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REVIEW

Fringe phenotypes in autism: a review of clinical, biochemical and cognitive studies

Véronique Goussé[a,b], Marie-Hélène Plumet[a], Nadia Chabane[a,b], Marie-Christine Mouren-Siméoni[a], Nathalie Ferradian[c], Marion Leboyer[a,b,c]*

[a] *Consultation autisme, service de psychopathologie de l'enfant et de l'adolescent, hôpital Robert Debré, assistance publique-hôpitaux de Paris, 75019 Paris, France;* [b] *INSERM U 513, hôpital Henri Mondor, 94000 Créteil, France;* [c] *Service de psychiatrie, hôpital Albert Chenevier et Henri Mondor, assistance publique-hôpitaux de Paris, 40, rue de Mesly, 94000 Créteil, France*

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Summary – Progress in identifying the genetic vulnerability factors in autism requires correct identification of the inherited phenotype(s). This can be achieved not only by the accurate description of the affected subject but also by the identification of vulnerability traits in non-affected relatives of autistic probands. This review will focus on this last strategy and principally on clinical, biochemical and cognitive traits. © 2002 Éditions scientifiques et médicales Elsevier SAS

Autism / Psychiatric genetics / Phenotypes / Cognitive, clinical and biochemical assessments

Advances in molecular biology have opened up a variety of avenues by which to explore genetic effects in adult and child psychiatric disorders [42,56]. However, in the field of affective disorders and schizophrenia, progress has been fraught with difficulties encountered in linkage studies due to probable genetic heterogeneity, incomplete penetrance and uncertainties about phenotypic definition [46]. At this stage, it thus seems that genetic analyses would greatly benefit, first, from a more rigorous description of diagnostic entities and second, from a search for quantitative characteristics such as psychometric and/or biochemical measures that would provide more power to genetic analyses [19]. Whereas the emphasis on phenotypic research has only recently been outlined in adult psychiatry, the need to define a core phenotype in autism dates back to the early 1970s. In 1975, Bartak et al. [11] noted for the first time that family history of reading or language disorders was found in at least one first-degree relative of five of the 19 families studied (26%). Folstein and Rutter [25], in their famous twin study, reported a similar finding and thus made the assumption that a mild language-related cognitive impairment would define an underlying genetic liability. Indeed, the concordance rate for disorders of cognition and language was considerably higher than the concordance rate for autism as nine of the 11 monozygotic pairs (82%) were concordant for language or for cognitive disorder, compared with only one of the ten dizygotic pairs (10%). They thus proposed that autism might be the most severe expression of a genetically determined disorder of cognition.

The identification of other types of peculiarities, in particular social deficits, stereotypic behaviours, lan

*Corresponding author. Tel.: +33-1-49-81-30-51; fax +33-1-49-81-39-51.
E-mail address: leboyer@im3.inserm.fr (M. Leboyer).

guage disorders and cognitive and biochemical abnormalities was later described among first-degree relatives of autistic probands, thus raising different questions: What precisely are the components and the boundaries of the affected phenotype within families of autistic subjects? Are these different peculiarities all-present among relatives leading to a milder autism phenotype? Would the identification of fringe phenotypes using psychological, clinical and/or biochemical variables lead to an etiological account and/or to a precise mode of inheritance?

The aim of this paper is to summarise current knowledge about phenotypic expression in relatives of individuals with autism. This review will focus on clinical, biochemical and cognitive peculiarities.

PSYCHIATRIC DISORDERS AND PSYCHOLOGICAL DEFICITS

Since the early 1980s, many studies have investigated the familial aggregation of psychiatric disorders and/or psychological characteristics (see [8] for review). Although a large body of data has been replicated from one study to another, discrepancies might be explained by methodological differences such as heterogeneity of probands regarding recruitment, IQ level, gender and medical-associated conditions. In addition, various types of controls have been assessed. For instance, Down's syndrome families were often chosen as a control group in order to control for a potential stress effect on the non-affected relatives, whilst not conferring any specific genetic risk to family members. The various studies also differ according to the way the relatives are assessed. Most studies have used family history methods—interviews with the relatives—that enable a questionnaire on a large sample of family members; some studies have employed direct psychiatric assessments which are more rigorous but difficult to propose, but are also crucial to delineate the precise components of the broader phenotype. Indeed, as noted by Bailey et al. [8], the use of standardised measures across research groups is needed in the future to enable comparisons and replications of clinical and psychological results.

