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Minor Physical Anomalies in Bipolar Disorder

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ABSTRACT

Objective: High-arched palate is more frequent in schizophrenia and bipolar disorder (BD). Upto 40% of patients develop schizophrenia in 22q11.2 Deletion Syndrome manifested with cleft lip and palate, which originate from the first pharyngeal arch in embryo. The auricle also originates from the dorsal ends of the first and second pharyngeal arches; hence, we aimed to determine the associations between auricular anomalies and BD. Methods: We screened for 36 minor physical anomalies of the auricle in 146 patients with BD. Results: 7 out of the of 36 assessed anomalies highly differed between healthy subjects and BD patients. A regression model including the differing anomalies predicted healthy subjects and BD-patients by 78.8% and 68.5%, respectively.
Conclusions: Assessing minor anomalies in psychiatric disorders may help to discover novel pathogenesis pathways and even new endophenotypes.

1. Introduction

Since 1980's, it is well established that aberrant neurodevelopment is one of the important factors in development of psychiatric disorders [1]. Developed neuroimaging techniques provide important insights about the neurodevelopmental defects in psychiatric disorders, yet minor physical anomalies (MPA) which can be assessed by simple inspection can also provide important clues about the person's vulnerability and pathogenesis in regard to psychiatric disorders. Indeed, the central nervous system and the dermal tissues origin from the same ectodermal layer in utero, hence MPA may reflect mild anomalies of brain development [1]. The term "minor physical anomalies" collectively describes two different entities, which are minor malformations, which develop during organogenesis (first trimester and early periods of second trimester) and phenogenetic variants, which develop after organogenesis [1]. In schizophrenia and bipolar disorder, high-arched palate is seen more frequently. In 22q11.2 Deletion Syndrome with morphological abnormalities including cleft lip and palate, about 30%–40% percent of patients develop schizophrenia [2]. Lip and palate structures originate from the first pharyngeal arch in embryogenesis. The auricle also originates from six mesenchymal proliferations (hillocks) at the dorsal ends of the first and second pharyngeal arches, surrounding the first pharyngeal cleft at approximately 42th day of gestation (Fig.1) [3]. Differential growth and fusion of the hillocks by the end of the eighth week of gestation forms the characteristic morphology of the auricle. The auricle migrates up the side of the developing face from their original cervical location to reach their normal position by the fourth month of gestation, largely due to lower facial and mandibular growth [3]. Despite the auricles also develop from the pharyngeal archus, few studies exist which assessed auricle anomalies in psychiatric diseases. Moreover, these studies were conducted on a limited number of patients and assessed limited number of anomalies and/or used vague terms. For instance, Waldrop Scale assess very few number of anomalies including low seated auricles, adherent lobes, malformities, asymmetrical ears, soft and pliable ears. The Mehes Scale assess preauriculer tags and pits, cup ears, ear lob creases, lack of earlobe, double anti-helix, protruding auricles, asymmetrical size of ears. Abnormalities of auricular configuration are suggested as part of more than 100 syndromes described by Aase in 1990 [4] and it is very likely that this association is relevant even for more syndromes.

Bader et al. evaluated 3107 consecutive term and preterm neonates born in Haifa, Israel for minor auricular anomalies and revealed that these anomalies existed significantly more frequently in males, infants small and large for gestational age, and prematurity [4]. Higher rates were also associated with breech presentation, triplets, IVF pregnancies, gestational diabetes mellitus and parental consanguinity, although the last two findings did not reach statistical significance owing to the

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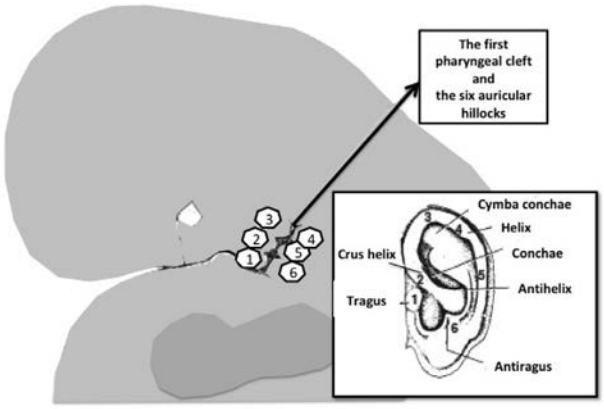

Fig. 1. Lateral side of the head of an embryo demonstrating the 6 auricular hillocks forming the dorsal end of the first pharyngeal cleft and transformation of the hillocks into the adult pinna.

small number of infants in these groups [4]. These results strongly indicate that minor auricle anomalies may reflect inherent defects of genes regulating embryogenesis, noxious physiological stress conditions in utero, or both. To reveal further associations with psychiatric disorders, we aimed to define minor anomalies of the auricle by employing 39 different parameters in 146 patients with bipolar disorder (Type I). To the best of our knowledge, this is the first study which employed the highest number of assessment parameters on the auricle anomalies in bipolar disorder. These parameters were described in Materials and Methods.

