Original Article

Parent-of-origin Effect in Schizophrenia and Non-affective Psychoses: Evidence from Dermatoglyphics

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ABSTRACT

Objective: This study aims at examining "parent-of-origin effect" (POE) in dermatoglyphic patterns among patients with schizophrenia and non-affective psychoses. **Materials and Methods:** Dermatoglyphic comparison was carried out for schizophrenia patients (n=200) and healthy controls (HC) (n=100). In addition, the effect of family history and POE was examined in the dermatoglyphic pattern. **Results:** Schizophrenia patients compared to HC had significantly lower left total finger ridge count (LTFRC) (t=3.63, P<0.001), right total finger ridge count (RTFRC) (t=4.86, P<0.001), and absolute finger ridge count (ATFRC) (t=4.80, P<0.001) compared to HC. It was also noted that patient group had significantly higher average number of arches (t=2.20, P=0.03). The comparison between the same sex POE group and the opposite sex POE group revealed that significant differences exist in LTFRC (t=2.91, P<0.01) and ATFRC (t=2.30, P=0.02). The same sex group also had lesser number of whorls compared to opposite sex group (t=2.04, P=0.04). **Conclusions:** The same sex parental inheritance group seem to be more developmentally compromised than the opposite sex parental inheritance group indicating a significant POE. Complex epigenetic mechanisms along with hormonal modulation could explain the sex specific disease phenotype expression, which is a plausible explanation as in the present study.

Key words: *Dermatoglyphics, epigenetic, neurodevelopmental, parent-of-origin effect, schizophrenia*

INTRODUCTION

Schizophrenia is a complex neurodevelopmental disorder conceptualized to be due to various insults of the brain with differing effects acting at different points of time.[1,2] It is currently understood that the pathophysiology of this condition is an intricate interplay between the genetic and environmental factors, which shape the phenotype.[3] It is essential to examine the reliable external biological markers to gain better understanding of the mechanisms behind neurodevelopmental pathology of schizophrenia. Dermatoglyphic anomalies are known to be markers, which are associated with various neurodevelopmental disorders such as epilepsy, Down's syndrome, mental retardation, neurofibromatosis, spinabifida, and schizophrenia.[4] Dermatoglyphics is heritable, state-independent, and it co-segregates with the illness. It is also considered as a reliable marker of aberrant neurodevelopment.[5] A number of studies have shown that dermatoglyphic anomalies are associated with

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schizophrenia.[6-9] It also is found more frequently in unaffected relatives of schizophrenia patients than in general population.[10]

The neurodevelopmental abnormalities including dermatoglyphic anomalies are considered to be the result of combined effect of physiological insults, which occur during the intrauterine fetal development such as viral infections, environmental toxins, and nutritional compromise and genetically mediated resistance to stress or the presence of disease genes[5,11,12] suggesting a "two hit" hypothesis. This implies that the study of dermatoglyphics may be helpful in understanding how developmental environmental stressors interact with genetic vulnerability in complex illnesses like schizophrenia. High heritability rates upto 77% for total finger ridge count (TFRC) have been reported by studies from India.[13] Significant dermatoglyphic differences were observed for fingerprint patterns, TFRC and "atd" angle between the schizophrenia patients with and without a positive family history of schizophrenia, suggesting a strong genetic loading for dermatoglyphic patterns in familial cases of schizophrenia.[14]

