Polygenic dissection of major depression clinical heterogeneity

The molecular mechanisms underlying Major Depressive Disorder (MDD) are largely unknown. Limited success of previous genetics studies may be attributable to heterogeneity of MDD that, similarly to other complex diseases, may represent a diagnostic aggregation of biologically different subtypes.
We examined the genetic overlap of MDD and two common clinical subtypes, typical and atypical, with major psychiatric disorders (MDD, bipolar-disorder, schizophrenia) and metabolic traits (BMI, C-reactive protein and triglycerides).
Data were from 1,530 patients of the Netherlands Study of Depression and Anxiety (NESDA) and 1,700 controls mainly from the Netherlands Twin Register (NTR). Polygenic risk profiles for the psychiatric and metabolic traits were generated from meta-analysis results of large international consortia.
Results highlighted partially different polygenic signatures across MDD subtypes: while typical MDD had a stronger genetic overlap with psychiatric traits, particularly with schizophrenia, atypical MDD showed an additional contribution of genetic signals from the metabolic traits of BMI and triglycerides. Results of the present study also showed that 31% of the variance in MDD liability was explained by the joint effect of all common genetic variants. The same estimates were higher for the subtypes: 38% for typical and 43% for atypical MDD.
In conclusion, MDD subtypes are characterized by partially distinct polygenic liabilities and may represent more homogeneous phenotypes. Disentangling MDD heterogeneity may help the psychiatric field moving forward in the search for molecular roots of depression.