2. Materials and methods

2.1. Patients selection criteria and determined parameters of auricle anomalies

The study included 146 Bipolar I disorder patients (73 male and 73 female, age range 18 to 60) that were selected from 1300 patients registered at Rasit Tahsin Mood Disorders Outpatient Unit (RTMDOU) of Bakirkoy Research and Training Hospital. All of the registered BD patients at RTMDOU continue to be evaluated with standardized medical forms based on a nationwide mood disorders follow-up program named SKIP-TURK (Tirpan et al.,2004). The SKIP-TURK form, which is similar to the "Clinical Monitoring Form" (CMF) used in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (Sachsetal.,2003). The diagnosis of the patients was confirmed both by using the Structured Clinical Interview for DSM-IV-AxisI (SCID-I) and by the SKIP-TURK procedure. The research study was approved by the local ethics committee and all the participants provided informed consent for the study. Control group consisted of 146 healthy subjects (73 male and 73 female, age range: 30 to 60) which themselves or first relatives do not suffer from bipolar disorder, schizophrenia, other psychotic diseases, attention deficit and hyperactivity disorder, mental retardation and autism. Simple randomized sampling method was used to select subjects belonging to the patients and control groups. Subjects younger than 30 years were excluded in the control group due to the fact that psychiatric disorder may not be manifest at the time of evaluation. Other exclusion criteria relevant for both groups were: presence of other psychiatric diseases and mental retardation, presence of burn or trauma wounds in the auricle, presence of collagenous diseases and systemic dermatological diseases, and being in active disease episode (mania or depression in the patients group).

In our study, we referred to the study of Hunter et al. which was published in American Journal of Genetics Part A, which defined the standart terminology for ear anomalies and also to human malformation terminology developed by the National Human Genome Research Institute (elementsofmorphology.nih.gov) and as suggested in the introduction, we evaluated 39 different anomalies of the auricle in our research. The evaluated minor anomalies were: Helix anomalies (crimped, squared superior portion, overfolded, underdeveloped, posterior pit, Darwin tubercle), crus helix anomalies (horizontal, expanded terminal portion, prominent, underdeveloped, connection to antihelix); anti-helix anomalies (anti-helical shelf, angulated, additional crus, prominent inferior crus, underdeveloped inferior crus, broad inferior crus, prominent superior crus, underdeveloped superior crus); antitragus anomalies (absent, underdeveloped, prominent size, bifid, everted); tragus anomalies (absent, underdeveloped, prominent size, bifid, everted); lobe anomalies (attached, cleft, anterior crease, large lobe); preauricular tag or pit; increased posterior angulation of ear; low-set ear; protruding auricle; asymmetrical ears. Before the study, 2 different researchers performed physical examinations on 40 volunteers in regard to MPA. For each different anomalies, Cohen's Kappa coefficients were calculated to determine inter-rater aggreement and all minor anomalies having Kappa coefficient values above 0.8 were included to the general analysis. Everted tragus, everted antitragus and cleft lobe were excluded from the general analysis because their Kappa coefficient values below 0.8. Eventually 36 different ear minor anomalies were examined.

2.2. Statistical methodology

Continuous variables were analyzed with Student's *t*-test. A $\chi 2$ test or Fisher's exact test was used to analyze the categorical data. The anomalies were grouped into 7 major categories (1-helix, 2-crus helix, 3- anti-helix, 4-tragus, 5- anti-tragus, 6-lobe, 7- others) and values of "0" or "1" were assigned according to the absence or presence of each minor anomaly existing either in the right or left auricle. Binary backward stepwise logistic regression analysis was performed in order to determine the specific ear abnormalities that most accurately discriminated bipolar disorder patients from control group. All the items with differences at $p < 0.05$ were entered for the regression analysis. All statistical analyses were performed using the SPSS version 20 and statistical significance was evaluated at the 0.05 level using 2-sided tests.