Studies which looked into the models of inheritance have found no single gene with major effect and supported the notion of a more complex nature of inheritance than Mendelian model.[15] "Parent-of-origin effect" (POE) is defined as the representative name for modes of inheritance in which sex of the transmitting parent differentially affects the expression of the illness in the offspring, without following Mendelian laws and some of the possible mechanisms for such phenomena include mitochondrial inheritance, genomic imprinting, and X linked transmission.[16] Data on POE in schizophrenia is not only limited, but also inconsistent. It has been shown that the negative symptom scores and clinical course scores in the off-spring generation of paternal transmission were significantly higher than for maternal transmission indicating possible POE.[17] Similarly, another study showed possible evidence of paternal effects.[18] Paternal transmission was associated with a trend for a younger age at onset in probands compared to that observed in the case of maternal transmission in periodic catatonia.[19] Rare copy number variants have been considered in neurodevelopmental disorders.[20] It has been documented recently that the presence of micro-duplications at chromosome 15q11.2-q13.1 that overlaps with the Prader-Willi/Angelman syndrome critical region may bear are risk factor for schizophrenia and other psychoses, emphasizing a possible POE.[21]

There is an emerging evidence that epigenetic alterations like POE operate at the neurodevelopmental level in psychosis.[22,23] The POE on markers of aberrant neurodevelopment and other clinical characteristics of schizophrenia are yet to be examined systematically. We hypothesized that there could be POE noticeable in the neurodevelopmental marker namely dermatoglyphics. This study aims at exploring the POE in dermatoglyphic pattern among patients with schizophrenia and non-affective psychoses.

MATERIALS AND METHODS

Patients with DSM-IV diagnosis of schizophrenia ($n=200$) who presented to the clinical services of National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, a tertiary mental health institute situated in South India, were recruited. The comparison group consisted of age and sex matched healthy controls (HC) ($n=100$) devoid of any axis I psychiatric diagnosis and family history of any psychiatric disorder in first-degree relatives. The study involved no invasive procedures/interventions, consent was taken from both patients and informants, confidentiality of all the information obtained was maintained and subjects had the right to withdraw consent at any stage. The study was cleared by the Ethics Committee of NIMHANS. The selection of subjects involved sampling during a period of 18 months ranging from March 2008 to September 2009. Figure 1 shows the study structure and the recruitment process.

The subjects who enrolled were assessed using the mini international neuropsychiatric interview (MINI Plus)[24] to ascertain the diagnosis of schizophrenia. The psychopathology was evaluated using scale for assessment of positive symptoms (SAPS) and scale for assessment of negative symptoms (SANS).[25,26] The severity of the illness and functioning were assessed using clinical global impressions (CGI),[27] global assessment of functioning (GAF) scales.[28] The subjects were assessed for obstetric complications using Lewis-Murray obstetric complications scale.[29] A detailed elicitation of family history with the help family interview for genetic studies[30] was carried out specifically exploring for schizophrenia or schizophrenia spectrum conditions in the first degree relatives. Using the available information, if non-affective psychosis was present in first degree relatives, but a confident diagnosis of schizophrenia could not be made, it was coded as schizophrenia spectrum disorder. Wherever possible, the information was collected from the mother. Whenever mother was not available, details were obtained either from father or the nearest relative. All available informants were interviewed for corroboration of the history. Wherever available, diagnostic clinical interviews of affected relative(s) or review of medical records from NIMHANS was done for better accuracy of ascertainment.

