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Dirk Lichtermann · Edith Karbe · Wolfgang Maier

The genetic epidemiology of schizophrenia and of schizophrenia spectrum disorders

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Abstract It has been known for a long time that schizophrenia and several related psychopathological traits aggregate in families on a common genetic basis. Improved methodology of recent family, twin and adoption studies has led to a better unterstanding of which psychopathologically defined syndromes and personality traits are part of a schizophrenia spectrum, and to which degree individual spectrum conditions share the same genetic background with schizophrenia. The spectrum concept has been extended to include neuropsychologically, neurophysiologically and neuroradiologically measurable familial traits as subclinical endophenotypes of schizophrenia that may be more fundamental to the development of the disease than overt psychopathology. This knowledge has been useful in designing molecular genetic linkage and association studies that aim at directly identifying individual risk genes. Replicable linkage findings have emerged from genome scans that imply at least seven chromosomal regions to harbour schizophrenia susceptibility genes. They strengthen the conviction that schizophrenia is indeed a genetically complex disorder, based on a larger number of susceptibility genes with risk-increasing alleles that are common in the population and exert a limited effect on the individual level. Although demanding increased investments into sample collection, genotyping and computational technology, identification of these genetic variants will be possible and worthwhile since they may have a large effect in terms of population attributable risk.

Key words Schizophrenia · Epidemiology · Spectrum · Linkage · Association

D. Lichtermann (✉) · E. Karbe · W. Maier
Department of Psychiatry
University of Bonn
Sigmund-Freud-Straße 25
53105 Bonn, Germany
Tel.: +49-22 82 87 52 06, Fax: +49-22 82 87 60 97
e-mail: lichtermann@uni-bonn.de

Introduction

Since its first description early in the twentieth century, schizophrenia has been recognised as a familial condition, and twin as well as adoption studies have shown that its familiality is largely genetic in origin. As molecular genetic techniques have become available in the 1980s and have been proven successful during the 1990s in the identification of individual susceptibility genes even in genetically complex disorders (e. g. breast cancer, Alzheimer disease), the study of the epidemiology of schizophrenia has gained renewed interest to answer the question: what actually is the phenotype being transmitted in schizophrenia families? Not unlike Munchhausen's astounding tale wherein he slowly pulled himself out of the swamp by his own beard, the relationship between schizophrenia epidemiology and molecular genetics is considered to be one of incremental mutual support; the power of molecular genetic studies depends critically on the ability of epidemiological work to delineate homogeneous subgroups of the disorder in whom the share of genetic risk is assumed to be particularly large. In return, the identification of risk genes, once accomplished, should help with a clearer differentiation of depending clinical subgroups. This paper will review contemporary studies on the epidemiology of schizophrenia and related phenotypes and briefly summarise the strategies of molecular genetic studies.

Familial recurrence and the genetic basis of schizophrenia

Five recent family studies applying operationalised diagnostic criteria have consistently shown a considerably higher risk of schizophrenia in the first-degree relatives of schizophrenia patients (lifetime risk 1–16 %) than in relatives of control probands from the general population (0–2 %) [11, 20, 31, 49, 61]. While family studies cannot differentiate between genetic and non-genetic sources of familial recurrence, the comparison of probandwise con-

cordance rates for schizophrenia in monozygotic and dizygotic twins (45–75 % vs. 4–15 %) [7, 14, 18, 46, 58] allows heritability, i. e. the share of genetic factors in the etiological variance, to be calculated at 50–87 % [53]. Heritability estimates have been found to vary according to the diagnostic system used, and DSM-III-R led to a particularly high heritability estimate [53], thereby recommending itself for preferential use in molecular genetic studies. Since monozygotic twin concordance rates and heritability are far from a perfect 100 %, there is ample room for non-genetic (environmental) factors in the etiology of schizophrenia, but are these bound rather to common (familial) or to unique (individual-specific) environment? Twin as well as adoption studies agree that unique environmental factors account for virtually all of the non-genetic portion of the etiological variance, while there is almost no role for familial environment [7, 34, 40, 52]. The substantial environmental contribution also explains why genetic transmission of schizophrenia can occur via psychopathologically healthy and via affected pedigree members alike; recurrence rates are similarly increased for offspring of the unaffected and of the affected members of monozygotic twin pairs discordant for schizophrenia. It is, however, unclear whether it is the absence of non-genetic risk factors or the presence of protective factors that leads to non-expression of schizophrenia in some transmitting risk gene carriers.