2.3. Findings

The patients mean age was 40.3 ± 9.02 and the controls mean age was 38.6 ± 7.37 ($t = 1.699$ $p = 0.09$). The patients mean duration of disease was 19.4±7.8 years; age at onset was 23.86±8.69 years. Any family history that included any diagnosis of mood disorders and/or psychotic disorders in the patient's first and/or second-degree relatives was positive in 56.2% (n=82) and history of episode with psychotic features was positive in 47.9% (n=70). We determined that the maximum number of auricular MPAs is 9 among patient and control groups. We assigned both the patients and controls into 4 groups according to the number of auricular MPA: i) 0, ii) 1–3, iii) 4–6 and iv) 7–9. The distribution of these groups in patients and control subjects is demonstrated on Table 1 and Fig. 2. Overall, we encountered that subjects having higher numbers of auricular MPAs accumulated in the patients group and the subjects with fewer or no MPA accumulated in the healthy controls ($p < 0.000001$ and $p < 0.000002$ for right and left auricles, respectively). Table 2 demonstrates the relative distributions of MPAs according to their localization. We evaluated 6 different MPAs of the helix and the ratios of the existence of any anomalies either in the right or left auricles were 63.7% and 49.7% in the patients and control groups, respectively ($p = 0{,}013$, $\chi 2 = 6{,}15$). We evaluated 5 different MPAs of the crus helix and the ratios of the existence of any anomalies either in the right or left auricles were 27.4% and 10.3% in the patients and control groups, respectively ($p = 0{,}00018$, $\chi 2 = 14$). We evaluated 8 different MPAs of the antihelix and the ratios of the existence of any anomalies either in the right or left auricles were 63% and 36.3% in the patients

Table 1
Total Number of MPA (right and left ear).

Ear		Right				Left			
		BPD	Control			BPD	Control		
		n(%)	*n*(%)	χ^2	*p*	*n*(%)	*n*(%)	χ^2	*p*
Total Number of MPA	0	3(2.1)	17(11.6)	46.23	**<0.0001**	5(3.4)	12(8.2)	29.33	**<0.0001**
	1-3	61(41.8)	97(66.4)			66(45.2)	97(66.4)		
	4-6	65(44.5)	32(21.9)			56(38.4)	36(24.7)		
	7-9	17(11.6)	0(0)			19(13)	1(0.7)		

and control groups, respectively ($p = 0{,}000005$, $\chi 2 = 20.84$). We evaluated 4 different MPAs of the tragus and the ratios of the existence of any anomalies either in the right or left auricles were 56.2% and 61% in the patients and control groups, respectively ($p = 0{,}406$, $\chi 2 = 0.69$). We evaluated 4 different MPAs of the antitragus and the ratios of the existence of any anomalies either in the right or left auricles were 51.4.% and 54.1% in the patients and control groups, respectively ($p = 0{,}639$, $\chi 2 = 0.22$). We evaluated 3 different MPAs of the ear lobes and the ratios of the existence of any anomalies either in the right or left ear lobes were 46.6% and 20.5% in the patients and control groups, respectively ($p = 0.000002$, $\chi 2 = 22.18$). Among the other evaluated MPAs including preauricular tags, preauricular pits, low seat ear, increased posterior angulation of the ear, asymmetrical ears and protruding ears, only the latest MPA exerted significant difference between patients and control groups, respectively (14.4.% and 6.8% for patients and control groups, respectively; $p = 0.037$, $\chi 2 = 4.37$). Table 3 demonstrates logistic regression analysis of MPAs in regard to their specific morphology, which exerted significant ($p < 0.05$) difference between patients and controls in the Chi-Square analysis (supplementary Table 1–7). In the logistic regression analysis, dependent variables 0 and 1 were assigned to controls and patients; and independent variables included sex and 13 types of MPAs including: overfolded helix, underdeveloped helix, prominent crus helix, antihelical shelf, prominent inferior crus of antihelix, prominent superior crus of antihelix, underdeveloped superior crus of antihelix, attached lobe, anterior crease lobe, large lobe, protruding ear, underdeveloped tragus, prominent tragus. Logistic regression analysis revealed 7 significant parameters which differed patients and controls including over folded helix, attached lobe, prominent inferior crus of antihelix, antihelical shelf, anterior crease lobe, protruding ears and prominent tragus. Lastly, Table 4 demonstrates sensitivity and specificity of the logistic regression analysis to discriminate patients and controls.

