Linkage analysis between schizophrenia and the Darier's disease region on 12q

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Abstract

There have been reports of an association between Darier's disease, an autosomal dominant genodermatosis, and psychiatric illness. Recently the gene causing Darier's disease has been mapped to an area on 12q, between D12S58 and D12S84. The findings of linkage analysis of 4 markers in the Darier's disease region on 12q in five families segregating schizophrenia are presented. They fail to support close linkage between schizophrenia and the Darier's disease region on 12q.

Keywords

Chromosome 12; Darier's disease; Linkage; Schizophrenia

INTRODUCTION

There have been reports of an association between Darier's disease and major mental illness (Getzler and Flint. 1966; Clark *et al.*, 1986; Milton *et al.*, 1990; Denicoff *et al.*, 1990; Craddock *et al.*, 1994). During linkage studies of schizophrenia, one large Canadian family was discovered in which Darier's disease and schizophrenia coexisted (Berg and Bassett, 1993). The two diseases overlapped in some family members. There are a number of reasons why these two conditions might coexist in a family, including a chance occurrence, but the finding raised the possibility that schizophrenia and Darier's disease might be genetically linked.

Darier's disease, a rare autosomal dominantly inherited skin disease has been mapped to a region on 12q, between D12S58 and D12S84 (Bashir *et al.*, 1993; Craddock *et al.*, 1993; Parfitt *et al.*, 1994; Kennedy *et al.*, 1995). We hypothesized that this might be a candidate

region for a susceptibility gene for schizophrenia. The current study reports the findings from analyses of four polymorphic markers in the Darier's region on chromosome 12q in five Canadian families segregating schizophrenia. The findings fail to provide evidence of genetic linkage between the Darier's disease region on 12q and schizophrenia.

METHODS

Subjects

Subjects were members of five families participating in a linkage study of familial schizophrenia ($n=88$). Families were selected for large size, availability of two or more generations of adults, and inheritance consistent with autosomal dominant transmission of schizophrenia and related disorders. The study was approved by the university ethics committee, and subjects provided written informed consent. Details of subject recruitment, inheritance patterns, and assessment are described elsewhere (Bassett *et al.*, 1993; Bassett and Honer, 1994). Briefly, data from a comprehensive clinical assessment, collateral information, and available medical records were reviewed independently by two psychiatrists, and a consensus lifetime DSM-III-R diagnosis was assigned for each subject. A 'narrow' diagnostic category ($n = 26$), included schizophrenia and schizoaffective disorder; a 'broad' diagnostic category consisted of psychosis not otherwise specified, and paranoid and schizotypal personality disorders ($n = 15$), as well as 'narrow' category diagnoses.

DNA studies

Venous blood was obtained from subjects and DNA extracted using standard techniques. Genotypes of relatives were determined with markers D12S58 from the database of J. Weber, and D12S79 and D12S84 from Genethon (Weissenbach *et al.*, 1992). An approximate map of this region is as follows: cen—//—D12S58—5.2cM—D12S84—6.0cM—D12S79—(7.2cM)—PLA2—(5.2cM)—D12S86—//—qter. The Darier's disease locus maps most closely to D12S84. Marker typings were performed as described elsewhere (Weber and May, 1989). The trinucleotide repeat for phospholipase A2 (PLA2) was typed as described by Polymeropoulos *et al.* (1990). Autoradiographs were interpreted separately by at least two of us, blind to diagnostic status. Marker allele frequencies were estimated from unrelated individuals who were married into these families.

Linkage analysis

Lod scores for pairwise linkage analysis were calculated using LIPED. Analysis was performed using autosomal dominant and autosomal recessive models of inheritance and both narrow and broad diagnoses of schizophrenia. Parameters for genetic linkage models used were: 70% penetrance, with phenocopies at 0.001. The disease gene frequency was set at 0.0085 for the autosomal dominant model and at 0.12 for the autosomal recessive model. A non-parametric sib pair analysis (SIBPAL) was also performed, using both the narrow and broad diagnostic models for schizophrenia.