Furthermore, identifying which mechanisms are relevant in the genesis of psychiatric disorders requires parallel assessment of social, communication and repetitive abnormalities.

However, if some differences in findings between studies may be due to different methods of assessment, studies on psychological deficits involving comparable measures of cognitive capacities (such as IQ) have produced divided results. Altogether, data obtained among relatives of autistic subjects are described in this section.

Pervasive developmental disorder (PDD)

Most family studies have reported an elevated rate of autism among siblings of autistic subjects ranging from 2 to 6% compared to a population base rate of about four in 10,000 [58]. Recently, Szatmari et al. [64] reviewed ten family studies of autism and found a pooled rate of 2.2% of autism among the siblings of autistic probands. Steffenburg et al. [62] and Bailey et al. [7] also found that the risk could extend to other PDDs. For example, Gillberg et al. [27,28] found high rates of Asperger syndromes among siblings of autistic children. More precisely, when the phenotype among siblings of autistic subjects includes Asperger syndrome and other pervasive developmental disorders, the rate rose to 5% [64]. In addition, it seems that psychopathology in relatives may differ according to IQ levels of autistic probands as Delong and Dweyer [22] found an increased rate of Asperger syndrome among relatives of autistic probands without comorbid mental retardation.

While some studies have explored syndromes such as Asperger syndrome, others have focused on the identification of specific impairments in one of the three behavioural domain defining the core phenotype of autism, namely, social, communication or repetitive domain. In particular, once PDD cases were excluded, several studies have found a combination of mild abnormalities in the three behavioural domains [15,47]. More precisely, Pickles et al. [47] showed that more than one behavioural domain was affected among relatives of more severely affected probands, thus suggesting that there is a spectrum of severity of the phenotypic expression. By contrast with these findings, other studies have assessed impairments in only one behavioural domain either in the social, communication or repetitive domain.

Social abnormalities

In the early 1940s, Kanner [32] and Asperger [4] were the first clinicians to notice parental personality characteristics that were qualitatively similar, though milder, to the behavioural difficulties of the affected children. These parental characteristics were initially interpreted

as environmental causes of autism acting through their effect on child-rearing practices. However, early family studies failed to find any evidence of abnormal child rearing [13,24], and later the elevated recurrence risk of autism in siblings and the higher concordance rate for autism among monozygotic twins compared to dizygotic twins (39% versus 0%) [25] led to the clear recognition of the genetic liability to autism.

Social impairment has been explored using the Family History Interview developed by Bolton et al. [15]. Social impairment, defined by lack of affection, social dysfunction, impaired friendship, impaired social play and odd behaviour, was observed in the majority of the non-autistic identical co-twins [7,39] and was found more frequently among the first-degree relatives [15,53] or more distant relatives [47] of autistic subjects than relatives of controls. Impaired rapport, lack of empathy, suspiciousness and low emotional responsiveness were found among parents of probands more often than controls.

Regarding social personality traits, Piven et al. [50] found increased rates of aloof and tactless traits among relatives of probands compared to controls. Botton et al. [16] also found that the traits aloof and shy made the greatest contribution to differences between relatives of probands and controls. Wolff et al. [66] observed that parents were rated higher than controls on lack of empathy, suspiciousness and low emotional responsiveness.

Altogether, the findings suggest that a range of social difficulties, and not one narrow abnormality, tends to co-occur in relatives more often than in the general population. These peculiarities might reflect underlying abnormalities of social cognition that remain to be unravelled.

Communication impairments

Folstein and Rutter [25] were the first authors to point to the importance of communication impairment in the definition of fringe phenotypes in autism. In their twin study, they noted that the concordance rate for language disorders such as reading and spelling with articulation disorder, language delay was 82% in the monozygotic group and 10% in the dizygotic group. Since then, several studies have been conducted to investigate if relatives of autistic children show an elevated rate of developmental language difficulties—language delay or articulation disorder—or reading and spelling difficulties. Bailey et al. [7] in a combined UK twin sample found that half of the non-autistic monozygotic (MZ) co-twins and 10% of the dizygotic (DZ) co-twins had developmental language difficulties such as language delay, articulation disorder, reading retardation and spelling difficulties. The majority of studies performed in first-degree relatives of autistic probands report a higher incidence of language delay and communication abnormalities [5,6,11,13,41,48,53,57]. Three studies did not find an elevated rate of communication impairment [17,28,63]. As pointed out by Bailey et al. [8], the likelihood that language delay signifies cognitive impairment rather than a transitory developmental lag is suggested by the psychometric data coming from Bolton et al. [15]. On direct cognitive testing, they showed that siblings with the broad phenotype had lower verbal IQ than unaffected relatives, and those findings were largely accounted for by those having a history of language delay [25]. Thus developmental language difficulties appear to be associated with current reading or spelling difficulties. Leboyer et al. [38] and Plumet et al. [55] reported respectively lower verbal abilities than controls and significant subtle verbal dysfunction in brothers of an autistic female. Communication problems also include conversational impairments as shown by Landa et al. [34]. Stories produced by parents were shown to be shorter and were poorer than those by parents of controls, and the parents were also characterized by difficulties in communication planning. Assessment of language using the pragmatic rating scale Landa et al. [34] revealed that 42% of the parents had inadequate or awkward expression and odd verbal interactions.

