Neurodevelopmental Interactions Conferring Risk for Schizophrenia: A Study of Dermatoglyphic Markers in Patients and Relatives

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Abstract

Schizophrenia is hypothesized to be the result of an interaction between specific genetic factors and nonspecific insults during embryonic development. Dermatoglyphic abnormalities appear to mark these putative insults—providing information about the temporal sequence of aberrant developmental events as well as the organism's vulnerability to their adverse effects. In the present study, dermatoglyphic measures thought to mark first and second trimester development were examined in patients with schizophrenia and first degree relatives and compared with those of healthy controls to examine whether genetic factors may mediate this vulnerability. Both patients with schizophrenia and relatives exhibited dermatoglyphic abnormalities compared with controls. Patients were more likely to exhibit dermatoglyphic abnormalities indicative of early second trimester development, which suggests that vulnerability interacts with the timing of insults to produce overt disease. These findings indicate that the two-hit model, in which schizophrenia-specific genetic factors combine in an additive fashion with environmental insults to produce the illness, may be oversimplified. Rather, the data are consistent with a more complex model in which nonspecific genetic factors that increase susceptibility to developmental abnormalities interact with insults and specific genetic factors.

Keywords: Dermatoglyphics, developmental instability, schizophrenia, phenotypic markers, genetic risk.
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The precise etiology of schizophrenia remains unknown, although several risk factors have been identified. There is considerable evidence from family and molecular genetic studies that the expression of the disease is mediated by genetic factors (Tsuang 1998; Pulver 2000). In addition, several environmental risk factors have been identified, including fetal malnutrition, hypoxia, and viral infection (e.g., Susser et al. 1996; Dalman et al. 1999; Cannon et al. 2000; Karlsson et al. 2001). These fetal insults are not specific to schizophrenia. However, they are hypothesized to contribute to its etiology when interacting with critical neurodevelopmental events and in the presence of schizophrenia-related genes (Moldin and Gottesman 1997; Tsuang 2000). The ability to directly examine these putative interactions is limited in human studies. However, several indirect approaches have been informative. Recently, there has been a resurgence of interest in the application of dermatoglyphic analysis to study neurodevelopmental interactions conferring risk for schizophrenia.

The study of dermatoglyphic abnormalities has been employed in a number of chromosomal disorders, congenital malformations, and neurological and neuropsychiatric conditions in order to gain insight into the complex interaction of environmental, developmental, and genetic factors leading to disease (Chakraborty 1991; see Schaumann and Optiz 1991 for a review). Disorders that have been shown to be associated with dermatoglyphic abnormalities include Down's syndrome (Rajangam et al. 1995), fragile X syndrome (Loesch et al. 2002), Brachmann-deLange syndrome (Barr et al. 1971), and bipolar disorder (Torrey 1999). The malformation of dermatoglyphic characteristics can result from a number of physiological insults that can occur during fetal development, including exposure to environmental toxins, viral infections, or genetic mutations. However, the ultimate effect of these insults will depend on the intensity, duration, and type of stress as well as on the organism's genetically mediated resistance to

stress (Newell-Morris et al. 1989; Chakraborty 1991; Murphy and Owen 1996; Goldberg et al. 1997; Møller and Thornhill 1997; Thornhill and Møller 1997). This suggests that the study of dermatoglyphics may be useful in trying to understand how developmental insults interact with genetic vulnerability in the case of schizophrenia. Other aspects of dermatoglyphic morphogenesis that make it potentially informative in the study of neurodevelopment and risk for schizophrenia include the following: (1) data suggest that the formation (as well as potential malformation) of these traits roughly coincides with the development of brain structures hypothesized to be involved in the pathogenesis of schizophrenia (Waddington et al. 1999*a*); (2) many of the dermatoglyphic measures are stable across time—once formed, they are not altered by subsequent genetic and environmental events; (3) in contrast to earlier studies of dermatoglyphics and schizophrenia (e.g., Mellor 1968), much more is now known about the proximate mechanisms underlying the formation of these traits—making more specific hypotheses about their relation to schizophrenia possible.

Previous Studies of Dermatoglyphics in Schizophrenia

The findings of several studies suggest that there is a higher incidence of dermatoglyphic abnormalities among schizophrenia patients than among healthy individuals (Kemali et al. 1976; Markow and Wandler 1985; Mellor 1992; Balgir 1993; Fananas et al. 1996). The small size of these effects, combined with differences in sampling and methodology, has produced some inconsistencies in the specific abnormalities reported. Most, however, point to a late first trimester to second trimester developmental abnormality—in the form of either reduced fingerprint ridge counts or palmar a-b ridge count abnormalities.