Are there genetically definded subtypes of schizophrenia?

Some clinical subtypes of schizophrenia might simplify the search for risk genes when their familial aggregation is stronger than in others and more homogeneous, i. e. excluding other subtypes. Unfortunately, none of the classically differentiated subgroups (paranoid, catatonic, disorganised, undifferentiated or hebephrenic) appears in an intrafamilially homogeneous way [28, 54]; familial risk in probands of one type is increased for any other type. Moreover, a large number of attempts failed to find clinical differences between a familial, supposedly largely genetic, and a sporadic, rather environmentally dependent, form of schizophrenia. Such basic distinction seems to be invalid since some of the characteristics typical of genetically complex diseases, such as a multitude of risk genes of small individual effect and low penetrance, may indeed obscure the trait in many genetic risk carriers, some of whom may have but a single family member manifesting the disease, yet on a basis no less genetic than in families where several members have been afflicted [55].

A notable exception to the lacking usefulness of clincial subtypes for risk gene identification may be one of a larger number of diagnostic entities formerly shaped by Leonhard, periodic catatonia, whose unusually high familial risk implies a dominant mode of inheritance [3], but so far there have been no independent samples to replicate this family study and a subsequent molecular genetic linkage study.

Focusing on cases with particularly low age at disease onset and high familial loading as an indicator of a likely monogenic disease subgroup has been a fruitful strategy in mapping risk genes of breast cancer and Alzheimer disease. For adult schizophrenia, however, the age at onset spread does not provide easily recognisable early outliers, nor was the possibly useful inverse relationship between age at onset (low) and familial recurrence risk (high) ever substantiated; also, the intrafamilial correlation of age at onset was found moderate at best [38]. Thus, age at onset appears to be under no significant genetic control, or at least at a different one than disease suceptibility as such.

One broad clinical distinction has finally been shown useful in identifying cases with a high familial schizophrenia risk: negative vs. positive symptomatology. It is mainly probands with prominent negative symptoms (social withdrawal, bizarre behaviour, formal thought disorder) and some positive symptoms in their history who have a high familial loading with psychotic disorders while those with predominant delusions and hallucinations alone and those with exclusively negative symptomatology (simple schizophrenia) appear to be less familial [35, 37, 72]. Twin studies are consistent with this view in that concordance rates are higher under diagnostic procedures that appreciate positive and negative symptoms in a balanced way (e. g. DSM-III) than under those that focus exclusively on positive items (like first-rank Schneiderian symptoms alone) [28].

Defining the transmitted phenotype

The aforementioned findings refer to a schizophrenia diagnosis as such, albeit according to different operational definitions. For long it has, however, been recognised that disorders and traits other than schizophrenia also appear at an increased rate in the families of probands with schizophrenia, and these may well underlie the same familial-genetic susceptibility.

Psychotic disorders and personality traits cosegregating with schizophrenia: the schizophrenia spectrum

The schizophrenia spectrum concept dates back to the historical observation by Kraepelin that some less severe, but likewise long-standing, schizophrenia-like characteristics abound in the families of patients with schizophrenia. In the wake of the Kopenhagen adoption study it has been forwarded that they share the same familial-genetic etiology with schizophrenia. In addition to schizophrenia, schizoaffective disorder, schizotypal personality disorder and other psychotic disorders (including psychotic affective disorders) can be regarded as valid members of the spectrum [32, 50], and biometric analyses of family study data suggest that their common familial recurrence with schizophrenia indeed derives from common familial-genetic factors [2, 36]. A more restricted spectrum emerged from an adoption study [34], encompassing only schizophrenia, ICD-10 schizotypal disorder and schizophrenia-like schizoaffective disorder. Biometric analysis of the Kopen-

hagen adoption sample confirmed the common genetic basis of schizophrenia and schizotypal personality disorder [71], the former of which may thus differ from the latter only in the presence of additional, especially perinatal, risk factors.

