Etiological Factors of Autism Spectrum Disorder

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ABSTRACT

People with autism spectrum disorder (ASD) have multifactorial etiology, combined by different factors, both genetic, psychological and environmental; however, it´s necessary sharply discriminate those significant factors or components, regarding elaborate an early action protocol for diagnostic processes and subsequent intervention guidelines, which co A total of 192 participants with ASD of three intensity levels (American Psychiatric Association -APA-, 2013) have collaborated in this study. ASD diagnostic shape the discrimination´ aim to 18 independent variables, considered, a priori, potentially influential over diagnostic intrinsic process.

Results of discriminant analysis include two axes it delimits the two main functions, represented by two variables: "karyotype" (Wilks´ Lambda statistic= .88) and "diagnosis" (Wilks´ Lambda statistic= .83). Both variables are complemented along structure matrix of discriminant analysis with variable "gene" for first function ("karyotype") and variable "age" to second function ("diagnosis" + "karyotype").

These allow defining the general characteristics to establish an effective action protocol for the specific diagnosis, which constitutes the general aim of this empirical research.

KEY WORDS: Autism spectrum disorder. Diagnosis. Genetic.

INTRODUCTION

People with autism spectrum disorders (ASD) present a particular shape of perceptual-cognitive processing that affects global development regarding criteria of interaction and social communication and over manifestation of restrictive and repetitive behaviors that cause specific needs in the scope personal and social at different levels or degrees of intensity of disorder, which are issued by International Classification of Disabilities (American Psychiatric Association –APA-, 2013). Therefore, the highly specificity of this disorder demand an intervention process rightly adjusted to processing way of perceiving, coding and recovering information along feedback between the incoming information (*input*) and consequent personal response action (*output*). This intervention is possible when there´s a specific clearly differential diagnosis that allows conclude with effective development program. In this sense, a specific diagnosis is essential process to assure an adapted vital development, hence it´s fundamental investigate the basic etiology of this disorder regarding delimit an action protocol to early specific diagnosis effectiveness that eases the corresponding specific action program.

Just to investigate this issue, Ojea (2018) performs a synthetic study that concludes the causes of this disorder are based over wide genetic and neurological basis. The support of these conclusions is founded on research that show, firstly, the disorder concurs with specific biological and neural conditions, related,

especially to psychiatric comorbidity processes (Freitag et al., 2008; Kohane et al., 2012; Levy et al., 2010; Rutherford & Troje, 2012) and, secondly, results found from clinical studies supported over specific genetic basis of ASD diagnosis, are characterized by disabilities founded in relationships and interneuronal synaptic fluency (Doshi-Velez, Ge & Kohane, 2014; Tuchman & Mamounas, 2013). Genetic analyzes are numerous and are supported over concurrence of mutations of different genes, among which the fragile X chromosome syndrome, whose relationship with the presence of ASD disorder is estimated around 30%, the tuberous sclerosis with a 1-4% prevalence within ASD disorder and highly correlation related with Rett syndrome (Acosta y Pearl, 2006). Also, Oviedo, Manuel- Apolinar, Chesnaye & Guerra- Araiza (2015) find a synopsis of interaction percentage between different syndromes of genetic etiology, among which, especially, the Prader-Willi syndrome (SPV), with 25.3% interaction percentage with criteria of ASD disorder, Angelman syndrome with 42%, Investment-Duplication syndrome (15q11-q13), of 2-4% interaction, the Fragile X syndrome with 25-33%, Permutation syndrome (SXF), with 10-60%, Deletion syndrome 2q37.3 with the presence of several reported cases and Mutation syndrome of the ARX gene. These studies are complemented by other research related to analysis of dysfunction over GABA way (Solís- Añez, Delgado- Luengo & Hernández, 2007), basically, concerning to gene-interval 15q11-q13, that codify the units β3, α5 y 3 of receptor $GABA_A$, which show highly correlations in monozygotic twins by 60%. Druand et al. (2006) conclude with strong association of this disorder regarding deficits over interneuronal synaptic processes, related to deletion or mutation of SHANK3 gene, which performs a fundamental role along development of synaptic functions affecting in way sensitive to performance of information cognitive processing. James, Shpyleva, Melnyk, Pavliv & Pogribny (2013) detect the presence of methyl CpG gene mutations, protein 2 (gen MeCp2).

