GENETICALLY TRANSITIONAL DISEASE

In an exome screen of 874 genes in 589,306 normal individuals, Chen et al.[1] found 13 adults carrying mutations for 8 severe Mendelian conditions, without any clinical manifestations of the indicated disease. This is just one major example of the pervasive influence of genetic background on both penetrance and expressivity of mutations, indicating that the simplified distinction between monogenic and polygenic Mendelian diseases is inadequate.

In an article in Trends in Genetics, Yao et al.[2] propose using a new term, "Transitional Genetic Disease" (GTD), to describe cases where a mutation that would have a large effect is present but which in itself is insufficient to cause the disease. They suggest that a genetic disease can be considered as the result of gradients of four types of genetic architecture: monogenic, polygenic, GTD, and mixed. They provide examples to explain their proposal which, they conclude, is a preliminary framework that needs input from the medical community and professional societies for further guidance and recommendations.

1. https://www.nature.com/articles/nbt.3514
2. https://www.cell.com/trends/genetics/fulltext/S0168-9525(22)00289-X?rss=yes