A still broader historical concept has been forwarded by Kretschmer [45], extending the spectrum over the currently accepted schizophrenia and schizotypy into a range of nearer to normal, yet still schizophrenia-like personality variation termed schizoidia. Though this concept was well received by some later authors [8, 9], clearly increased measures of perceptual aberration, bizarre behaviour or social anxiety could not be substantiated by self-report questionnaires among the relatives of probands with schizophrenia [26]. Less schizophrenia-specific personality measures like neuroticism [51] or anhedonia [16, 26] may be mildly increased among non-psychotic relatives of probands with schizophrenia but, all in all, their personality appears remarkably undisturbed in that respect, surprisingly different from what has been found in the relatives of probands with unipolar depression [4].

Two limitations should be considered with respect to spectrum conditions. Most of them do not occur exclusively in the familial context of schizophrenia. Schizotypal personality for instance also cosegregates with affective disorders [47, 68] in which case it may have no etiological relationship to schizophrenia whatsoever. Psychotic and psychotic affective disorders also have a familial recurrence pattern of their own beyond their cosegregation with schizophrenia. It is, thus, only subgroups of these disorders for which a set of genetic risk factors common with those for schizophrenia can be assumed. The only exception to this is schizoaffective disorder of a predominantly schizophrenic, chronifying type whose segregation pattern fully overlaps with that of schizophrenia [48]. The second limitation in this context refers to the incomplete ability to reflect etiological closeness to schizophrenia in the current polythetic symptom sets used to arrive at a categorical diagnosis of a spectrum condition. For instance, only the following individual items have been found to be particularly specific for schizotypal personality in the familial context of schizophrenia: subthreshold thought disorder, social withdrawal, bizarre behaviour and alogia [22, 37, 42, 50].

Non-psychotic disorders cosegregating with schizophrenia

The aforementioned psychotic spectrum disorders are quite similar in their symptom profiles to schizophrenia and they occur with about double frequency among the relatives of probands with schizophrenia as in the general population, both of which may be taken to indicate a substantial sharing of genetic risk factors. Several other disorders are known with only remote similarity to schizophrenia and a less than twofold but still moderately increased risk in schizophrenia families. This constellation may be due either to only partial overlap of risk factors with those of schizophrenia, to poor diagnostic reliability or poor diagnostic validity (in that one diagnosis covers a broad array of etiological conditions – etiological heterogeneity).

Affective disorders

Kraepelin grounded his postulate of a dichotomy of schizophrenia and affective disorders on purported differences in outcome as well as on a lack of cosegregation (that is affective disorders were assumed to be no more common in the families of probands with schizophrenia than in the general population, nor was schizophrenia risk deemed to be increased among the relatives of probands with affective disorder). Only since the 1980s have methodologically sound family studies begun to resolve the latter issue. Consistent with Kraepelin's view, several of these excluded increased risk for affective disorders in relatives of probands with schizophrenia [11, 33, 70] but several others found unipolar depression at a risk ratio of two [20, 49, 69]. Results obtained by one group in an independent replication sample indicate that this finding is no artifact of the particular diagnostic interview used (unpublished data by Karbe). A reanalysis of controlled family studies confirmed increased risk ratios of between 1.5 and 2.5 both for bipolar disorder and unipolar depression in schizophrenia families, but not significantly so due to limited sample sizes [29]. However, a meta-analysis of all available family, twin and adoption data concluded that the relative risk for unipolar depression was indeed significantly increased at a risk ratio of two [29]. The following familial risk factors common to schizophrenia and affective disorders have been considered: obstetric complications (that are known to run in families and to predispose to schizophrenia as well as to affective, namely bipolar, disorders [5, 41]) and personality factors such as neuroticism [51].

Alcoholism

Studies on the familial rate of alcoholism in schizophrenia have been inconclusive. As one study found alcoholism risk clearly increased in families of probands with psychotic disorder [30], the inclusion of different proportions of psychotic disorders other than schizophrenia into different samples may have been the reason for discrepant results.

Anxiety disorders

Although anxiety disorders are often seen in the prodromal phase of schizophrenia, no increased familial risk for anxiety disorders was observed [30].

