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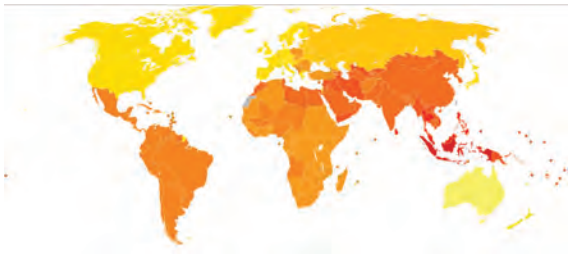
Schizophrenia affects about 0.5-1.0 % of the population at any one point in time, and the incidence is fairly homogenous from country to country. Individuals with schizophrenia typically exhibit both positive and negative behavioral symptoms—that is, the presence of some behaviors that are considered abnormal as well as the absence of some that are considered normal. Positive symptoms may include delusions of grandeur, auditory or visual hallucinations, and incoherent thought and speech. Negative symptoms include lack of typical emotional responses, flat affect, and lack of motivation.

The pathophysiology of schizophrenia is not completely understood, though it is generally accepted that the disorder arises as a result of dysregulated neurotransmitter systems. In particular, faulty dopaminergic and glutamatergic neurotransmission has been implicated. Furthermore, the risk of developing schizophrenia is known to be elevated in individuals with certain genetic predispositions. However, the specific genetic architecture underlying schizophrenia is not known.

In a recent study at Washington University in St. Louis School of Medicine, researchers completed a large-scale genetic study including more than 4,000 individuals with schizophrenia and 3,800 healthy individuals for comparison. They identified several specific "gene clusters," which they concluded may be associated with eight distinct phenotypic variants of schizophrenia. By matching any individual's genetic variations with that individual's specific symptoms, the team of researchers was able to delineate these separate classes of schizophrenia, a disease for which attempts at subclassification have historically been difficult and controversial. Specifically, the researchers looked for sets of a certain type of genetic variant known as a single-nucleotide polymorphism (SNP). This ad hoc grouping of SNP sets yielded 42 sets associated with at least a 70 % risk of schizophrenia. In total, 2891 SNPs were analyzed out of a total of 696,788; these 2891 were pre-selected based on their degree of association (p-value < 0.01) with a "global phenotype of schizophrenia" (Arnedo, J., et al. 2014).

Such a separation of schizophrenia into different disorders based on underlying genetic factors is potentially desirable for many reasons. In particular, it may enable prediction of the onset of schizophrenia, and thus increase the ability of healthcare providers to provide effective treatment. This refinement of a broad diagnostic category into subclasses is not a new idea in the field of mental illness; many other psychiatric illnesses are thought to have an underlying



A color-coded world map showing the global disease burden of Schizophrenia in terms of Disability-Adjusted Life Years, i.e., years of "healthy" life lost due either to early death or to living with disease, per 100,000 people. Burden ranges from yellow, at fewer than 185, to red, at more than 295.

heterogeneity similar to that now believed to exist in schizophrenia.

Dr. C. Robert Cloninger, one of the principal investigators of the Washington University in St. Louis study, has been widely quoted on his statement regarding the nature of genes: "Genes don't operate by themselves. They function in concert much like an orchestra, and to understand how they're working, you have to know not just who the members of the orchestra are but how they interact." The rise of genome-wide association studies such as Cloninger's have facilitated research regarding the dynamic interplay of genes and "allowed the identification of individual genetic risk loci or at least markers linked to them" (Wray, N.R. & Visscher, P.M. 2010).

Recent work from other labs has complemented this increased understanding of schizophrenia's diagnostic subclasses with an increased understanding of its etiology. A study published in the journal *Nature* this past summer showed as many as 108 genes that may play into the onset and pathophysiology of schizophrenia, though it is difficult to ascertain which of these put otherwise healthy individuals at risk of developing the disorder (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

Often, neuropsychiatric illnesses lack a determinant phenotype. This is particularly true for schizophrenia, a disorder for which there are neither firm diagnostic tests nor a simple neuropathology. As such, large molecular genetic studies are often the most effective approach for identifying risk loci across the wide gamut this disorder runs. Such studies further the possibility of eventually identifying certain clinical syndromes by their underlying etiology. In turn, this makes person-centered treatment of complex disorders an

increasingly plausible mode of day-to-day clinical psychiatry in the near future.

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