This interpretation is based on the work of Penrose and Ohara (1973), Okajima (1975), and Babler (1990, 1991), who have shown that finger ridge formation occurs over a period of 24 weeks beginning around week 10 to 11 postfertilization. At this time, epidermal ridges first appear in the basal layer of the epidermis. These ridges, termed primary ridges, continue to proliferate until approximately 14 weeks postfertilization. At around 14 weeks, sweat gland anlagen begin to develop along the apices of the primary ridges, primary ridge formation ceases, and secondary ridges begin to form between existing primary ridges. Secondary ridge formation continues until approximately 24 to 25 weeks postfertilization (Babler 1991). Developmental events thought to determine the type of dermatoglyphic pattern observed on the digits precede the development and subsequent proliferation of ridges.

Specifically, the shape of the volar pads has been shown to be associated with fingerprint pattern type (Babler 1987). Studies have shown that the development and subsequent regression of the volar pads occurs over a period of 5 weeks beginning at around week 6 postfertilization (Lacroix et al. 1984; Babler 1991). Moore and Munger (1989) have also suggested that axonal growth, which can be observed in the epidermis in embryos as young as 6 weeks, may influence pattern type.

Davis and Bracha (1996) used the differential timing of these dermatoglyphic traits to study the developmental divergence of monozygotic (MZ) twins discordant for schizophrenia. Consistent with previously reported patient-control differences in dermatoglyphic traits such as finger ridge counts and a-b ridge count abnormalities, they found that the emergence of dermatoglyphic differences suggested a second trimester insult. No differences in pattern asymmetry were found between discordant and concordant MZ twins compared with control twins, while intratwin pair correlations for a-b ridge counts were lower in discordant MZ twins compared with concordant and control twins.

These studies highlight one dimension of the analysis of dermatoglyphic traits—namely, that patterns of abnormality may be helpful in differentiating the timing of developmental insults. However, they do not examine how genetic factors may mediate vulnerability to these adverse developmental events. Møller and Thornhill (1997) and others (e.g., Newell-Morris et al. 1989; Chakraborty 1991; Murphy and Owen 1996; Goldberg et al. 1997) have suggested that insults are not necessarily sufficient to produce an aberrant phenotype; in some cases, insults interacting with a vulnerable genotype are required. It is not known whether schizophrenia patients are more likely to be exposed to insults during embryonic development—for example, whether mothers of children who will later develop schizophrenia are at increased risk for influenza infection during pregnancy or are more likely to smoke. It is possible that maternal health habits (e.g., smoking) and obstetric complications are influenced by psychopathology and its susceptibility genes. Another possibility is that schizophrenia patients are more vulnerable to potential insults; that is, they may exhibit what developmental biologists refer to as developmental instability (Goldberg et al. 1997; Møller and Thornhill 1997). This is supported by a recent study by Brown et al. (2000), who found that maternal exposure to upper respiratory tract infection, which is relatively innocuous and common, was associated with an increased risk of schizophrenia.

One way to examine the role of genetic factors in mediating vulnerability to developmental insults in patients with schizophrenia is to study their biological relatives. Although several dermatoglyphic studies involving

MZ and dyzgotic (DZ) twins have been conducted (Markow and Gottesman 1989; Bracha et al. 1992; Davis and Bracha 1996; Van Os et al. 1997), only Davis and Bracha (1996) provide direct comparisons of affected versus unaffected twins, and none provide direct comparisons of unaffected twins versus controls.

In the present study, we combine the use of multiple measures to mark the temporal sequence of putative insults with the inclusion of both patients and first degree relatives in order to examine how insults may interact with familial status (a proxy for genetic vulnerability). This study design provides a means of testing the following hypotheses: (1) that increased susceptibility to developmental stress is a component of risk for schizophrenia—that is, that both schizophrenia patients and first degree relatives exhibit increased prevalence of dermatoglyphic abnormalities compared with controls; and (2) that the timing of putative developmental insults may contribute to divergent phenotypes—that is, that individuals with schizophrenia are more likely to exhibit dermatoglyphic abnormalities associated with second trimester development of central nervous system (CNS) structures thought to be involved in the pathogenesis of schizophrenia (Waddington et al. 1999*a*, 1999*b*).

