Lessons learned from postnatal diagnostics: phenotype-driven penetrance analysis in the assignment of disease liability of genetic variants

Milan Macek, Czech Republic

Currently, massively parallel sequencing is becoming broadly available in preimplantation, prenatal and postnatal diagnosis. Consequently, an increasing number of patients and apparently healthy individuals undergo whole exome sequencing which identifies a large number of variants. However, their disease liability is mostly not known and various software prediction tools have a limited utility. Proper assessment of their penetrance is thus important since the majority of databases assume disease association of variants based on their prevalence in clinically diagnosed cases. This ascertainment bias is particularly relevant in preimplantation and prenatal diagnosis. An international effort focused on the comprehensive penetrance analysis in cystic fibrosis (www.cftr2.org) may serve as a model for other initiatives of this kind