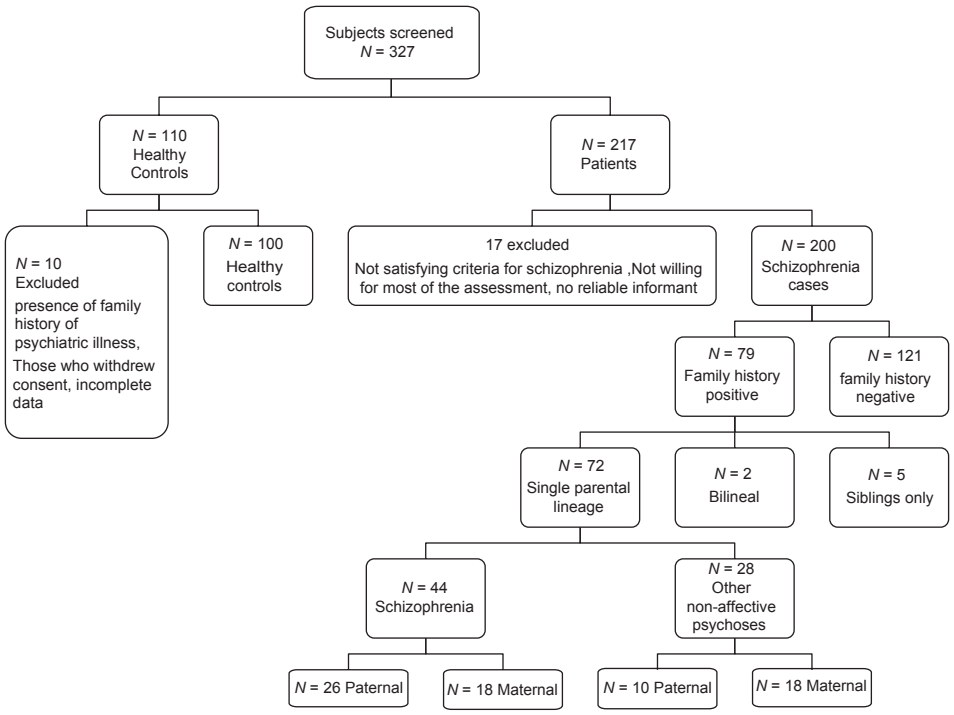

Figure 1: Depicts the subject recruitment format

Dermatoglyphic evaluation was done after obtaining images of all available digits of subjects using a digital scanner (CanoscanLiDE 25™) at 1200dpi. Once all the images were obtained, a common image database for cases and controls was made. Next, blinding was done by another independent member by random mixing of the images of cases and controls after removing any names, identification numbers from each of them, and coding with a four digit random number obtained from random number tables. The coded images were then returned to the rater and then, manual rating of the qualitative and quantitative aspects was done by the rater, being blind to the subject's status. The images were opened using Adobe Photoshop and images were rated for image quality. Poor quality images were coded appropriately and was not included in either qualitative or quantitative study. Then, the finger print patterns were identified for each finger and appropriately classified. Finger ridge counts were determined by counting the number of ridges that intersected a straight line connecting the triradial point (the point of ridge intersection) to the point of the core (the ridge in the center of the pattern). If more than one triradius was present on a finger, multiple ridge counts were made (e.g., two triradii yielded two ridge counts). TFRC was computed for both left hand lower left total finger ridge count (LTFRC) and right hand right total finger ridge count (RTFRC) by summing the ridge counts of both radial and ulnar counts of each finger for all five fingers of each hand. Absolute finger ridge count (ATFRC) was determined by adding all of the ridge counts from each of the 10 fingers. In addition, the ridge count asymmetry was calculated using the formula: (LTFRC–RTFRC)/(LTFRC+RTFRC). Inter-rater reliability was calculated and intra-class correlation co-efficient was noted to be >0.95.

Statistical analysis

Data entry and statistical analyses were done using the Statistical Package for Social Sciences (SPSS 11.0) (SPSS Inc., Chicago, IL, USA). Data were assessed using Kolmogorov-Smirnov test and was found to be normatively distributed. The independent samples *t*-test was used for comparison of continuous variables and Chi-square test was used for categorical variables.

RESULTS

The results are presented in a hierarchical format with:

a. Comparison between the case and HC groups
b. Comparison between family history positive and family history negative groups
c. Within the family history positive group comparison between the paternal and maternal lineages to detect any "POE"
d. Comparing the same sex group (defined as the paternal lineage family history and son as probands or maternal lineage family history and daughter as the probands in the study) and the opposite sex group (i.e., paternal lineage to daughter or maternal lineage to son).