RESULTS

Pairwise linkage results at various recombination fractions were determined for each of the four markers studied. When the five families were pooled, each of the 12q markers generated significantly negative lod scores under the broad dominant and broad recessive models (Table I). Under the narrow model, the absolute value of the lod scores was smaller, but still significantly negative. They all exclude linkage out to 5% recombination. Individual families, including the one segregating Darier's disease (011), all showed negative results. However, individual families were not informative for all markers (Table II). Simulation studies showed that using a four allele marker with 100% of families linked, the average lod score, under the assumption of linkage, is greater than 5 for these families.

Non-parametric sib pair analysis showed allele sharing of approximately 50% (Table I). There is no indication of significant allele sharing amongst affected pairs. The same non-parametric analyses were performed using the narrow diagnostic model, and those results were also not significant.

DISCUSSION

The current study fails to provide evidence to support linkage between schizophrenia and the Darier's disease region on 12q. This result is consistent with a study of 163 cases of Darier's disease which found no significant association between Darier's disease and psychiatric symptoms (Burge and Wilkinson. 1992). Linkage between bipolar disorder and a similar region on 12q has also recently been excluded (Ewald *et al.*, 1994).

What could explain the coexistence of Darier's disease and schizophrenia? Firstly, the presence of the two diseases in one family may have occurred by chance alone, given the high prevalence of schizophrenia. This explanation seems plausible since there were members of the family who demonstrated Darier's disease but not schizophrenia and vice versa. Also, if both of these conditions occur as a result of disrupted fetal development, it is possible that one could potentiate the other. Alternatively, the physical disfigurement and subsequent social isolation often associated with Darier's disease may increase the likelihood of assortative mating with patients with schizophrenia or related illnesses.

One major limitation of the current study is that only five families were investigated. Schizophrenia is likely to be genetically heterogeneous, and it is possible that the Darier's 12q region might be important for other families segregating schizophrenia. In addition, the results of this study have not excluded the presence of a susceptibility locus for schizophrenia elsewhere in the human genome. It also remains to be determined whether markers in the Darier's region on 12q are linked to neuropsychiatric conditions other than schizophrenia.

The interface between neuropsychiatric and dermatologic conditions remains an interesting area of research because of the common ectodermal origin shared by the skin and nervous system.

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References

- Bashir R, Munro CS, Mason S, Stephenson A, Rees JL, Strachan T. Localisation of a gene for Darier's disease. *Human Molecular Genetics*. 1993; 2:1937–1939. [PubMed: 7506604]
- Bassett AS, Honer WG. Evidence for anticipation in schizophrenia. *American Journal of Human Genetics*. 1994; 54:864–870. [PubMed: 8178826]
- Bassett AS, Collins EJ, Nuttall SE, Honer WG. Positive and negative symptoms in families with schizophrenia. *Schizophrenia Research*. 1993; 11:9–19. [PubMed: 8297809]
- Berg D, Bassett AS. Darier's disease: current understanding of pathogenesis and future role of genetic studies. *International Journal of Dermatology*. 1993; 32:397–400. [PubMed: 8320017]
- Burge SM, Wilkinson JD. Darier-White disease: a review of the clinical features in 163 patients. *Journal of the American Academy of Dermatology*. 1992; 27:40–50. [PubMed: 1619075]
- Clark RD, Hammer CJ, Patterson SD. A cutaneous disorder (Darier's disease) evidently exacerbated by lithium carbonate. *Psychosomatics*. 1986; 27:800–801. [PubMed: 3099325]
- Craddock N, Dawson E, Burge S, Parfitt L, Mant B, Roberts Q, Daniels J, Gill M, McGuffin P, Powell J, et al. The gene for Darier's disease maps to chromosomes 12q23-q24.1. *Human Molecular Genetics*. 1993; 2:1941–1943. [PubMed: 8129825]
- Craddock N, Owen M, Burge S, Kurian B, Thomas P, McGuffin P. Familial cosegregation of major affective disorder and Darier's disease (keratosis follicularis). *British Journal of Psychiatry*. 1994; 164:355–358. [PubMed: 8199789]
- Denicoff KD, Lehman ZA, Rubinow DR, Schmidt PJ, Peck GL. Suicidal ideation in Darier's disease. *Journal of the American Academy of Dermatology*. 1990; 22:196–198. [PubMed: 2312801]
- Ewald H, Mors O, Flint T, Kruse TA. Linkage analysis between manic depressive illness and the region on chromosome 12q involved in Darier's disease. *Psychiatric Genetics*. 1994; 4:195–200. [PubMed: 7712114]
- Getzler NA, Flint A. Keratosis follicularis: a study of one family. *Archives of Dermatology*. 1966; 93:545–549. [PubMed: 5940918]
- Kennedy JL, Berg D, Bassett AS, Roy R, King N, Perkins M. Genetic linkage for Darier's disease (keratosis follicularis). *American Journal of Medical Genetics*. 1995; 55:307–310. [PubMed: 7537018]
- Milton GP, Peck GL, Fu JL. Exacerbation of Darier's disease by lithium carbonate. *Journal of the American Academy of Dermatology*. 1990; 23:926–928. [PubMed: 2123895]
- Parfitt E, Burge S, Craddock N, Roberts E, McLean WH, Weissenbach J, McGuffin P, Owen M. The gene for Darier's disease maps between D12S78 and D12S79. *Human Molecular Genetics*. 1994; 3(1):35–38. [PubMed: 7512859]
- Polymeropoulos MH, Rath DS, Xiao H, Merrill CR. Trinucleotide repeat polymorphism at the human pancreatic phospholipase A2 gene (PLA2). *Nucleic Acids Research*. 1990; 18:7468.
- Statistical Analysis for Genetic Epidemiology (SAGE) version 2.1, copyright by R. Elston, Case Western Reserve University, Cleveland, Ohio, USA.
- Weber J, May P. Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. *American Journal of Human Genetics*. 1989; 44:388–396. [PubMed: 2916582]
- Weissenbach J, Gyapay G, Dib C, Vignal A, Morissette J, Millasseau P, Vaysseix G, Lathrop M. A second generation map of the human genome. *Nature (London)*. 1992; 359:794–801. [PubMed: 1436057]