Epidemiological studies also indicate evidence of multiple recurring genetic factors between 4-8% among brothers and sisters of children with ASD and the studies with twins, that report a prevalence of 60% concordance in monozygotic twins versus 0 in dizygotic twins, hence the wide phenotypic variety attributed to ASD diagnosis disorder is conclusive (Andres, 2002; Muhle, Trentacoste & Rapin, 2004; Veenstra-Van der Weele & Cook, 2004). Likewise, it´s estimated, at least, 10 genes highlight specially as explicative responsible to etiology of ASD diagnosis, which 7q31- q33 gene be specifically highlighted, with descriptions of duplicity on chromosome 15. Others genes of lower incidence are indicated, FOXP2 gene, Ray1/ ST7 gene, IMMP2L gene, RELN en 7q22- q33, GABA (A) and UBE3A genes, located on chromosome 15q11- q13, as well as, 5-HTT serotonin transporter gene variants en el cromosoma 17q11-q12 and interactions found at oxytocin receptor on chromosome 3p25-p26, that Bayés et al. (2014) extends to consistency of 2q, 3q, 16p y 17q chromosomes.

Calahorro (2011) shows the significant association of ASD disorder with the 5HTTLPR-S allele of SLC6A4 gene promoter, which gets a reduction over serotonin transporter expression. Also, investigate the patterns of single and double mutant behaviors by deletion in nrx-1 and nlg-1 genes, which codify neuronal adhesion proteins, which affects the synapse and found alterations along defecation cycle, mechanosesorial response, exploration capacity, movement speed and the response capacity to an osmotic shock.

Camacho (2013) realice studies about neurexina-1ß (NRXN1ß) gen and finds the identification of heterozygous variants not described, located in two regions of gene, one atbeginning of translation, other in protein juxtamembrane region.

In summary, there´s wide research based on multifunctional etiology studies, where genetic etiology is an essential component. Various authors (Gilissen et al. 2014; Helsmoortel et al. 2014; Deciphering Developmental Disorders 2015; Wright et al. 2015), conclude with basic presence of 217 candidate genes, among which 13 genes specially harmonized to X chromosome stand out: *ATRX*, *CUL4B*, *DMD*, *FMR1*, *HCFC1*, *IL1RAPL1*, *IQSEC2*, *KDM5C*, *MAOA*, *MECP2*, *SLC9A6*, *SLC16A2* y *PHF8* and 10 de novo mutations in 8 autosomal dominant genes: *DYRK1A*, *GRIN1*, *MED13L*, *TCF4*, *RAI1*, *SHANK3*, *SLC2A1* y *SYNGAP1*, as well as, the presence of 10 rich genes in variants with potential loss of functionality: *ADNP*, *DYRK1A*, *NRXN1*, *NRG3*, *SETBP1*, *ZMYND11*, *DNM3*, *CYFIP1*, *FOXP1* y *SCN2A.*

Upon, this research attempts corroborate of autism causes are supported this studies lines, based on multi-factoriality with specific dominance of genetic etiology.

METHOD

Research aims

This study aims: 1) define main components of autism spectrum disorder etiology, and 2) deduce, hence, an action protocol to facilitate specific diagnostic processes.

Design

This research is supported for experimental study, based over application of an ad hoc designed questionnaire. Questionnaire is formed set of questions with structured response alternatives designed online through the Drive application (see Annex 1). Likewise, the quality levels of this questionnaire has been previously supervised by statistical experts, whose recommendations have been included over final design.

Participants

A total of 192 participants have participated in this study. Samples correspond to educational (153 participants), clinical (27 participants) or social (12 participants) ambit, related to individual diagnostic analyzes of 192 people with ASD of 3 levels or degrees of intensitr, of which, 111 correspond to ASD level 1, 31 to ASD level 2 and 50 are ASD level 3. Likewise, 150 men and 42 women.