Methods

Research Volunteers. All participants gave written informed consent. Eighty-six individuals with schizophrenia attending inpatient and outpatient programs at the Maryland Psychiatric Research Center (MPRC) participated in the study. Fifty-one first degree relatives of schizophrenia patients were recruited through letters and MPRC family seminars. Forty-six participants from the community were recruited through a series of newspaper advertisements. The Structured Clinical Interview for *DSM–III–R* (Spitzer et al. 1990) was conducted with patient participants, patients whose family members participated in the study, and community and family volunteers. Family history interviews based on Family History Research Diagnostic Criteria (Andreasen et al. 1986) were conducted with community volunteers. Clinical assessments were administered by master's- and doctoral-level trained clinicians. Interviews and patient clinical information from medical records were reviewed in a consensus diagnostic meeting chaired by a senior psychiatrist (G.K.T.) to confirm patient diagnoses and determine Axis I diagnoses for community and family volunteers. Family and community volunteers with an Axis I diagnosis were excluded (exceptions included participants who met criteria for a previous single episode of depression ending a minimum of 1 year prior to study participation, and sub-

jects with a history of substance abuse ending at least 6 months before study participation). Community volunteers with a family history of psychosis were excluded. Study participants with a history of serious medical or neurological illness (e.g., cancer, seizure disorder, encephalopathy) were also excluded. Interrater reliabilities for clinical assessments exceeded 0.81 (κ). Twenty-three of the 86 patient volunteers had at least one family member also participating in the study. The average number of family volunteers per family was 1.14 ± 0.42. Four families contributed two related members, while one family contributed three related members; all other families were represented by one family volunteer. Clinical and demographic information for the patient and nonpatient groups are given in table 1.

Data Collection and Dermatoglyphic Measures. Fingerprints were collected using a digital imaging device (Model 290 Fingerprint Capture Device—Cross Match Technologies, Inc.) and interactive computer software (Rollprint). Digital images were analyzed using interactive computer software (WinFing32, CE Computer Experts AG, Boniswil, Switzerland) and by visual inspection. Palm prints were obtained using the ink and paper method recommended by the U.S. Department of Justice, Federal Bureau of Investigation (FBI) (*The Science of Fingerprints*). The following dermatoglyphic features were examined: (1) fingerprint pattern asymmetry, (2) absolute total finger ridge count (ATFRC) asymmetry, (3) total finger ridge count (TFRC), (4) ATFRC, (5) *atd* angle, and (6) *atd* angle asymmetry. Each of these measures is described below.

Mid- to late first trimester. Differences in corresponding left-right fingerprint pattern type and ATFRC were used to mark aberrant developmental events associated with the mid- to late first trimester. Pattern asymmetry scores were derived by assigning a value of 1 to each corresponding left-right finger pair that differed in pattern type and summing these values across finger pairs (pattern matches were given a value of 0). Pattern asymmetry scores ranged from 0 (no pattern asymmetry) to 5 (complete pattern asymmetry). Fingerprints were classified based on the three-pattern system (i.e., loops, arches, and whorls) described by Cummins and Midlo (1943) and Mellor (1992), and the eight-pattern system used by the FBI. In the latter, arches are subclassified into plain and tented; loops subclassified into radial and ulnar; and whorls subclassified into plain whorl, central pocket loop, double loop, and accidental whorl. Examples of these additional pattern types are provided in figure 1. The FBI system was used to determine whether inclusion of these biologically distinct subpatterns (Dankmeijer et al. 1980) would increase the sensitivity (i.e., effect size) of asym-
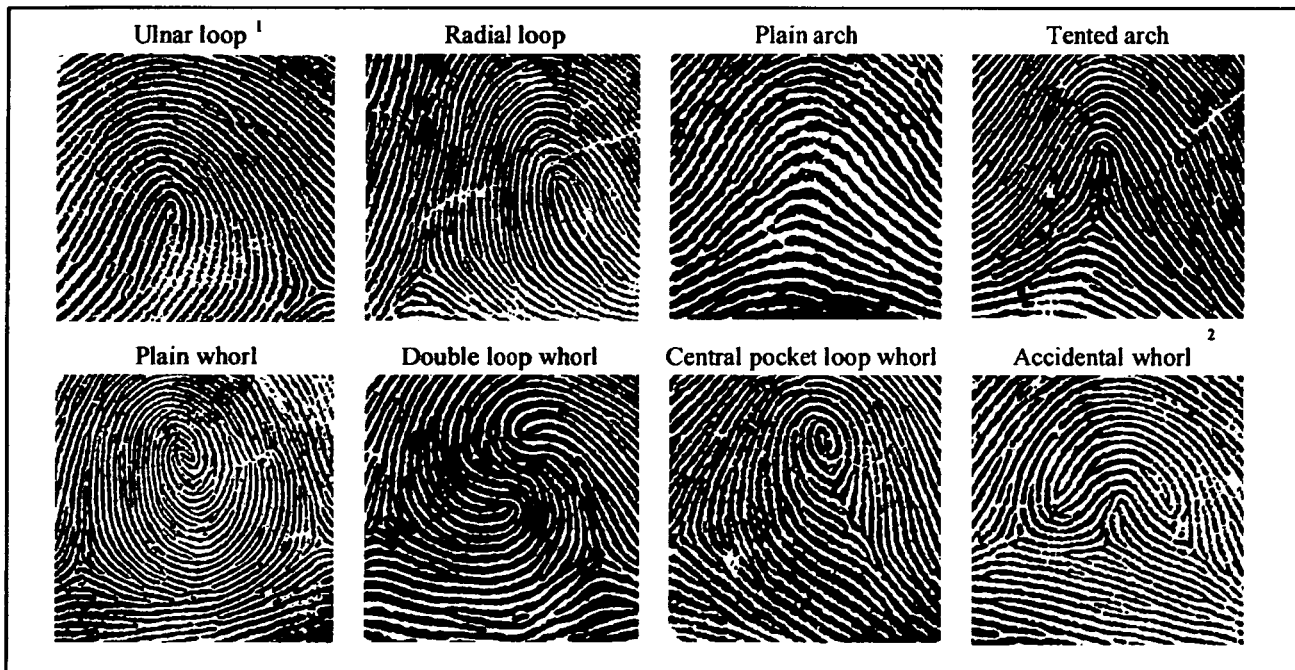
Table 1. Sociodemographic information