Analyses b, c, and d were done with those with a family history of schizophrenia alone and subsequently including the schizophrenia spectrum to the above groups. The schizophrenia group was comparable to HC in terms of age, sex distribution, and family income. However, the HC differed significantly ($P \leq 0.001$) from patients, having on anaverage 2.5 years more education. There was no significant difference in the demographic characteristics between the groups in the subsequent analyses lower down in the hierarchy as shown in Table 1. Schizophrenia patients compared to HC had significantly lower LTFRC ($t=3.63$, $P<0.001$), RTFRC ($t=4.86$, $P<0.001$) and ATFRC ($t=4.80$, $P<0.001$) compared to HC. It was also noted that the patient group had significantly higher average number of arches ($t=2.20$, $P=0.03$) as depicted in Table 2.

When the family history positive group ($n=79$) was compared to the family history negative group ($n=121$), no differences were observed in any of the dermatoglyphic parameters as shown in Table 3. In addition, we did not observe significant differences on comparing the paternal and maternal inheritance groups as depicted in Table 4. The clinical parameters such as positive and negative symptom scores, CGI severity and GAF scores did not differ in either comparison. There was no evidence of differential involvement by perinatal events as assessed by Lewis-Murray obstetric complication scale.

As shown in Table 5, the comparison between the same sex POE group and the opposite sex POE group revealed that significant differences exist in LTFRC ($t=2.91$, $P<0.01$), ATFRC ($t=2.30$, $P=0.02$) in schizophrenia family history group. Similar results were seen if the family had schizophrenia spectrum conditions. The same sex group of schizophrenia (but not the schizophrenia spectrum conditions) also had lesser number of whorls compared to opposite sex group ($t=2.04$, $P=0.04$).

DISCUSSION

In the present study, we examined the POE in dermatoglyphic anomalies. POE is known to occur in schizophrenia even though the data on this is relatively sparse. We sought to study the POE using a peripheral marker of neurodevelopmental aberrations, namely dermatoglyphic anomalies. Development of skin and brain occurs from the ectoderm and their development overlaps ontogenetically.[31] The timing of the proposed events is at 8-16 weeks of fetal development when the neural cells migrate to the cortex and form critical brain regions, which are postulated to be structurally and/or functionally compromised in schizophrenia. Hence, the deviation in dermatoglyphics is an indirect evidence for the early neurodevelopmental insults. Thus, dermatoglyphic anomalies are generally considered as evidence for aberrant neurodevelopment and might be a marker for both genetic and environmental insults.[5] The main findings of the study are:

- The LTFRC, RTFRC, and ATFRC were noted to be lesser in the male-paternal and female-maternal groups as compared to the male-maternal and female-paternal groups put together revealing a POE
- TFRC, LTFRC, and RTFRC in patients were reduced compared to HC, but there were no differences in the TFRC asymmetry
- The differences in finger ridge counts were not significant based on family history positive and negative status of the subjects.

The pathogenesis of psychotic illness is multifaceted and it shows concordance rates of less than 70% in monozygotic twins. In addition, it has non-Mendelian inheritance pattern and a probable sexual dimorphism in picture.[32,33] Sexual dimorphism in various phenotypes of expression has been noted for many psychiatric and neurological disorders such as Alzheimer's disease, mood disorders, substance abuse related disorders, and schizophrenia.[34] In this study, the same sex parental inheritance group seem to be more developmentally compromised than the opposite sex group indicating a significant POE. One of the possible explanations for such specific POE could be epigenetic mechanisms in

Table 1: Comparison of demographic variables between schizophrenia patients and controls