Although the absolute rate of language abnormalities in relatives remains low, concordant results have repeatedly demonstrated the high level of verbal and communication impairments among relatives of autistic subjects. The precise nature of these impairments has not yet been precisely described. In particular, it is not yet known if relatives with developmental language difficulties also show impairments in conversational language [8].

Repetitive behaviours

Obsessional behaviours have also been described in relatives of autistic probands. In particular, rigidity, repetitive behaviours, circumscribed interests and obsessions/compulsions have been found more frequently among the first-degree relatives of probands than controls although they were relatively uncommon

among the non-autistic co-twins [7,15]. These behaviours and/or the whole syndrome of obsessive–compulsive disorder were however less frequent than social abnormalities and never occur without co-occurrence of social abnormalities. Obsessive–compulsive disorder occasionally occurs alone in the sample of Bolton et al. [15]. An elevated rate of tics has also been observed among relatives but no link with Tourette's syndrome has been established. Results concerning personality traits among parents are unclear: Piven et al. [50] and Bolton et al. [16] did not find increased rates of rigidity or conscientiousness, while Piven et al. [60] found that rigidity characterized an important proportion of parents from controls.

Altogether, obsessive and repetitive behaviour usually occur in association with either social or communication difficulties according to Bolton et al. [11] and/or anxiety according to Piven et al. [53]. Thus, the relationship between the three domains of repetitive behaviour, communication difficulties and social impairments and the underlying cognitive peculiarities need to be further clarified.

Other psychiatric disorders

Piven et al. [49] found an increased rate of anxiety disorder in the parents of autistic individuals and Smalley et al. [60] found an elevated rate of social phobia (20.2%) among relatives of autistic probands compared to controls (2.4%). This was not replicated by Bolton et al. [16], which might be explained by the fact that elevated social phobias were mainly observed among relatives of autistic persons without comorbid mental retardation. Bolton et al. [16] and Piven et al. [53] have also reported elevated rates of anxiety-related personality traits among relatives. Concerning affective disorders, DeLong and Dwyer [22] reported an increased rate of manic-depressive disorder among the relatives of autistic subjects. Subsequently, they found that relatives of high functioning probands were at risk for bipolar and unipolar depression [23, 65]. However, studies that have used standardized interviews did not find an elevated risk of bipolar disorder among relatives [16,49,60]. However, relatives seem to be at risk for affective disorders, particularly females and parents [16]. Piven et al. [49] used the SADS-L to assess lifetime RDC criteria among 81 parents of autistic probands compared to 39 parents of Down's syndrome cases. They report elevated rates of anxiety disorders and major depressive disorders (respectively 23.5% and 27.2%) among parents of autistic persons compared to parents of Down's (2.9% and 14.8%). In addition, they found that the first depressive episode occurred prior to the birth of the autistic child in 77% of parents affected with PDD. Whereas Bolton et al. [16] found some evidence for an association between the reported rate of depression in second- and third-degree relatives and the presence of disorder in first-degree relatives. Abramson et al. [2] also found elevated rates of treatment for mood disorders among 18.2% of first-degree relatives of autistic persons compared to population estimates but did not find increased rates of anxiety disorders. Smalley et al. [60] used the K-SADS-E (ages 7–17 years) and the SADS-LA (ages above 18 years) to interview parents and siblings of autistic probands compared to severe epileptic conditions. Major depression with or without hypomania is twofold greater both in parents (27.2%) and siblings (30.6%) compared to controls. Altogether, anxiety and affective disorders appear more frequently in relatives of autistic probands. Further studies are required to demonstrate if their increased frequency is a direct or an indirect consequence of genetic liability to autism.

