Clinical research

Diagnostic classification of psychiatric disorders and familial-genetic research

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The validity of diagnostic definitions in psychiatry is directly related to the extent to which their etiology can be specified. However, since detailed knowledge of causal or susceptibility factors is lacking for most psychiatric disorders with a known or suspected familial-genetic origin, the current widely accepted classification systems largely fail to achieve this ideal. To illustrate this problem, this paper looks at the difficulties posed by the criteria for schizophrenia as laid down in the International Classification of Diseases, 10th revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R), and highlights the discrepancies between the majority of diagnostic boundaries and the various phenotype aggregation patterns observed in family studies. Progress in our understanding of psychiatric disorders requires to be firmly based on the findings of epidemiological studies as well as on a clear appreciation of the limitations of classification tools.

Two major criteria of validity have been proposed:

• The stronger the genetic determination, the more valid the diagnostic definition; consequently, heritability estimates derived from twin studies may serve as criteria of validity.

• The stronger and more specific the familial aggregation, again, the more valid the diagnostic definition.

Diagnostic distinctions based on familial-genetic studies

The two aforementioned criteria of validity were the very ones that were used, in the past, to establish the now widely accepted classification of affective disorders that...
distinguishes bipolar disorder and unipolar depression:
• Twin studies established a higher degree of heritability for bipolar disorder than for affective disorders in general.2
• Family studies consistently demonstrated that bipolar disorders aggregate only in families of probands with bipolar disorder, and not in families of probands with other subtypes of affective disorder.3

On the basis of these findings, all currently used classification systems, in particular the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD), define the now well-known diagnostic criteria for the two groups of affective disorders.

More recently, an intermediate syndrome between unipolar depression and bipolar disorder, so-called bipolar II disorder, has been defined. This condition is characterized by depressive episodes with manic states too short in duration or too mild in intensity to qualify as a manic episode. A series of family studies (eg, Dunner et al4) showed that bipolar II disorder followed a specific intrafamilial pattern of aggregation. Other family studies found that bipolar II disorder, but not other types of bipolar disorder, strongly aggregated in families of probands with bipolar II disorder.5,6 However, in contrast to the Research Diagnostic Criteria (RDC), the currently most widely distributed classification systems, DSM-III-R, DSM-IV, and ICD-10, included the intermediate constellation bipolar II disorder under the heading bipolar disorder.

To further illustrate the contribution of familial-genetic studies to the classification of psychiatric disorders, this paper takes a closer look at how the aforementioned considerations have impacted on the diagnostic definitions of schizoaffective disorders.

The first criteria-based definition of this disorder was proposed by the RDC. This disorder was shown to aggregate in families, but not in a specific manner.7 Some variants of this disorder also occurred more commonly than would be expected by chance in families of probands with schizophrenia and other variants in families of probands with affective disorders, and vice versa. The clinical characterization of these variants demonstrated that cosegregation with schizophrenia was preferentially associated with the more chronic, schizophrenia-like schizoaffective disorder, whereas other subtypes coaggregated preferentially with affective disorders.8 As a consequence, the schizophrenia-like schizoaffective disorders were distinguished from other schizoaffective disorders, which were subsequently considered to belong to the affective disorders in DSM-III-R and DSM-IV and likewise in ICD-10.

Diagnostic definitions ignoring familial-genetic evidence

Several studies were recently conducted applying one of the aforementioned criteria of validity to competing diagnostic definitions or diagnostic criteria, particularly with regard to the definition of schizophrenia and psychotic disorders. Twin and family studies focused primarily on the positive/negative distinction. It was demonstrated that the complex of negative symptoms was fairly consistently associated with a high familial similarity, a higher familial loading with psychotic disorders, and a higher genetic load than positive symptoms.9

One twin study even found no genetic influence at all on the occurrence of positive symptoms (first-rank Schneiderian symptoms), whereas other definitions, including positive and negative symptoms in the definition of schizophrenia, were associated with at least a moderate degree of heritability.10 If a classification system relies on the specificity and magnitude of underlying genetic determinants, a redefinition of the concepts of schizophrenia and other psychotic disorders should result from these findings. In contrast to this empirical evidence, even the most recent definitions of schizophrenia and psychotic disorders in DSM-III-R, DSM-IV, and ICD-10 give priority to positive symptoms. As an exception, ICD-10 proposes the residual category of latent schizophrenia (schizophrenia simplex), which is only defined by the presence of negative symptoms, in the absence of positive symptoms. The familial-genetic nature of this condition is not widely known, as most research into the genetics of schizophrenia is based on cases with a mixture of positive and negative symptoms. The most distinctive difference between the DSM-III-R, DSM-IV, and ICD-10 classification of schizophrenia is the minimal duration of the disease episodes. ICD-10 requires the presence of symptoms for just 1 month. DSM-III-R and DSM-IV require 6 months, and consider psychotic patients meeting the symptom criteria for schizophrenia for less than 6 months to belong to the category of schizophreniform disorders. Several studies have shown that the course of schizophrenia
(including episode duration) is independent of the familial loading. Given this body of evidence, a differential validity of the ICD-10 and DSM-III-R and DSM-IV definitions of schizophrenia is unlikely. In keeping with this expectation, we found in a family study a similar degree of familial aggregation of schizophrenia as defined by DSM-III-R and DSM-IV or ICD-10, although the prevalence rates were very different (Table I).

