridman et al., in their recent paper in Am. J. Hum. Genet., investigated the mutational burden in Dutch and Estonian populations (4,120 and 2,327 unrelated individuals, respectively) by testing the exons of 1,929 OMIM genes that are associated with an autosomal recessive monogenic disorder. They found that, on average, each individual carries 2.3 (range 0-11) (Dutch) or 2.0 (range 0-9) (Estonian) pathogenic or likely pathogenic (PLP) variants. Of these 1,929 genes, 1,119 are associated with severe phenotypes and frequency of PLPs was 1.5 (range 0–8) and 1.1 (range 0–6) in the Dutch and Estonian cohorts, respectively. They comment that these figures represent a lower bound-estimate due to their strict selection criteria.

The main objective of the study was to provide figures on genetic risk for the two populations and for the European population in general. They estimated that 0.8% –1% of unrelated European couples are at risk for a child with a severe AR condition (~ 225 per 100,000 births). 90% of this risk is due to the ~ 100 most frequent genes. The risk increases by ~ 16 times if the partners are first cousins (~ 3,400 per 100,000 births). Many other details on risks and selection against deleterious variants are reported in the study.