	Schizophrenia patients (*n* = 86)	First degree relatives (*n* = 51)	Community controls (*n* = 46)
Age (yrs), mean ± SD[1]	40.8 ± 11.4	52.9 ± 14.8	43.7 ± 17.1
Race (%)			
African-American	34	20	24
Caucasian	65	72	70
Other	1	8	6
Sex (% male)[2]	72	40	50
Education (yrs), mean ± SD[3]	11.5 ± 2.4	14.1 ± 2.9	14.8 ± 2.5

Note.—SD = standard deviation.

[1] First degree relatives are significantly older than patients and controls ($F_{(2, 179)}$ = 12.13, $p < 0.001$).

[2] The percentage of males is significantly higher in patients compared with relatives and controls (chi-square$_{(2)}$ = 14.83, $p = 0.001$).

[3] Patients have significantly less education than relatives and controls do ($F_{(2, 176)}$ = 29.55, $p < 0.001$).

Figure 1. Eight-pattern classification system

| Ulnar loop [1] | Radial loop | Plain arch | Tented arch |
| Plain whorl | Double loop whorl | Central pocket loop whorl | Accidental whorl [2] |

[1] Loops depicted in the figure are from the left hand; thus, the direction of flow for ulnar loops is to the left toward the thumb of the fingerprint card.

[2] The accidental whorl pattern is a pattern consisting of a combination of two different types of patterns (in this case, a loop and a central pocket loop).

metry detection. The sum of the differences in ATFRC between corresponding left-right finger pairs was also used as a measure of pattern asymmetry.

Late first trimester to end of second trimester. TFRC and ATFRC were used to assess developmental abnormalities occurring between the end of the first trimester and the end of the second trimester. Methods for ridge counting were based on those described by Holt (1968) and the Identification Unit of the FBI (*The Science of Fingerprints*). Briefly, delta (triradii) and core (i.e., center of the pattern) were marked on the digital image using interactive computer software. The number of ridges crossing the computer-generated ridge count line were counted and summed across all fingers on both hands. Whorl patterns contain two delta-core lines and therefore two ridge counts—TFRC uses the higher of the two whorl ridge counts, while ATFRC sums the counts. Arch patterns do not contain deltas and therefore have a ridge count of zero.

Mid- to late second trimester and beyond. The *atd* angle and *atd* angle asymmetry were used to assess developmental integrity beyond 17 weeks. Formation of the *atd* angle is thought to be related to events occurring later than 17 weeks in fetal development (Davis and Bracha 1996)—for example, *t* delta migration (David 1981) and skeletal growth of the hand (Schaumann and Alter 1976; McLeod and Coupland 1992). The *atd* angle is derived using vectors drawn from delta *t* (thenar and hypothenar area of the palm) to delta *a* (interdigital area II) and delta *d* (interdigital area IV) (see Penrose and Loesch [1970]). *Atd* angle asymmetry was calculated using absolute angle differences (in degrees) between the left and right hand.