3. Discussion

3.1. Previous findings which demonstrated minor physical anomalies of the auricle in psychiatric disorders

There exist contradictions between studies on minor physical anomalies among adults and children with different neuropsychiatric disorders, which was – partly – attributed to the problems in employment of the Waldrop-scale for the detection of these signs. The Waldrop-Scale exerts insufficient internal consistency because of the heterogeneity of the anomalies in location, character and occurence in different prenatal development periods. The Waldrop-Scale includes only 18 minor physical anomalies [5] while more than 50 anomalies were defined in the pediatric literature [1]. An other major obstacle with the Waldrop-scale is that it does not differentiate between minor malformations and phenogenetic variants [1]. To overcome these limitations, several investigators have improved the scale. The pattern of

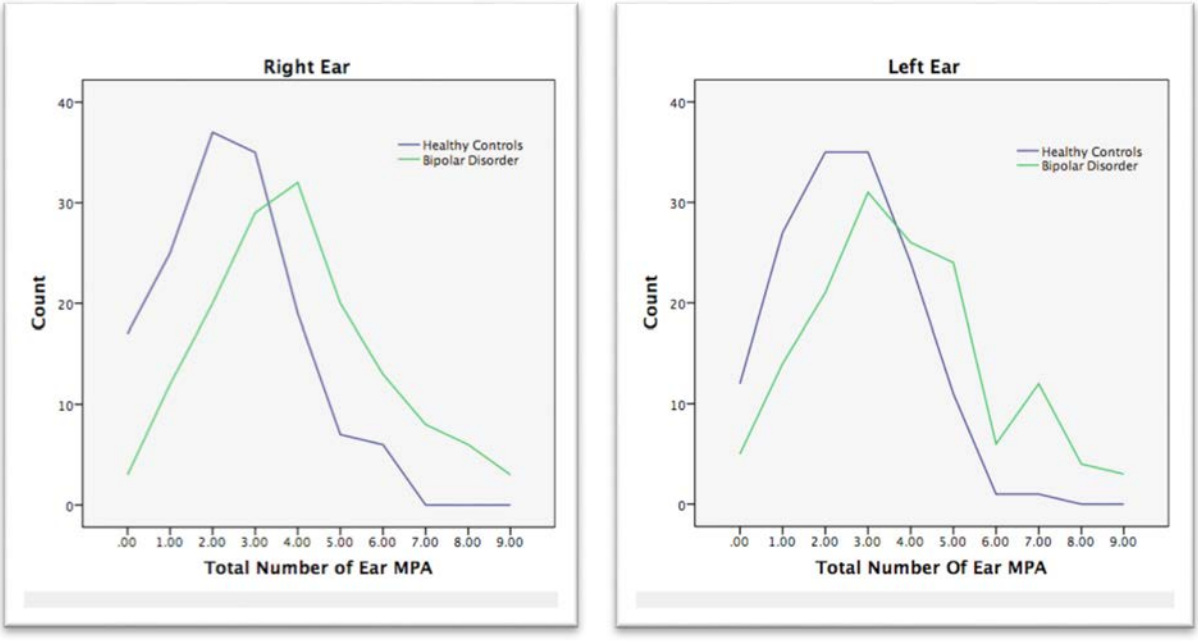

Fig. 2. Distributions of ear MPA in healthy subjects (blue line) versus patients with bipolar disorder (left line). The right and left ears are separately demonstrated.

Table 2
Regional types of MPA in healthy subjects versus patients with bipolar disorder.