Neuropsychological traits cosegregating with schizophrenia

Beyond purely psychopathological phenomena as they have been discussed above, there is a great number of neu-

ropsychological and neurophysiological measures that have been found aberrant in patients with schizophrenia. Some of them are also characteristic of their psychopathologically healthy biological relatives [6, 10, 12, 17, 21, 27, 43, 60], for example:

- Discrete motor disturbances in general (termed neurological soft signs) and, more specifically, smooth pursuit eye movement (SPEM) impaired by insufficient inhibition of reflexive saccades;
- Attentional deficits (especially of vigilance) and diminished cognitive flexibility;
- Slowed-down information processing as it can be documented by reduced habituation of the P50 EEG wave, by reduced amplitude and increased latency of the P300 wave upon auditory stimulation and by discriminative visual tasks (backward masking);
- Reduced memory function, especially of spacial working memory and of verbal long-term recall.

Of these parameters, pursuit eye movement has been studied most extensively. Although SPEM deficits also appear in psychopathologically healthy relatives of probands with affective disorder (just as schizotypal personality features do; s. a.), anticipatory saccades could be shown to specifically occur with increased frequency in the healthy relatives of patients with schizophrenia [63]. Thus, common genetic factors can be assumed behind schizophrenia and this particular endophenotype [25] which may be regarded as a correlate of reduced visual attention in schizophrenia (since experimentally induced enhancement of visual attention can ameliorate the deficit). However, there is also a different type of visual attentional impairment measured by the Continuous Performance Test in schizophrenia families that does not cosegregate with SPEM.

Neuropsychological aberrations are more prominent in male than in female schizophrenia patients, but in contrast they appear more often in their female than in their male psychopathologically healthy relatives [44]. Knowing that age at onset of schizophrenia is on average higher in females than in males, this observation can be seen as an indicator of stronger protectional mechanisms in females that prevent manifestation of the full-blown syndrome in a larger proportion of at-risk females than in male risk gene carriers. Pilot brain imaging studies indicate that neuropsychological deviations in healthy relatives may go along with discrete brain morphometric aberrations [39, 66] such as enlarged third ventricle or reduced volumes of the amygdala and hippocampus.

Neuropsychological traits as reviewed above that cosegregate with schizophrenia in families are called true vulnerability markers [74]. Their actual relationship to schizophrenia may be twofold:

- The familial predisposition to schizophrenia is expressed already premorbidly in the guise of subclinical deviations [56]. Prospective studies in children of mothers with schizophrenia (high-risk studies) have shown subclinical motor disabilites, social withdrawal, social anxiety, reduced affective responsivity [57, 71], attentional disturbances and reduced information processing capabilities [10] to precede the outcome of schizophrenia or schizotypal personality which was the more likely under the additional influence of stressful life events [10].
- Under the influence of protective factors familial schizophrenia vulnerability may lead to the manifestation not of schizophrenia but of a less severe spectrum condition. Confirmation of this hypothesis can be obtained by examining obligate risk gene carriers, that is, healthy parents of patients with schizophrenia [e. g. 15, 23, 64, 65].

Strategies for the identification of risk genes

Two complementary strategies are used in the search for molecular genetic risk factors of schizophrenia: linkage and association studies. Linkage studies aim at finding a pattern of co-transmission of the disease in families with several affected members with a DNA marker whose chromosomal location is known. With classical monogenic diseases, samples of a single or a few large multigenerational families are sufficient since every affected member of a given pedigree is in possession of the same disease-causing variant (genetic homogeneity). In genetically complex diseases like schizophrenia, however, it is more advisable to collect large samples of small nuclear pedigrees consisting of at least two affected siblings and their parents since the existence of a large number of susceptibility-increasing genes (genetic heterogeneity) is to be taken into account: distantly related affected family members may have acquired the disease for quite different genetic reasons. Under the null hypothesis of no linkage between marker and disease, affected siblings are supposed to share a random 50 % of alleles at the marker locus; a linked marker, however, will be identified by above-random allele sharing. It is, thus, possible to screen the whole chromosomal genome for linkage with a set of markers evenly distributed over the chromosomes, mostly length variants of repetitive DNA sequences (polymorphic CA-repeats) that are transmitted in families according to Mendelian rules. About 350 of these are sufficient to detect linkage signals in the first pass [24], followed by genotyping the family sample with a denser set of markers around screening markers that gave a linkage signal over a predefined statistical strength. Alternatively, variants of genes that are likely candidates for being involved in the pathophysiology of schizophrenia (e. g. neurotransmitter and transporter genes, neurotrophic factors) can be tested for linkage directly. A drawback of linkage studies is their limited power to detect susceptibility genes of small effect, a multitude of which is actually the most likely scenario in complex disease genetics. Their contribution is easier to be resolved by association studies that are most meaningful when those variants either in the coding sequence or in the promoter region of candidate genes are studied for which functional consequences on the structure of the translated protein or on the transcriptional regulation of the gene, respectively, are known. However, classical case-control comparisons are prone to false-positive findings in that a detected association may be due to

