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Clinical Neuroscience Research 5 (2005) 3–14

Clinical Neuroscience Research

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Neurogenetics: insights into degenerative diseases and approaches to schizophrenia

Christopher A. Ross*, Russell L. Margolis

Division of Neurobiology, Department of Psychiatry, Johns Hopkins University School of Medicine, 720 Rutland Avenue, Baltimore, MD 21287, USA

Abstract

The etiology and pathogenesis of neurodegenerative disorders has been greatly advanced by the discovery of mutations that cause Mendelian forms of these disorders. For instance, the CAG repeat expansion diseases have provided the opportunity to clarify the genotype-phenotype relationship in an entire group of disorders. Understanding of Alzheimer's disease pathogenesis has been greatly advanced by the appreciation that APP or presenilin mutations, duplication of *APP* in trisomy 21, and the ApoE4 allele may all function to increase accumulation of the toxic A-beta peptide. Similarly, interactions among the protein products of the genes implicated in rare Mendelian forms of Parkinson's disease suggest pathogenic pathways of potential relevance to the common sporadic forms of PD. Most cases of schizophrenia appear to arise from a combination of genetic and environmental factors, each making a small contribution to the phenotype, but identifying these factors has proven difficult. However, as in AD and PD, rare pedigrees exist in which major mental illness appears to be inherited in a Mendelian fashion, including two pedigrees in which schizophrenia or affective disorder is associated with mutations in *DISC1*. Determining the cellular localization, protein partners, and function of the normal and mutated *DISC1* protein may provide important insights into the more common forms of major mental illness. Thus the same approaches that have been successful for understanding neurodegenerative diseases may help elucidate the etiology and pathogenesis of schizophrenia and other psychiatric disorders.

Keywords: Psychosis; Bipolar disorder; Trinucleotide; triplet; Translocation; Neurodevelopment; Neurodegeneration; Schizophrenia; Huntington's disease; Parkinson's disease

1. Introduction

There is strong evidence for genetic contribution to schizophrenia, bipolar illness, and other psychiatric disorders. However, progress in uncovering specific genetic etiologies has been slow, for several reasons. First, the behavioral phenotypes have been difficult to define. This is manifested in the broad classifications of these disorders and their connections. There is uncertainty, for instance, in the relationship between bipolar disorder and schizophrenia. In addition this is manifested within each disorder, as it has been very difficult to define consistent subtypes or phenotypic variants. Second, unlike the classic neurodegenerative disorders, such as Huntington's disease, Alzheimer's disease and Parkinson's disease, there is no gold standard of neuropathology to help define classifications. Third, the genetics has turned out to be complex. While there is strong evidence for a genetic contribution to psychiatric disorders, the nature of this contribution remains elusive. Segregation analyses have failed to support classical Mendelian transmission. Current models are consistent with the contribution of at least a few genes, and quite possibly many genetic risk factors, perhaps with complex interactions. Even when candidate genes have been proposed, in most cases there have not been clear mutations identified, to help confirm causality, and to begin to delineate pathogenesis. Finally, the possible contribution of environmental factors such as infection or stress remains undefined.

By contrast, the genetics of neurodegenerative disorders has been more tractable. We believe that the experience in the neurodegenerative disorders may help to provide a framework to guide possible approaches to psychiatric genetics. The neurodegenerative disorders suggest how

* Corresponding author. CMSC 8-121, 600 North Wolfe Street, Baltimore, MD 21287. Tel.: +1 410 614 0011; fax: +1 410 614 0013.
E-mail address: caross@jhu.edu (C.A. Ross).

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doi:10.1016/j.cnr.2005.07.001

mutations in a relatively small number of genes can give rise to a complex and overlapping set of phenotypes. Furthermore, they provide insight into how the interactions of different gene products can provide clues to pathways which can elucidate pathogenesis, in turn clarifying etiology, classification and diagnosis. Ultimately the goal is to provide a rational approach to therapeutics. Examples will be drawn from Huntington's disease and other related diseases, Parkinson's disease, and Alzheimer's disease and fronto-temporal dementia. These may suggest precedents, as we approach the more complex problems of schizophrenia and other psychiatric disorders.

