RARE VARIANTS IN DOMINANT GENES CAUSING MILD PHENOTYPIC CONSEQUENCES

It is well known that monogenic variants can display different effects in different individuals.
In a paper which appeared in Nature Biotechnology in 2016 Chen et al.[1] reported results of exome analysis of 874 genes in 589,306 individuals. Unexpectedly, they found 13 "normal" adults harboring mutations for 8 severe Mendelian conditions, with no clinical manifestation of the indicated disease.

A very similar task was performed by Kingdom et al. (Am J Hum Genet *in press*) who took advantage of the UK Biobank (UKB) to investigate phenotypes associated with rare protein-truncating and missense variants in 599 monoallelic DDG2P genes (clinically curated Developmental Disorders Gene2Phenotype Database) by using whole-exome-sequencing data from ~200,000 individuals and rare copy-number variants overlapping known developmental disorders loci by using SNP-array data from ~500,000 individuals.

They suggest that (1) many genes routinely tested within pediatric genetics have deleterious variants with intermediate penetrance that may cause lifelong sub-clinical phenotypes in the general adult population; (2) clinical studies may overestimate the penetrance of such rare variants, while population cohorts like UKB are likely to underestimate the penetrance as a result of ascertainment bias toward healthy individuals.

1. https://www.nature.com/articles/nbt.3514
2. https://www.sciencedirect.com/science/article/pii/S0002929722002178?via%3Dihub