Group	*N*	Sex		Age			Years of education			Family income (Indian rupee)		
		M	F	Mean (SD)	*t*	*P**	Mean (SD)	*t*	*P**	Mean (SD)	*t*	*P**
Schizophrenia patients	200	106	94	31.61 (8.53)	1.64	0.10	10.49 (5.42)	4.36	<0.01	6501.50 (10409.60)	1.67	0.09
Healthy controls	100	53	47	33.82 (12.07)			12.81 (3.67)			8448.00 (7211.43)		
FH+	79	46	33	31.05 (8.73)	0.74	0.45	10.81 (5.46)	0.67	0.50	7272.15 (11888.96)	0.84	0.39
FH−	121	60	61	31.97 (8.42)			10.28 (5.40)			5994.16 (9327.09)		
P	36	23	13	31.78 (8.68)	1.34	0.18	11.42 (5.21)	0.36	0.72	8008.33 (13450.97)	0.48	0.63
M	36	21	15	29.25 (7.26)			10.97 (5.21)			6625.00 (10849.20)		
SS	37	23	14	32.38 (9.20)	1.95	0.55	11.22 (5.18)	0.51	0.95	7821.62 (13150.52)	0.23	0.81
OS	33	21	12	28.70 (6.06)			11.15 (5.35)			7133.33 (11413.52)		

F^+ – Family history positive; FH^- – Family history negative; *P* – Paternal; M – Maternal; SS – Same sex group; OS – Opposite sex group; *$P \leq 0.05$ is considered significant

the operation.[35] An epigenetic mechanism, namely genomic imprinting in which epigenetic changes happen depending on the parental origin can be considered to be the reason for POE.[36]

A wide variety of diseases, which are related to complications in-utero or pregnancy outcome are considered to be working through maternal fetal interactions or POEs. These can range from spina bifida[37] to the illness under question here like schizophrenia.[38] It has been shown that some epi-mutations in schizophrenia could be meiotically persistent and this is believed to result in genetic anticipation.[39] Hence, such changes are described based on the differential de-methylation followed by re-methylation, which happens in a sex specific manner in the germline.[39-41] Many of the psychotic illness related DNA methylation changes differentially affect male and female subjects.[22] Sex steroids are known to play a key role in this process.[32,42] The sex differences in the brain have been convincingly linked to prenatal sex steroid hormone exposure.[43] In addition, the nature of epigenetic alterations is such that, it is possible for environmental factors to modify it in a sex-specific manner during neurodevelopment.[44] Thus, an adverse programming of this kind could thus lead to diverse susceptibility to diseases between males and females. At a second level, these are further subjected to hormonal modulation at a later stage, for instance, during puberty. This paves way to precipitating the illness as in the case of

Table 2: Comparison of dermatoglyphic parameters between patients and healthy controls

Dermatoglyphic parameters	Patients (*N*=200) mean (SD)	Healthy controls (*N*=100) mean (SD)	*t*	*P**
RCA	0.05 (0.32)	0.02 (0.24)	0.81	0.41
LTFRC	58.12 (33.43)	72.62 (30.61)	3.63	<0.001
RTFRC	52.38 (30.93)	71.15 (32.57)	4.86	<0.001
ATFRC	110.51 (56.27)	143.77 (56.93)	4.80	<0.001
Loops	5.76 (2.85)	5.98 (2.81)	0.61	0.54
Whorls	3.15 (3.03)	3.42 (2.99)	0.71	0.48
Arches	0.67 (1.50)	0.36 (0.93)	2.20	0.03
Indeterminate	0.18 (0.65)	0.11 (0.34)	1.35	0.17
Unclear	0.21 (0.59)	0.13 (0.46)	1.34	0.18

RCA – Ridge count asymmetry; LTFRC – Left total finger ridge count; RTFRC – Right total finger ridge count; ATFRC – Absolute total finger ridge count; *$P \leq 0.05$ considered significant