A trained research assistant blind to group membership conducted pattern classification, ridge counting, and calculation of *atd* angle. A random subset of data (10%) was scored by one of the authors (M.T.A.) to assess reliability. Kappas exceeded 0.91 for all measures.

Statistical Analyses. Skewness and kurtosis estimates for the dependent measures were within acceptable limits (e.g., $^{skewness}/_{standard\ error} < 2.00$). As described above, some research participants were related to each other. The generalized estimating equations (GEE) method for analysis of covariance for unbalanced repeated measures data was used to take account of potential within-familial correlations of the dependent variables in regression models (Liang and Zeger 1986). The GEE method allows inclusion of varying numbers of members from each family (one, two, or more members), with either family-specific or participant-specific covariates. Ethnicity and sex, which some studies have shown to be associated with difference in pattern type, were included as covariates. GEE analyses were implemented using SAS PROC GENMOD.

A summary of the results, including means, standard deviations, and effect sizes (Cohen and Cohen 1983), is given in table 2. Correlations among the various dermatoglyphic measures are given in table 3.

Results

Pattern and Ridge Count Asymmetry. Type 3 GEE statistics for the three-pattern asymmetry score showed a significant effect of group ($\chi^2_{(2)} = 9.56$, $p = 0.008$). No significant effects of ethnicity or sex were observed. Least-squares means, employing Tukey's post hoc comparisons, showed that after controlling for interfamilial correlation, gender, and ethnicity, first degree relatives exhibited significantly higher three-pattern asymmetry scores compared with community subjects ($\chi^2_{(1)} = 11.28$, $p < 0.001$). Although relatives scored higher than patients, this difference was not statistically significant ($\chi^2_{(1)} = 3.12$, $p = 0.08$). Patients' scores were higher than controls' scores (i.e., intermediate between family members and controls), but this difference was not statistically significant ($\chi^2_{(1)} = 3.55$, $p = 0.06$).

A clearer separation of the groups was observed using eight-pattern asymmetry scores ($\chi^2_{(2)} = 10.78$, $p = 0.005$). First degree relatives exhibited significantly higher eight-pattern asymmetry scores compared with both community and patient participants ($\chi^2_{(1)} = 13.67$, $p < 0.001$ and $\chi^2_{(1)} = 7.02$, $p = 0.008$, respectively). Patients did not differ from controls ($\chi^2_{(1)} = 1.74$, $p = 0.19$). As was expected, the use of the eight-pattern system increased the effect size for group differences (table 2). No significant effects of ethnicity or sex were observed. When pattern asymmetry was assessed using ATFRC difference scores, there was no significant effect of group ($\chi^2_{(2)} = 3.89$, $p = 0.14$), although the pattern of group differences was similar to that observed for eight-pattern asymmetry scores (i.e., least-squares means comparisons of relatives vs. controls and patients were significant [*p* values < 0.05], while patients did not differ from controls [*p* = 0.76]). No significant effects of ethnicity or sex were observed.

TFRC and ATFRC. Analysis of TFRC yielded a significant effect of group ($\chi^2_{(2)} = 8.58$, $p = 0.014$). Patients exhibited significantly lower ridge counts compared with community subjects ($\chi^2_{(1)} = 8.62$, $p = 0.003$). TFRC among relatives and community controls did not differ ($\chi^2_{(1)} < 1.00$, $p = 0.34$). Differences in TFRC for patients versus relatives did not achieve statistical significance ($\chi^2_{(1)} = 2.78$, $p = 0.09$). The same pattern of results was observed for ATFRC ($\chi^2_{(2)} = 7.38$, $p = 0.025$). Patients exhibited significantly lower ridge counts compared with community subjects ($\chi^2_{(1)} = 6.30$, $p = 0.012$). ATFRC