overlooked stratification. Family-based designs have been developed that circumvent this problem by studying cases and their parents whose non-transmitted alleles are regarded as a perfectly matched virtual control group [13]; although more difficult to collect than samples of single cases and unrelated control subjects, this design should clearly be preferred. A future prospect is to make the unique density of base exchange polymorphisms (i. e. biallelic markers) at about every 1000 base pairs in the genome useful for systematic, genome-wide association studies [62].

Selecting an appropriate phenotype for molecular genetic study

Linkage and association studies demand that, despite the increasing elaborateness of the schizophrenia spectrum concept as discussed above, the diagnostic status of probands be drastically reduced to the two basic categories, affected or unaffected. In addition to schizophrenia only diagnostic members of the spectrum for which a particularly large overlap of genetic risk factors with those of schizophrenia is known should be selected. Thus, discarding in linkage studies any diagnosis beyond schizophrenia and schizoaffective disorder (predominantly schizophrenic or chronic subtype) may seem like a deplorable loss of power, but it has been shown that still more power gets lost when disease phenotypes with little or no overlap of genetic risk with that of schizophrenia are included (so-called phenocopies). For the same reason it is also advisable to include in the linkage analysis genetic information only of those pedigree members who are affected according to this narrow concept ("affecteds only") which is accomplished by considering anybody else as with "phenotype unknown" rather than "unaffected" (the latter of which is impossible to say in anyone who is not beyond the age at risk for schizophrenia). Nevertheless, the full spectrum concept is still useful in analyses secondary to linkage findings obtained on the narrow model; as mentioned in the introduction, its validity with respect to the particular linkage finding can be examined directly by testing whether the statistical parameter of the linkage signal increases or decreases upon incremental inclusion of further spectrum diagnoses as affected cases. Also, considering particular familial endophenotypes instead of the schizophrenia diagnosis as the trait of interest can lead to meaningful linkage results [1, 19].

Linkage and association findings with schizophrenia

Numerous linkage and association studies have been conducted, during the last three years mainly in the form of systematic genome scans (for a timely review see [59]). Among these, the following broad chromosomal regions emerged, either by a high threshold of significance in a single study (e. g. 1q, 13q) or by converging evidence from several studies, as the most likely ones to harbour one or several schizophrenia susceptibility genes: 1q, 5q, 6p, 8p, 10p, 13q, 18p, 22q. For some of these (e. g. 8p, 13q, 18p) attempts at positional cloning of a gene after having narrowed down the candidate region by further linkage or linkage disequilibrium studies are under way, but have not yet led to the reporting of any unsuspected susceptibility gene. The pharmacological knowledge about the action of neuroleptic drugs implicates polymorphisms of the diverse dopamine or serotonine receptor genes as likely candidate genes, but none of them has been shown to contribute to a larger degree to individual genetic schizophrenia susceptibility. It is likely that many negative studies may have lacked sufficient power to identify minor contributions of single candidate genes. Detection of such small effects may indeed be amenable to multi-center collaborations [67, 73]. However, it is exactly this seemingly slow progress over 10 years in identifying risk genes that reinforces the message of segregation studies: that schizophrenia is indeed a genetically complex disease in which most likely no single major gene, but a large number of susceptibility genes, each of small effect, will have their role. The most likely candidates will be genetic variants that are phylogenetically old and common in the population. Identification of these may require further increases on sample sizes, genotyping efficiency, and computational power, but the effort is worthwhile since their effect on disease susceptibility, small as it may be for the individual, can be quite impressive in terms of population attributable risk [73]. Finally, the most immediate benefit of molecular genetic studies may be expected in a substantial refinement of pharmacological treatment approaches for the individual.

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