Variables

For this study analysis, the following variables have been operationalized. Firstly, variable related to group of levels (1-2-3) of ASD participants: "ASD", which constitutes the aim of explanatory-causal analysis of this diagnosis, which configures the dependent variable (DV); and, secondly, a set of factors or independent variables (IV) are described, that are hypothetically explanatory factors of the variance found along DV: "ASD", that involves the disorder diagnosis, whose names are following:

1. The age of diagnosed participants: “age”.
2. The age of diagnostic process was carried out: "diagnosis".
3. The sex of diagnosed participants: “sex”.
4. The place of origin of participants with ASD: “location”.

5. The center of diagnosis: "center".
6. The performance of genetic karyotype within diagnostic process: "karyotype".
7. The detection of gene/s type or combination of genes: "gene".
8.Other possible psychological, environmental, psychological, educational causes indicated through diagnostic process report: "multi".
9. Level of ancestry of "multis" causes (father-mother, brother, grandfather, uncle, cousin, others...): “Family-multi”.
10. The Indication of family history related to autistim disorders: "autism-type".
11. Level of ancestry of causes related to "autism-type": "family- autism".
12. The presence of family history related to disorders of organic type: “organic-type”.
13. Level of ancestry of organic causes: "Family-organic".
14. The family history concourse related to schizoid disorders: “schizoid-type”.
15. Level of ancestry of causes chizoid symptoms: "Family-schizoid".
16. The detection of family history related to depressive type alterations: “Family-type-depressive”.
17. The presence of family history related to anxiety, lability or others emotional factors: “anxiety-type”.
18. Level of ancestry of causes related to anxiety...: "Family-anxiety".

Processure

Once questionnaire has been constructed with, it was sent to educational services, to orientation departments of the educational centers, likewise, to clinical, social services and different associations and federations that labor with people with ASD within Autonomous Community of Galicia (Spain).

Data analysis

Corresponding responses were received, statistical analyzes resulting from sample were carried out according SPSS statistical package, whose fundamental test is configured by discriminant analysis, throughout stepwise selective method.

RESULTS

General analysis

From global viewpoint, observed in Table 1, critical *p* levels associated with the *F* of statistical *Wilk´s Lambda* test are significant for 4 study variables, which seem show highest level of specificity for explain discriminant functionality with respect to group formed by DV: "ASD". The 4 significant variables are: “diagnosis” (*Wilk´s Lambda*= .94, *F*= 6.01, *p*= .00), “karyotype” variable (*Wilk´s Lambda*= .88, *F*= 12.70, *p*= .00), “gene” variable (*Wilk´s Lambda*= .91, *F*= 8.98, *p*= .00) and “autism-type” variable (*Wilk´s Lambda*= .96, *F*= 3.31, *p*= .03). Within these four variables, higher level of initial specificity is observed in “karyotype” variable, hence, a priori, it´d be the variable best defines the discriminant function explaining of variability found in "ASD". Other study variables don´t show related significant level.

Table 1: Test de Wilk´s Lambda (N= 192).

	Wilks' Lambda	F	df1	df2	p
1. Age	.97	2.52	2	189	.08
2. Diagnosis	**.94**	**6,01**	**2**	**189**	**.00**
3. Sex	.98	1.14	2	189	.32
4. Location	.99	.70	2	189	.49
5. Center	.97	2.00	2	189	.13
6. Karyotype	**.88**	**12.70**	**2**	**189**	**.00**
7. Gene	**.91**	**8.98**	**2**	**189**	**.00**
8. Multi	.99	.98	2	189	.37
9. Family- multi	.99	.60	2	189	.54
10. Autism-type	**.96**	**3.31**	**2**	**189**	**.03**
11. Family-autism	.98	1.63	2	189	.19
12. Organic-type	.99	.92	2	189	.39
13. Family-organic	.97	1.98	2	189	.14
14. schizoid-type	.97	2.06	2	189	.13
15. Family- shizoid	.99	.24	2	189	.78
16. Family- type-depressive	.99	.26	2	189	.76
17. Anxiety-type	.99	.30	2	189	.73
18. Family-anxiety	.99	.27	2	189	.75

VD: TEA.