Table 2. Group comparisons

Measure	Schizophrenia patients (n = 86), mean ± SD	First degree relatives (n = 51), mean ± SD	Community controls (n = 46), mean ± SD	Effect Size (Cohen's *d*)	
				Relatives vs. controls	Patients vs. controls
3-pattern asymmetry	1.27 ± 0.96	1.66 ± 1.01	0.95 ± 0.94	0.73	0.34
8-pattern asymmetry	1.59 ± 1.08	2.20 ± 1.15	1.36 ± 0.92	0.81[1]	0.23
Ridge count differences	22.64 ± 11.84	28.05 ± 12.34	22.23 ± 10.91	0.50	0.04
TFRC	114.17 ± 42.24	130.67 ± 45.70	140.00 ± 50.09	0.19	0.55
ATFRC	138.49 ± 69.41	169.13 ± 80.46	175.46 ± 84.60	0.08	0.44
Total *atd* angle	84.00 ± 11.77	82.16 ± 9.72	82.53 ± 8.25	0.04	0.15
Atd angle asymmetry	2.43 ± 2.14	3.13 ± 4.15	2.21 ± 2.17	0.29	0.10

Note.—ATFRC = absolute total finger ridge count; SD = standard deviation; TFRC = total finger ridge count.
[1] Note that the 8-pattern asymmetry score yielded a larger effect size than the 3-pattern score.

Table 3. Correlations among dermatoglyphic measures[1]

	3-pattern asymmetry	8-pattern asymmetry	Ridge asymmetry	TFRC	ATFRC	Total *atd*	*Atd* asymmetry
3-pattern asymmetry	1.00						
8-pattern asymmetry	0.82*	1.00					
Ridge asymmetry	0.50*	0.55*	1.00				
TFRC	-0.02	0.09	0.41*	1.00			
ATFRC	-0.03	0.12	0.39*	0.94*	1.00		
Total *atd*	0.02	0.00	0.06	0.03	0.00	1.00	
Atd asymmetry	-0.01	-0.01	0.00	-0.06	-0.07	0.23*	1.00

Note.—ATFRC = absolute total finger ridge count; TFRC = total finger ridge count.
[1] Correlations < 0.005 are listed as 0.00 in the table.
* *p* < 0.05 level (2-tailed)

among relatives and community controls did not differ $(\chi^2_{(1)} < 1.00, p = 0.69)$. Differences in TFRC for patients versus relatives did not achieve statistical significance $(\chi^2_{(1)} = 3.28, p = 0.07)$. Ethnicity and sex were not significant in either model.

***Atd* angle and *atd* angle asymmetry.** Analyses of *atd* angle and *atd* angle asymmetry did not yield significant group effects $(\chi^2_{(1)} = 1.67, p = 0.43$ and $\chi^2_{(1)} = 1.68, p = 0.43)$. Ethnicity and sex were also not significantly associated with *atd* measures.

Discussion

Findings in Patients. We found that patients exhibited significantly lower finger ridge counts compared with community controls. Previous studies of finger ridge counts in schizophrenia patients have varied widely in the comparison groups and finger ridge count measures employed and the particular contrasts reported. Consistent with our finding, Kemali et al. (1976) found reduced ridge counts in patients compared with controls, although it is not clear whether TFRC or ATFRC was used. Studies by Srinivasa Murthy and Wig (1977) and Balgir (1993) included finger ridge counts, but patient-control comparisons were not reported. Patient means in the two studies were 135.51 and 131.8, similar to the mean ATFRC reported in the present study (138.49; table 2). Fananas et al. (1996) failed to find patient-control differences in TFRC, although they found reduced a-b ridge counts—which, like finger ridge counts, are thought to be sensitive to developmental abnormalities in the second trimester. Markow and Wandler (1985) and Mellor (1992) also reported patient abnormalities in a-b ridge counts. Kemali et al. (1976) failed to find patient-control differences in a-b ridge counts. Unfortunately, in the present study, a-b ridge counts were not available for a significant number of study participants and therefore could not be included in the analyses.

Patient pattern and finger ridge count asymmetry scores did not differ from those of controls in the present study. In contrast, Markow and Wandler (1985) found that patients exhibited greater asymmetry based on three-pattern asymmetry scores. Mellor (1992) found that patients exhibited higher pattern and ridge count asymmetry compared with controls, although the digit rather than the individual subject was treated as the unit of analysis (e.g., right-left variance estimates for digits 1–5 in males and females were pooled [tables 1 and 2 in Mellor 1992]).

Findings in Relatives. We found that first degree relatives of patients with schizophrenia exhibited increased

dermatoglyphic asymmetry compared with controls. To our knowledge, this is the first family study of dermatoglyphics in schizophrenia. Although several dermatoglyphic studies involving MZ and DZ twins have been conducted (Markow and Gottesman 1989; Bracha et al. 1992; Davis and Bracha 1996; Van Os et al. 1997), only Davis and Bracha (1996) provided direct comparisons of affected versus unaffected twins (see Previous Studies of Dermatoglyphics in Schizophrenia section), and none provided direct comparisons of unaffected twins versus controls. Weinstein et al. (1999) reported increased finger ridge count asymmetry in adolescents with schizotypal traits, a group that like first degree relatives is likely to be at increased risk for schizophrenia.