Table 3: Comparison between family history positive and negative groups

Variable	Group							
	Schizophrenia				Schizophrenia spectrum			
	FH+ (*N*=53) mean (SD)	FH− (*N*=147) mean (SD)	*t*	*P**	FH+ (*N*=79) mean (SD)	FH− (*N*=121) mean (SD)	*t*	*P**
RCA	0.04 (0.33)	0.05 (0.32)	0.09	0.92	0.06 (0.33)	0.04 (0.31)	0.54	0.58
LTFRC	62.83 (33.68)	56.43 (33.30)	1.19	0.23	61.58 (34.03)	55.86 (32.98)	1.18	0.23
RTFRC	55.22 (29.98)	51.36 (31.30)	0.77	0.43	53.45 (30.74)	51.68 (31.16)	0.39	0.69
ATFRC	118.05 (56.08)	107.78 (56.29)	1.14	0.25	115.03 (57.02)	107.55 (55.82)	0.91	0.35
Loops	5.82 (2.84)	5.74 (2.87)	−0.18	0.85	5.90 (2.75)	5.67 (2.92)	0.55	0.57
Whorls	3.28 (3.03)	3.11 (3.04)	−0.36	0.71	3.13 (2.86)	3.17 (3.15)	0.09	0.92
Arches	0.59 (1.41)	0.70 (1.53)	0.43	0.66	0.50 (1.24)	0.78 (1.63)	1.29	0.19
Indeterminate	0.13 (0.34)	0.20 (0.73)	0.69	0.48	0.26 (0.89)	0.14 (0.43)	1.09	0.27
Unclear	0.15 (0.41)	0.23 (0.64)	0.85	0.39	0.19 (0.46)	0.22 (0.66)	0.31	0.75

FH^+ – Family history present; FH^- – Family history absent; RCA – Ridge count asymmetry; LTFRC – Left total finger ridge count; RTFRC – Right total finger ridge count; ATFRC – Absolute total finger ridge count; *$P \leq 0.05$ is considered significant

Table 4: Comparison between paternal and maternal inheritance groups

Variable	Group							
	Schizophrenia				Schizophrenia spectrum			
	Paternal (*N*=26)	Maternal (*N*=18)	*t*	*P**	Paternal (*N*=36)	Maternal (*N*=36)	*t*	*P**
RCA	0.04 (0.33)	0.08 (0.38)	0.32	0.74	0.06 (0.32)	0.07 (0.37)	0.97	0.33
LTFRC	63.11 (35.87)	68.55 (32.50)	0.51	0.61	60.27 (35.18)	65.02 (34.07)	0.58	0.56
RTFRC	56.76 (35.97)	55.94 (24.99)	0.08	0.93	52.77 (35.06)	55.66 (28.45)	0.38	0.70
ATFRC	119.88 (63.05)	124.50 (50.24)	0.25	0.79	113.05 (61.23)	120.69 (55.45)	0.55	0.58
Loops	5.68 (2.85)	5.55 (2.81)	0.14	0.88	5.8 (2.88)	5.65 (2.67)	0.29	0.77
Whorls	3.36 (3.16)	3.61 (2.97)	0.26	0.79	2.97 (2.96)	3.54 (2.82)	0.82	0.41
Arches	0.76 (1.83)	0.44 (1.04)	0.65	0.51	0.61 (1.61)	0.40 (0.91)	0.69	0.49
Indeterminate	0.04 (0.20)	0.22 (0.42)	1.68	0.10	0.35 (1.25)	0.17 (0.45)	0.80	0.42
Unclear	0.16 (0.47)	0.16 (0.38)	0.04	0.96	0.20 (0.53)	0.22 (0.42)	0.19	0.84

Paternal – FH^+ on paternal lineage; Maternal – FH^+ on maternal lineage; RCA – Ridge count asymmetry; LTFRC – Left total finger ridge count; RTFRC – Right total finger ridge count; ATFRC – Absolute total finger ridge count; FH^+ – Family history present; *$P \leq 0.05$ is considered significant