There is little consistent evidence showing that the relatives are at risk for other psychiatric disorders. No study found an increased risk for schizophrenia. Findings regarding alcoholism and drug abuse are inconsistent. The suggestion of an increased risk of anorexia nervosa [28] has not been replicated.

Altogether, these findings do show the presence of subtle impairments among relatives of autistic subjects in either one or in the three domains of autistic dysfunction, namely social, communicative and repetitive behaviour. However, it is not yet known if this represents either a quantitative liability to a global, more or less severe autistic phenotype or the familial aggregation of distinct behavioural traits that could be transmitted in an independent way. The review of the literature also strongly suggests that the disorders and/or behavioural peculiarities found among relatives vary with the autistic proband, in particular with the degree of mental retardation. Thus, further work is needed to simultaneously explore different domains and various psychiatric entities in potential subgroups of autistic probands defined, for example, according to gender, verbal level, or mental retardation.

BIOLOGICAL ABNORMALITIES

So far, serotonin has been the most investigated biological marker among relatives of autistic subjects. Whole blood serotonin (5-hydroxtryptamine, 5-HT) levels have consistently been found to be elevated in 25–33% of autistic subjects [3,35], and some parents and siblings of children with autism have been shown to have elevated blood 5-HT levels. For example, we have recently shown that, within a sample of 122 non-affected first-degree relatives of 62 autistic probands, 51% of mothers, 45% of fathers and 87% of siblings have hyperserotonemia [36]. Several studies have found a positive correlation between either platelet 5-HT [33,49] or whole blood 5-HT [1,21,40,49] levels of children with autism and 5-HT levels of their mothers, fathers and siblings. In addition, autistic children with siblings affected with autism have much higher 5-HT levels than probands without affected siblings [49], thus reinforcing the hypothesis that elevated 5-HT level may be associated with genetic liability to autism. Parents with elevated whole blood 5-HT levels have more depressive and obsessional symptoms than parents with normal levels [20].

In parallel with the studies of hyperserotoninemia in families of autistic probands, a search for the familiarity of opioid dysfunction might also be of interest. Indeed, opioid dysfunction in autism has recently been suggested to be the consequence of an abnormal processing of the opiomelanocortin gene in infantile autism since C-terminally directed β-endorphin protein immunoreactivity was found to be elevated in a sample of 67 children with autism, while N-terminally directed β-endorphin protein immunoreactivity was found to be diminished [37]. Elevated levels of C-terminally directed β-endorphin protein immunoreactivity has been found only among mothers of autistic children [36]. This preliminary observation awaits replication.

COGNITIVE PECULIARITIES

As previous studies suggest that around 25% of first-degree relatives of children with autism are affected by a lesser variant of autism (i.e., impairment in one of the three autism-diagnostic domains: sociability, communication and cognitive or behavioural flexibility), several studies have looked for possible underlying cognitive abnormalities, which could be found in parents/siblings of autistic probands. *Table 1* gives a tentative summary of the cognitive domains observed among relatives, which might correspond to the three autism-diagnostic domains.

Communication difficulties

Early studies have looked for mental retardation among relatives. It became clear that mental retardation occurs only in association with autism and it was shown that genetic liability is not for mental retardation alone [7,39,61]. However, several studies have found a pattern of verbal performance discrepancies in relatives similar to those seen in autism. Minton et al. [43] observed that relatives had a verbal IQ 15 points or more below their performance IQ. Brothers of autistic females were also found to have a discrepant profile with better visuo-spatial skills than verbal abilities [38]. By contrast, Piven and Palmer [52] and Fombonne et al. [26] found a superior verbal IQ in parents and siblings compared to controls. These discrepancies might reflect differences in autistic proband assessment.

Language delays observed in some relatives are thought to be related to the verbal-performance dis

Table 1. Domains of impaired functioning in autism and the possible corresponding clinical and cognitive processes found in first-degree relatives

Diagnostic domains in autism	Clinical evaluations among relatives	Cognitive processes
Communication deficit	Language delay	*Anomalous cerebral dominance*
	Reading delay	Left/right asymmetry, low verbal abilities vs. high visuo-spatial capacities
	Articulation disorder	
	Spelling difficulties	
Social deficit	Limited social relationships	*Impaired social cognition*
	Lack of affection	Theory of mind, pragmatics
	Impaired social play	
	Odd social behaviours	
Restrictive/ repetitive activities or interests	Circumscribed interests	*Executive dysfunction*
	Rigidity, perfectionism	Planning, flexibility, working, memory

crepancies observed by some studies in relatives of autistic probands. The heterotypic continuities between language disorders [14] and reading/spelling difficulties could explain that an atypical profile was found in siblings of autistic children.