The degree of familial aggregation is indicated by the odds ratios (OR) with 1.0 indicating the risk in the general population and values higher than with 1.0 indicating the degree of increased risk with respect to the general population. A similar degree of familial aggregation is apparent for DSM-III-R and ICD-10 in Table I, although a difference in criteria for minimal episode duration may result in differences in cumulative lifetime prevalence rates.

In conclusion, although DSM-III-R and ICD-10 have different definitions for schizophrenia, these differences have no relevant impact on the degree of familial aggregation.

### Spectrum of conditions defining the familial phenotype as exemplified by schizophrenia

Another strategy to explore the boundaries of a familial disorder is to delineate the range of syndromes and durations coaggregating with schizophrenia in families. This strategy is particularly informative if relatives of schizophrenics who are likely to have a genetic vulnerability to schizophrenia (so-called obligate carriers) are investigated. Obligate carriers are relatives of schizophrenics located in the pedigree between two cases with schizophrenia, eg, the mother of a schizophrenic index case is considered to be an obligate carrier if one of her siblings or one of her parents was also suffering from schizophrenia or another psychotic disorder (independently of the phenotype of the mother of the index case). As the familial aggregation of schizophrenia is unlikely to be due to random variation (because of the low prevalence rate in the general population), or nongenetic familial factors (as evidenced by twin studies), the only remaining possibility is genetic factors. Thus, differences in the prevalence of obligate carriers of disorders, syndromes, and behavioral deviations in families of schizophrenics are likely to be expressed by the genetic diathesis of schizophrenia. Table II shows the cumulative lifetime prevalences of psychiatric disorders (DSM-III-R) for obligate carriers identified in our aforementioned family study. The excess of diagnosis-specific prevalence rates is only significant for two groups of disorders (due to sample size limitation). It is apparent that the genetic vulnerability to schizophrenia is not only expressed as schizophrenia. These findings are in keeping with those of another series of family studies, which showed that all variants of nonaffective psychotic disorders (schizotypal personality disorders and schizoaffective disorders) cosegregated with schizophrenia. Similarly, some family studies reported an excess of affective disorders (particularly psychotic affective disorders) in subjects at elevated risk for schizophrenia. In addition, one series of family studies demonstrated that

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| Diagnosis of schizophrenia in relatives of schizophrenics | Lifetime prevalence rates | Relative risk (OR) [95% confidence interval] |
|----------------------------------------------------------|----------------------------|---------------------------------------------|
| by ICD-10 by ICD-10 | Relatives of probands with schizophrenia (ICD-10: n=620, DSM-III-R: n=485) | Relatives of general population probands (n = 500) |
| by DSM-III-R by DSM-III-R | 6.5% | 0.9% | 7.1 |
| | [3.5; 11.9] | |
| | 3.0% | 0.5% | 6.0 |
| | [2.0; 12.0] | |

Table I. Cumulative lifetime prevalence rates for schizophrenia: first-degree relatives of probands with schizophrenia by two diagnostic systems. Abbreviations: DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition; ICD-10, International Classification of Diseases, 10th Revision; OR, odds ratio.
A heterogeneous collection of deviations (e.g., personality deviations not qualifying as a disorder, neuropsychological deficits) might also develop as a consequence of an increased risk for schizophrenia. Thus, the range of the phenotype transmitted in families of schizophrenics is not at all identical to the diagnostic boundaries proposed by any diagnostic manual.

On the other hand, there is also evidence that specific subtypes of schizophrenia aggregate in families with a very specific pattern of aggregation. Recently, Beckmann et al. demonstrated that periodic catatonia defined a homogeneous familial aggregation pattern. However, this specific psychotic syndrome is only remotely associated with the catatonic subtype of schizophrenia defined by ICD-10 and DSM-III-R. Taken together, the diagnostic distinctions and boundaries defined by ICD-10 and DSM-III-R are not compatible with the phenotype of schizophrenia transmitted in families, although these diagnostic categories were shown to be familial and under genetic control.