Any MPA ın Rıght or Left Ear							
		BPD	Control				
		n(%)	*n*(%)	χ^2	*p*	OR	%95CI
Helix	Present	93(63.7)	72(49.3)				
	Absent	53(36.3)	74(50.7)	6.15	**<0.05**	**1.29**	**1.05-1.59**
Crus helix	Present	40(27.4)	15(10.3)				
	Absent	106(72.6)	131(89.7)	14	**<0.001**	**2.67**	**1.54-4.61**
Antihelix	Present	92(63)	53(36.3)				
	Absent	54(37)	93(63.7)	20.84	**<0.0001**	1.74	1.35-2.23
Tragus	Present	82(56.2)	89(61)				
	Absent	64(43.8)	57(39)	0.69	>0.05	0.92	0.76-1.19
Antıtragus	Present	75(51.4)	79(54.1)				
	Absent	71(48.6)	67(45.9)	0.22	>0.05	0.95	0.76-1.18
Lobe	Present	68(46.6)	30(20.5)				
	Absent	78(53.4)	116(79.5)	22.18	**<0.0001**	**2.27**	**1.58-3.26**
Protruding Ears	Present	21(14.4)	10(6.8)	4.37	**<0.05**	**2.1**	**1.03-4.3**
	Absent	125(85.6)	136(93.2)				

Table 3
Logistic regression analyses of specific types of MPA [Model x^2:88.22, df:9 ($p < 0.0001$), Cox & Snell R^2: 0.261, Nagelkerke R^2: 0.348, Hosmer–Lemeshow test: x^2:5.54, df:6 (*p*:0.476)].

In Right Or Left Ear	B(S.E)	OR (%95C·I)	p
Over Folded Helix	1.04(0.49)	2.82(1.07–7.42)	**<0.05**
Antihelical Shelf	1.05(0.38)	2.85(1.35–6.03)	**<0.01**
Prominent İnferior Crus Of Antihelix	1.54(0.39)	4.69(2.18–10.07)	**<0.0001**
Attached Lobe	1.26(0.33)	3.52(1.83–6.77)	**<0.001**
Anterior Crease Lobe	1.84(0.7)	6.29(1.59–24.92)	**<0.01**
Prominent Tragus	2.3(1.07)	9.94(1.23–80.61)	**<0.05**
Protruding Ears	0.95(0.47)	2.58(1.03–6.48)	**<0.05**
Constant	4.27(0.76)		

Table 4
Table of classification.

Actual group (*n*)	Predicted group membership	
	Healthy Controls	BPD
	n(%)	*n*(%)
Healthy Controls	115(78.8)	31(21.2)
BPD	43(31.5)	103(68.5)
Totals	218(73.6)	

external ear abnormalities in patients with schizophrenia and bipolar disorder was studied. Praharaj et al. analyzed 67 male patients having schizophrenia ($n = 30$) and bipolar disorder ($n = 37$) using a scale which they constructed [3]. Stepwise logistic regression analysis revealed that 'prominent crux of helix' and 'ear lobe crease' could differentiate between schizophrenia and bipolar disorder [3]. Berecz et al. evaluated 30 patients with bipolar I disorder and 30 patients with bipolar II disorder using a list of 57 minor physical anomalies collected by Méhes (1988) [1]. They determined that bipolar I group significantly differed from the control group in the total number of minor malformations and phenogenetic variants prominently in ear and the mouth regions [1]. The bipolar II group showed significantly different prevalences from the control group in the total number of minor malformations but not in the prevalence of phenogenetic variants and differences in minor malformations were again significant for the ear and mouth regions [1].

3.2. Overlap of genes which involve in auricle development and in psychiatric diseases or neurodevelopment. GWAS findings in regard to MRPS22

Relatively recently, Adhikari et al. published a genome-wide association study (GWAS) for non-pathological auricle morphology in over 5000 Latin Americans [6]. One of the determined single nucleotide polymorphism (SNP) is rs10212419 and the closest gene near to this SNP encodes mitochondrial ribosomal protein S22 (*MRPS22*), mutations of which can cause combined oxidative phosphorylation deficiency 5 (COXPD5), which phenotype can include low-set, posteriorly rotated ears (OMIM #611719) [6]. Another publication in regard to a patient with a similar ear phenotype found a non-synonymous substitution at a conserved site within *MRPS22* [6]. *MRPS22* gene involvement in psychiatric disorders are suggested by studies of Iwamoto et al. and Tobe et al. [7,8]. Iwamoto et al. conducted a large-scale DNA microarray analysis of postmortem brains of patients with bipolar disorder or schizophrenia, and determined expression patterns of mitochondria-related genes [7]. They observed a global decrease of mitochondrial genes, including those encoding respiratory chain components, in bipolar disorder and schizophrenia specimens. Nonetheless, this phenomenon appeared to occur due to the effects of medication, since medication-free patients with bipolar disorder showed tendency of increase of subset of mitochondrial genes. Very noteworthy, one of the upregulated genes is MRPS22 [7]. Tobe et al. utilized proteomic analysis of human-induced pluripotent stem cells (hiPSCs) obtained from lithium treated bipolar disorder patients and revealed that one of the proteins which associated with lithium response was MRPS22 [8].