Social deficits

As social impairments tend to occur more frequently among first-degree (or more distant) relatives of autistic individuals than control groups [15,51], the key issue is whether the subtle differences found in relatives of individuals with autism may not reflect a different pattern of cognitive impairments? As autistic individuals have difficulties in selective aspects of social cognition, especially in tests involving the ascription of mental states to others [9], it is interesting to determine the extent to which relatives perform in the same way. In the first experimental study of mental-state awareness in autism family members, Ozonoff et al. [45] presented siblings of high-functioning autistic boys and of a mixed control group with three story-based false belief tasks: no group differences in these tests of theory of mind were found; however, the authors suggested that the measures employed, which are typically used with autistic individuals, were not sufficiently sensitive to detect any group differences. More recently Baron-Cohen et al. [10] used a task involving the interpretation of emotional expression in photographs of eyes in a study of parents of individuals with Asperger syndrome: parents of the Asperger group were less accurate than controls on this task. Hughes et al. [31], testing the Smalley and Asarnow [59] hypothesis of impaired processing of emotional information in siblings of autistic children, showed a significant gender difference in the recall of emotional words (girls performed better than boys) but no group difference was found either in terms of total emotion words recalled or in terms of relative performance across emotion concrete lists.

Taken together, the results of these studies suggest that the cognitive processes underlying all 'social' tasks are subtler to assess in relatives of autistic individuals than in the subjects themselves.

Restrictive and/or repetitive interests

In order to explore whether cognitive processes underlie circumscribed interests and/or repetitive activities observed among relatives, several studies have explored the possibility of a link between executive function and repetitive and stereotyped behaviour.

'Executive function' is typically associated with frontal-lobe functioning and used to encompass the processes that underlie goal-directed behaviour such as planning, working memory, inhibition of pre-potent responses and cognitive flexibility. Studies directly testing relatives of individuals with autism provide converging evidence of impairments in planning [30,45,52] in siblings and parents; Hughes et al. [30] also reported impairments in a working-memory task—despite intact or superior spatial span—in the autism parent group; the authors also found clear impairments in flexibility among the autism relatives.

Hughes et al. [31] confirmed these results, showing an increased prevalence of executive dysfunction among siblings of children with autism compared with controls: significantly more siblings than controls perform poorly on tests of planning, attentional flexibility, and verbal fluency as no particular deficits were found in working-memory tasks. The results of this latest investigation converge with findings from other studies [44,54], indicating that autism's broader phenotype should include executive dysfunction. But, as different processes are included in the term 'executive function', future studies have to identify exactly the nature and the mechanisms underlying the deficits observed among autism relatives. Another question concerns the 'consequence' of these executive dysfunctions on everyday behavioural problems, as these deficits may offer an explanation for some repetitive and/or circumscribed interests but also rituals and perhaps social problems. A relation between executive function performance and clinical traits have been found by Hughes et al. [30], showing that not only were the executive performances of the relatives of autistic individuals lower compared with the control group, but also these performances were correlated with social impairments, one of the domains of the broad phenotype.

In conclusion, and beyond executive dysfunction, results tend to suggest that the broader phenotype for autism is characterized by an uneven profile of cognitive ability [31]. The profile of cognitive strengths and weaknesses identified in three studies among autism relatives [10,18,29], showing superior spatial abilities and poor social understanding, mirrors findings obtained on individuals with autism. What needs to be specified is the exact relationship among these impairments and their link with verbal capacities as executive

dysfunction could play a causal role not only in repetitive behaviours but also in sociability and communication [12,31].

CONCLUSION

The presence of milder phenotypic expression among some relatives of autistic probands is now widely recognized. The data reviewed here show that some relatives have impairments ranging from pervasive developmental disorders to isolated communication or social impairments. However, the precise boundaries of this milder phenotype are unknown. In addition, genetic heterogeneity of autism being very likely, this mild phenotype is very likely to depend on some yet unknown characteristics of the proband. As the identification of subgroups of autistic children progresses, it might be hypothesized that the phenotype observed among some relatives will probably also be shown to vary according to proband characteristics such as gender, mental retardation, degree of severity, head circumference, and associated medical conditions. In addition, it is not yet known if the different aspects of the behavioural phenotype are transmitted simultaneously or separately, and if they are associated with independent genes or genes in epistatic interactions. Once these phenotypes are better defined, their use in genetic studies will help discover the genetic vulnerability factors underlying autism.

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