**Diagnostic definitions and linkage studies**

Consequently, it is not surprising that linkage studies tracing the localization of susceptibility genes for a specific psychiatric disorder have failed to reveal a specific relationship to diagnostic categories. Two examples of this are discussed in the following:

- One replicated linkage finding in schizophrenia is on 6p. Maximal logarithm of the odds of linkage (LOD) scores indicate the strength of cosegregation of genetic markers and the disease. Comparison of the maximal LOD scores across diagnostic definitions (by DSM-III-R), varying by restrictiveness, revealed maximal diagnosis-specific LOD scores for the broadest definition including all variants of psychotic disorders; the maximal LOD score for narrowly defined schizophrenia was substantially lower.

- Several candidate regions in the genome are likely to host susceptibility genes for bipolar affective disorders. One of these regions is 18p. A suggested linkage to bipolar disorder was found by several independent linkage studies in bipolar disorder. Recently, Schwab et al. also found suggested linkage for schizophrenia to the same pericentromeric candidate region. In addition, the diagnosis-specific maximal LOD score was substantially increased by including not only schizophrenia and schizoaffective disorders in the phenotype, but also affective disorders.

### Table II. Lifetime prevalences in relatives of schizophrenics (obligate carriers) and controls. *

| Diagnosis                                      | Obligate carriers (n=41) | Matched controls (n=41) |
|------------------------------------------------|--------------------------|-------------------------|
| Schizophrenia/schizophreniform disorders       | 8.2%                     | 0.9%*                   |
| Schizoaffective disorders                      | 1.2%                     | 0%                      |
| Other nonaffective psychoses (including schizotypal personality disorders) | 2.3%                     | 1.1%                    |
| Psychotic affective disorders                  | 3.0%                     | 1.0%                    |
| Nonpsychotic affective disorders               | 18.0%                    | 9.1%*                   |
| Other psychiatric disorders                    | 20.9%                    | 18.4%                   |

*P ≤ 0.05.
Conclusion

These two examples highlight the limited value of the currently most widely accepted diagnostic definitions of psychotic disorders for the identification of specific genetic vulnerabilities. However, there is currently no other option to the diagnosis-based linkage and association approach to localize disease genes. The limited validity of diagnostic definitions and their putative loose relationship to specific genetic vulnerabilities have to be compensated for by extension of sample size. Once the first susceptibility genes have been detected, more specific genotype–phenotype relationships can be identified.  

Clasificación diagnóstica e investigación familiar y genética en los trastornos psiquiátricos

La validez de las definiciones diagnósticas en psiquiatría se relaciona directamente con la posibilidad de especificar su etiología. Ya que se carece de un conocimiento detallado de la etiología o de los factores de susceptibilidad de gran parte de los trastornos psiquiátricos con un origen familiar-genético, conocido o sospechado, los sistemas clasificatorios actuales no permiten conseguir este objetivo. Con el fin de ilustrar este problema, el presente artículo examina las dificultades planteadas por los criterios de esquizofrenia establecidos en la Clasificación Internacional de Enfermedades en su décima versión (CIE-10) y en el Diagnostic and Statistical Manual of Mental Disorders, en su tercera edición revisada (DSM-III-R). Se destacan las discrepancias entre la mayoría de los límites diagnósticos y los diversos modelos de agregación fenotípica observados en estudios familiares. El progreso en la comprensión de los trastornos psiquiátricos requiere de una base firme en los hallazgos de los estudios epidemiológicos como también en una apreciación clara de las limitaciones de los instrumentos clasificatorios.

Classification diagnostique et recherche sur l'étiologie familiale/génétique des maladies psychiatriques

La validité des définitions diagnostiques en psychiatrie est directement liée à la possibilité de spécifier l'étiologie des maladies concernées. Or, à partir du moment où pour la plupart des maladies psychiatriques, avec une origine génétique connue ou suspectée, on ne connaît que peu les facteurs causaux ou prédisposants, les classifications actuelles, largement acceptées, ne permettent généralement pas de remplir cet objectif. Cet article illustre ce problème à travers les difficultés rencontrées avec les critères de la schizophrénie de l’International Classification of Diseases, 10e révision, du Diagnostic and Statistical Manual of Mental Disorders, 3e édition révisée (DSM-III-R). L’auteur souligne à quel point le fossé est grand entre la plupart des entités diagnostiques et les divers modèles phénotypiques observés dans les études familiales. Si notre progression dans la compréhension des troubles psychiatriques doit se fonder sur les résultats des études épidémiologiques, il faut garder à l’esprit les limites des outils de classification qui sont à notre disposition.
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