2. Huntington's disease and related disorders

Huntington's disease is an autosomal dominant neurodegenerative disorder characterized clinically by abnormalities of voluntary and involuntary movement, dementia, and psychiatric symptoms [1–3] The prevalence is about 1/10,000, with onset typically in mid-adulthood. While chorea is prominent in most cases, in some individuals, especially those with very young onset, rigidity, dystonia, and bradykinesia predominate. The disease is relentlessly progressive, with death occurring 10–20 years after disease onset. Neuropathology is most striking in the caudate nucleus and putamen, though the cerebral cortex is involved, and multiple other brain regions may be affected. The cerebellum is generally relatively spared.

The defining feature of the autosomal dominant spinocerebellar ataxias, in addition to mode of inheritance, is degeneration of the cerebellum, with concomitant clinical evidence of ataxia and dysmetria. Several regions of the cerebellum and its outflow tracts can be affected, and there is variable involvement of other brain regions, including the basal ganglia, brain stem, retina, and cerebral cortex. The variability exists within and between families. Prevalence of all autosomal dominant ataxias taken together is about the same as HD, and the clinical course, like HD, may be progressive over a few decades to death, or may be slow, with severe loss of functional capacity occurring late, if ever [4–6]

The genetic etiologies of both HD and the spinocerebellar ataxias has been largely solved over the past 12 years (Table 1, Fig. 1). HD is caused by an expanded CAG repeat in the huntingtin gene on chromosome 4p, resulting in a huntingtin protein containing an abnormally long polyglutamine tract [7]. However, it became clear after the discovery of the HD gene that a small percentage of cases diagnosed on the basis of clinical findings did not have the HD mutation [8]. Some of these cases turned out to have dentatorubal-pallidoluysian atrophy (DRPLA), a disease also caused by an expanding CAG repeat coding for polyglutamine, but in the gene atrophin-1 located on chromosome 12p [9,10]. Adult onset cases of this disease can be clinically indistinguishable from HD. However, juvenile onset cases with longer repeat expansions have a phenotype somewhat distinct from juvenile HD, characterized by progressive myoclonus epilepsy [11] Also, the cerebellum is more commonly involved than in HD [12,13] A third group of patients, with a clinical and pathological phenotype that cannot be clinically distinguished from HD, have an expansion mutation on chromosome 16q that does not appear to encode polyglutamine [14] The disorder caused by this mutation has been termed Huntington's disease-like 2 (HDL2) [15]. Reliable distinction among HD, DRPLA, and HDL2 was only possible after the causative mutations were discovered.

Until the 1990's, two opposing models contended to account for the variable phenotypes observed in the SCAs: 1) a few genetic mutations with extremely variable clinical manifestations, or 2) many different genetic mutations each resulting in a relatively defined phenotype [16]. The current model is somewhere between the two extremes, though closer to the latter. About 25 different autosomal dominant SCAs have now been identified on the basis of linkage to different loci. Genes have been identified for SCA1, 2, 3, 6, 7, 8, 12, 14, 17, and *FGF14*-associated ataxia [4,5]. The causative mutation has turned out to be a repeat expansion in 8 of the 10 diseases, encoding polyglutamine in six (SCA1, 2, 3, 6, 7, 17). Most of these disorders are difficult to distinguish on the basis of clinical findings. However, a few SCAs are distinguished by a particular feature, such as the retinopathy of SCA7 [17] or the tremor of SCA12 [18].

Some of the disorders, most notably SCA2 [19], SCA3 [20], and SCA17 [21], are remarkable for considerable variation in phenotype. In some cases the clinical presentation of SCA17 may resemble HD [22], and the presentation of any of the three may resemble Parkinson's

Table 1
Selected genetic causes of HD, SCA, and related syndromes

Disease	Gene symbol	Protein	Inheritance	Mutation	Effect on protein
HD	*HD*	huntingtin	AD	CAG expansion	Polyglutamine expansion
HDL2	*JPH3*	junctophilin-3	AD	CTG expansion	unknown
DRPLA	*DRPLA*	atrophin-1	AD	CAG expansion	Polyglutamine expansion
SCA17	*TBP*	TATA-binding protein	AD	CAG expansion	Polyglutamine expansion
SCA3	*MJD*	ataxin-3	AD	CAG expansion	Polyglutamine expansion
SCA6	*CACNA1A*	alpha 1A subunit of the voltage-dependent P/Q type calcium channel	AD	CAG expansion	Calcium channel dysfunction?
SCA14	*PRKCG*	Protein kinase C, gamma subunit	AD	Point mutations	Enzyme dysfunction?