Developmental Instability, Physiological Stress, and CNS Development. Thus, in the present study both schizophrenia patients and first degree relatives exhibited morphological deviations in dermatoglyphic traits compared with community controls. These data support the hypothesis that increased susceptibility to developmental insults, or developmental instability (marked by abnormal dermatoglyphics), aggregates in families affected by schizophrenia. This is presumed to reflect a shared nonspecific genetic risk factor for the illness, although shared environmental effects cannot be ruled out in a family study design.

Interpretation of the differences in the type of dermatoglyphic abnormalities observed among patients and relatives is difficult and should be considered tentative. Caution is warranted (1) because of the apparent inconsistencies in the literature about the types of abnormalities observed among patients (see comments in Previous Studies of Dermatoglyphics in Schizophrenia section and this section); and (2) because although significant progress has been made in elucidating the proximate mechanisms underlying dermatoglyphic morphogenesis, several uncertainties remain (e.g., the precise timing of particular events). Despite these ambiguities, the data in the present study are interesting and potentially informative.

It is important to recall that pattern and ridge count development are thought to occur at different times and through different physiological processes (Penrose and Ohara 1973; Okajima 1975; Lacroix et al. 1984; Babler 1987, 1990, 1991; Moore and Munger 1989). The pattern of correlations among the dermatoglyphic measures reported here supports this, showing that asymmetry measures cluster and ridge count measures cluster but that overlap between the two sets of measures is minimal (table 3). The dissociation between asymmetry and ridge count abnormalities observed in patients and relatives is consistent with our hypothesis that the timing of developmental insults may lead to divergent phenotypes among

vulnerable individuals and that markers of second trimester developmental abnormalities (reduced ridge counts in the present study) are more likely to be observed in individuals who develop schizophrenia.

Thus, these data highlight two aspects of development that may be involved in the pathogenesis of schizophrenia: (1) the presence of nonspecific factors (presumably genetic) that increase vulnerability to physiological stress during development (developmental instability); and (2) the nature of any insults experienced during development—that is, whether insults occur during critical periods in brain development. A diagrammatic representation of how these various factors may interact is shown in figure 2. According to this scheme, mid- to late first trimester insults are likely to produce pattern abnormalities among vulnerable individuals. However, because these insults are not associated with periods of critical brain development, they are less likely to be associated with the development of schizophrenia. In contrast, second trimester insults are more likely to produce ridge count abnormalities among vulnerable individuals. Because these insults occur during a critical period in the development of important CNS structures such as the hippocampus, the cingulate gyrus, and the thalamus (Waddington et al. 1999*a*), this pheno-

type is more likely to be associated with schizophrenia. Of course, these interactions are likely to be significantly influenced by the presence of other (currently unidentified) disease-specific genetic factors.

Based on the interactions described above, one would expect that other developmental abnormalities associated with early (first trimester) and late (late second trimester and beyond) development would occur more often among unaffected relatives, as these would not correspond with insults during critical second trimester neurodevelopmental events. The pattern of results in *atd* angle asymmetry is consistent with this prediction (table 2), although it did not achieve statistical significance. It is interesting to note that several studies have failed to find patient differences in *atd* angle (Kemali et al. 1976; Mellor 1992; Balgir 1993; Davis and Bracha 1996). However, unlike pattern formation and ridge formation, *atd* angle is known to be affected by events occurring after birth, including growth of the hands (Schaumann and Alter 1976; David 1981; McLeod and Coupland 1992) and therefore would be less sensitive to and specific for the effects of developmental instability. Other more time-specific developmental markers are needed to test for similar patterns of dissociation in patient-family abnormalities. For example, investigators have