Table 5: Comparison between same sex and opposite sex groups

Variable	Group							
	Schizophrenia				Schizophrenia spectrum			
	Same sex (*N*=24)	Opp. sex (*N*=20)	*t*	*P**	Same sex (*N*=37)	Opp. sex (*N*=33)	*t*	*P**
RCA	0.01 (0.39)	0.12 (0.29)	1.12	0.26	0.07 (0.39)	0.10 (0.27)	0.31	0.75
LTFRC	52.66 (33.07)	80.55 (29.74)	2.91	<0.01	55.21 (35.54)	72.78 (31.07)	2.19	0.03
RTFRC	51.70 (34.52)	62.10 (27.53)	1.08	0.28	48.64 (34.17)	59.27 (28.88)	1.39	0.16
ATFRC	104.37 (61.72)	142.65 (45.25)	2.30	0.026	103.86 (63.64)	132.06 (49.78)	2.04	0.04
Loops	6.13 (3.01)	5.05 (2.48)	1.27	0.21	6.08 (3.00)	5.43 (2.51)	0.95	0.34
Whorls	2.60 (3.05)	4.45 (2.79)	2.04	0.04	2.68 (2.89)	3.87 (2.81)	−1.70	0.09
Arches	0.86 (1.89)	0.35 (0.98)	1.10	0.27	0.65 (1.58)	0.37 (0.94)	0.87	0.38
Indeterminate	0.13 (0.34)	0.10 (0.30)	0.30	0.76	0.31 (1.20)	0.18 (0.53)	0.54	0.58
Unclear	0.26±0.54	0.05±0.22	1.71	0.09	0.25±0.56	0.12±0.33	1.15	0.25

Same sex – Male proband with FH^+ on paternal lineage or female proband with FH^+ on maternal lineage; Opp. sex – Opposite sex means male proband with FH^+ on maternal lineage or female proband with FH^+ on paternal lineage; RCA – Ridge count asymmetry; LTFRC – Left total finger ridge count; RTFRC – Right total finger ridge count; ATFRC – Absolute total finger ridge count; FH^+ – Family history present; *$P \leq 0.05$ is considered significant

schizophrenia.[39] These models explain not only the early neurodevelopmental insults which are sexually dimorphic, but also the latent period thereafter where mild developmental deviances can be observed. What is more interesting in the current study is the sex specific transmission with father-son and mother-daughter pattern. There is recent molecular genetic evidence suggesting an X-chromosome contribution to the pathogenesis of schizophrenia.[45,46] In addition, there is some evidence for the role of Y-chromosome in the causation of this illness although the evidence is not compelling.[47] However, at an epidemiological level, rate of schizophrenia among sons of mothers with psychosis was significantly higher than among the daughters of these women and vice versa when the parent with illness was father.[48] Males have been associated with earlier age of onset of illness and a poorer prognosis while for women the age of onset is later with better prognosis.[49,50] Higher frequency of dermatoglyphic abnormalities may reflect a more developmentally compromised status and hence a more severe illness– suggesting the possibility that greater neurodevelopmental insult is needed to precipitate the disorder in the father-son/mother-daughter transmission.

Our study showed a significantly lower LTFRC, RTFRC, and ATFRC in patients than HC. We also noted a higher than average number of arches in patients than controls, which showed a trend toward significance. Schizophrenia patients have lower TFRC relative to controls, though this finding is not always replicated,[8] While TFRC indicates the size of the finger print pattern, ATFRC is an indicator of both size and intensity of the pattern; the latter is also hypothesized to be more sensitive to non-geneticinfluences.[31] However, the difference was not significant when family history status was considered, in contrast to studies that have shown that patients with a negative family history of schizophrenia exhibited lower TFRC than patients with a positive family history and controls.[51]

The strengths of the present study are relatively large sample size, use of structured instruments for phenotype characterization and the use of blinded measurements of dermatoglyphic characteristics. However, it is limited by the smaller numbers of family history positive probands and the use of family history method for the ascertainment of psychiatric diagnosis of family members. Markers of aberrant neurodevelopment like dermatoglyphic aberrations which are more proximal to genome would be a promise for future neuropsychiatric research. Thus, complex epigenetic mechanisms along with hormonal modulation could explain the sex specific disease phenotype expression which is a plausible explanation as in the present study. Studying a larger sample of subjects with schizophrenia with familial loading and examining the POE could substantiate our preliminary finding.

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