MRPS22 gene encodes a mitochondrial ribosomal protein [9] and its mutation in humans was shown to cause several structural anomalies in brain, including agenesis of the corpus callosum, multiple periventricular cysts, and intracerebral calcifications [10]. Human brain with its high demand to oxygen constitutes 2% of the total body weight, while it receives 20% of cardiac output [11] and mostly depends on mitochondrial oxidative metabolism to cope with its high energy demands. Hence, it is not surprising that mutation of a gene encoding a mitochondrial protein causes cerebral anomalies and associates with psychiatric disease pathogenesis and drug responses. But why could a mitochondrial gene would associate with auricle morphology? The auricle highly contains cartilage tissue, which exerts very few vessels including chondrocytes with a very limited access to oxygen. Hence, defects in mitochondrial respiration may further damage the fragile energetic pathways of these cells and effect chondrocyte biogenesis and subsequently the morphology of the auricle.

An important gene which involves in auricular development and psychiatric disorders is *TFAP2A*. *TFAP2* gene mutations cause branchiooculofacial syndrome (https://ghr.nlm.nih.gov/condition/branchio-oculo-facial-syndrome). In this syndrome, the ears are also frequently affected, resulting in malformed or prominent ears. The *TFAP2A* gene encodes transcription factor AP-2 alpha (AP-2α) which regulates embryogenesis and is particularly active in the neural crest and in tissues derived from the first and second branchial arches. Brainstem levels of TFAP2A positively correlates to monoamine measures in rat forebrain [12] and chronic treatment with *N*-methyl-D-Aspartate (NMDA) increases TFAP2A levels in rat forebrain [13]. Excessive NMDA signaling is thought to contribute to bipolar disorder symptoms [13]. TFAP2 protein controls transcription of synapsins which are neuron-specific phosphoproteins regulating synaptic vesicle docking, synaptogenesis, and synaptic plasticity. Dopaminergic agents increase synapsin II protein in the striatum, medial prefrontal cortex, and nucleus accumbens and its transcription is blocked when *TFAP2A* gene is blocked with antisense deoxyoligonucleotides [14]. The TFAP2A protein is a repressor of CHRNA7 gene, which encodes the α7 nicotinic acetylcholine receptor (α7*nAChR), which is also implicated as a candidate gene in schizophrenia [15].

Mutations in Fibroblastic Growth Factor Receptors FGFR2, FGRF3 and FGRF10 cause Lacrimo-auriculo-dento-digital (LADD) Syndrome (https://ghr.nlm.nih.gov/condition/lacrimo-auriculo-dento-digital-syndrome). Fibroblast growth factors (FGFs) are glial growth factors; which control the patterning of specific brain structures and regulate the maintenance neuronal tissues [16]. A direct interaction also exists between FGFRs and adenosine A(2A) receptors, leading to corticostriatal plasticity and antagonizing the signaling pathway of dopamine D(2) receptors [16]. A SNP near FGFR2 is found to associate with bipolar disorder in a large scale case-control study in Chinese Han population, which included 1139 bipolar disorder, 1112 schizophrenia, 1119 major depressive disorder patients and 1135 healthy subject [17].

To the best of our knowledge, our study is the most detailed study conducted on the highest number of patients which assessed associations between auricular MPA and bipolar disorder. However, there still exist limitations in our study. We defined MPA as “absent” or “present”; yet there exist gray zones in regard to their existence. Nevertheless, this study may guide future studies with more precise 3D measurements and new phenotyping methods. We selected controls from subjects above 30 years of age in order not to overlook potential patients; hence, the education levels between the control and patient groups were also not matched. MPAs of the auricles are higher in psychiatric patients; yet there is also the possibility that subjects with higher IQ have distinct patterns of auricular morphogenesis. In future studies, matching groups according to their education and/or IQ levels may provide more sensitive results. Overall, study of MPAs in psychiatric disorders may provide new insights in understanding their complex pathogenesis. In future projects, combined evaluations of the morphology and single nucleotide polymorphisms may even lead to develop better classifications of the endophenotypes of psychiatric disorders.

Declaration of Competing Interest

None to declare.

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