Figure 2. The relationship between vulnerability to and timing of developmental insult, critical periods in dermatoglyphic morphogenesis and brain development, and liability to schizophrenia[1]
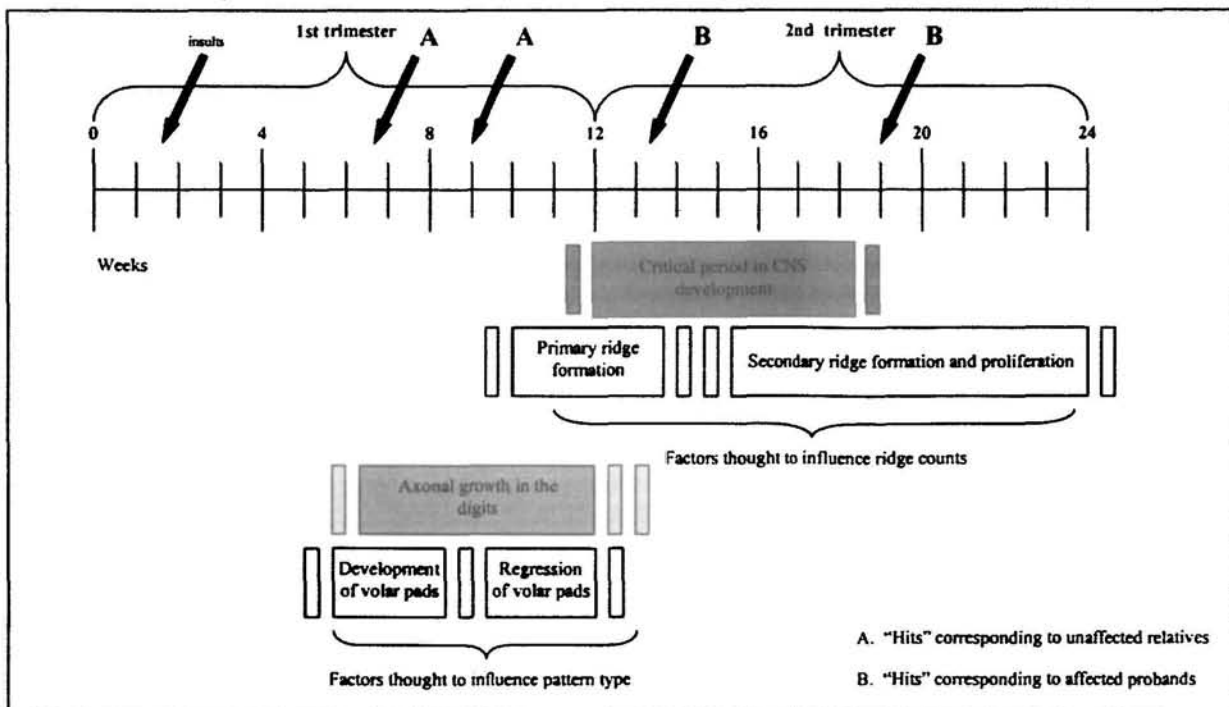
[1] The timing of dermatoglyphic morphogenesis is approximate, based on the work of Penrose and Ohara (1973), Okajima (1975), Lacroix et al (1984), Babler (1987, 1990, 1991), and Moore and Munger (1989).

reported abnormalities in craniofacial morphology (e.g., palate, eyes, ears) in schizophrenia patients (Lane et al. 1997; Trixler et al. 1997; Waddington et al. 1999a). This is consistent with the model based on the developmental timing of these traits occurring between 12 and 15 weeks (Moore 1977). These features have not yet been assessed in first degree relatives but are expected to be within normal limits. Other morphological and/or physiological traits for which vulnerability to developmental stress is time-specific might be expected to exhibit dissociation between relatives and patients, depending on when those traits are formed.

Conclusions

This investigation is a preliminary attempt to use a family study design and phenotypic markers to explore genetic, neurodevelopmental, and perhaps environmental interactions involved in the pathogenesis of schizophrenia. The results of the present investigation are consistent with and expand upon neurodevelopmental findings described by Weinberger (1995), Waddington et al. (1999a, 1999b), Weinstein et al. (1999), and others. The data support the role of vulnerability to developmental stress (developmental instability) in conferring risk for schizophrenia. The data also suggest that the nature of the stress (i.e., the timing of insults) interacts with developmental instability and second trimester neurodevelopment to create phenotypes characterized by overt disease expression and covert liability. These findings suggest a revision of the traditional two-hit model of schizophrenia (Bayer et al. 1999), in which disease-specific genetic factors combine in an additive fashion with environmental insults to produce disease. Rather, the data are consistent with a more complex model in which nonspecific factors that increase susceptibility to developmental abnormalities interact with insults and disease-specific genetic factors to produce the illness. Several investigators have proposed alternative etiologic models of this form (Moldin and Gottesman 1997; Petronis et al. 1999; Tsuang 2000). The present study suggests that dermatoglyphic measures may be useful in attempting to understand schizophrenia's complex etiology.

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