TABLE I
Pairwise lod scores and Sib Pair Analysis using broad diagnosis of schizophrenia and 12q markers (all five families)

Marker	Model 1 (AD/Broad) ¹				Model 2 (AR/Broad) ²				Sibpair analysis		
	$\theta=0.0$	$\theta=0.1$	$\theta=0.2$	$\theta=0.3$	$\theta=0.0$	$\theta=0.1$	$\theta=0.2$	$\theta=0.3$	Number of affected sib pairs	Mean allele sharing i.b.d. ³ in affected sib pairs	p-value
D12S58	-8.45	-4.12	-1.93	-0.74	-6.45	-2.57	-0.82	-0.17	48	0.472	1.000
D12S79	-8.18	-3.81	-1.96	-0.84	-5.75	-2.45	-1.03	-0.32	51	0.498	1.000
D12S84	-7.71	-4.27	-2.08	-0.89	-5.06	-2.30	-0.96	-0.34	44	0.525	0.317
PLA2	-7.25	-3.65	-1.77	-0.72	-9.99	-3.92	-1.61	-0.58	50	0.531	0.246

¹Model 1: Autosomal dominant, 70% penetrance, 0.0085 gene frequency, 0.001 phenocopies; broad diagnosis.

²Model 2: Autosomal recessive, 70% penetrance, 0.12 gene frequency, 0.001 phenocopies; broad diagnosis.

³i.b.d.: identical by descent.

TABLE II
Pairwise lod scores between broadly defined schizophrenia and D12S84 (assuming dominant mode of transmission)

Marker	Family	Number of typings	Lod score									
			$\theta^I=0.0$	$\theta=0.001$	$\theta=0.01$	$\theta=0.05$	$\theta=0.1$	$\theta=0.2$	$\theta=0.3$	$\theta=0.4$		
D12S84	A	19	-2.08	-2.07	-2.01	-1.71	-1.21	-0.52	-0.20	-0.05		
	B	9	0.14	0.14	0.14	0.13	0.12	0.08	0.03	0.01		
	C	9	-0.21	-0.20	-0.14	0.03	0.10	0.10	0.05	0.01		
	D	22	-3.80	-3.79	-3.61	-2.71	-2.04	-1.15	-0.55	-0.17		
	011	18	-1.76	-1.75	-1.73	-1.58	-1.24	-0.59	-0.23	-0.06		
	Total	78	-7.71	-7.68	-7.35	-5.84	-4.27	-2.08	-0.89	-0.26		

θ^I =recombination fraction.