Discriminant analysis

In fact, to implement an analysis of specific discriminant functions, a discriminant analysis of step selection method is carried out. In Table 2 are observe that discriminant analysis select 2 steps, represented by 2 axes corresponding to: 1) the "karyotype" variable; and 2) it adds "diagnosis" variable (diagnosis age).

Table 2: Step discriminant analysis.

Step		Tolerance	F to Remove	Wilks' Lambda
1	Karyotype	1.00	12.70	
2	Karyotype +	.99	12.15	.94
	Diagnosis	.99	5.53	.88

Wilk´s Lambda values related two previous steps can be seen in Table 3. Both values aren´t very small, that´s, it aren´t next to zero level ("karyotype": *Wilks´Lambda* statistic= .88; and "diagnosis": *Wilks´Lambda* statistic = .83), which indicates that groups may be bit differentiated for discriminant analysis. However, *Wilks´Lambda p*-values and related exact *F* statistic indicate a right explicative capacity

for two variables collected by discriminant analysis: "karyotype": exact *F* statistic: 12.70, *Sig*= .00; and "diagnosis": Exact *F* statistic: 9.02, *Sig*= .00.

Table 3: Variables Entered- removed (a, b, c, d).

Steps	Variables	Wilks' Lambda							
		Statistic	Df1	Exact F				Df2	Df3
				Df2	Df3	Statistic	Df1		
1	Karyotype	.88	1	2	189.000	12.70	2	189,00	,00
2	Diagnosis	.83	2	2	189.000	9.02	4	376,00	,00

Explicative variance

Variables selected determine discriminant functions of analysis. First discriminant function (1), represented by "karyotype" variable, explains the higher of explanatory variance found over variability of "ASD" variable: variance = 80.5%, while secong function (2), corresponding to "diagnosis" variable explain the 19.5% of variance (see Table 4).

Also, it´s observed the 1 function indicate a canonical correlation = .36 (Chi-square = 34.55), which is almost double the canonical correlation of 2 function = .19 (Chi-square = 7.05). Therefore, 1 function ("karyotype") (development of previous genetic diagnosis study) are decisive to conform the main explanatory component of diagnosis variable "ASD".

Table 4: Eigenvalues.

Function	Eigenvalue	% of Variance	Cumulative %	Canonical Correlation	Chi-square	Wilks' Lambda	Sig.
1	.15(a)	80.5	80.5	.36	34.55	.83	.00
2	.03(a)	19.5	100.0	.19	7.05	.96	.00

Particular analysis of frequencies corresponding to both explanatory variables allows conclude that, in effect, with respect “karyotype” variable, it was realized on 112 occasions (58.3%), while was not on 80 reports (41.7%), constituting most important variable of this discriminant process. Accumulated “diagnosis” variable concludes that explanatory incidence of variability in “ASD” variable is greater when age range of diagnosis is lower, thus, over 0-5 age range it´s detected one or several genes of diagnostic processes reports in 23 situations; in 6-11 age range it´s detected 18 times; in 12-17 interval 8 times; in 18-25 interval years and more than 26 years were found in 0 reports. Moreover, developing of corresponding karyotype is more explanatory when age range is smaller, so in 0-5 age range it´s performed 61 times; in 6-11 interval 36 times; in 12-17 interval in 14; in interval of 18-25 years in 1 and in more 26 years was never not realized.

Structure matrix

La matriz de la estructura discriminante muestra que las dos variables "cariotipo" y "gen" tienen la mayor correlación con la primera función (1), representada por la variable "cariotipo": .90 y .28, seguido de otras variables con menores puntuaciones correlativas; mientras que la segunda función (2), representada por la variable "diagnosis": "cariotipo+diagnosis" está conformada por las variables "diagnosis" y "edad" con mayores correlaciones: .88 y .44, seguido de otras variables (ver Tabla 5).

Table 5: Structure matrix.

	Function	
	1	2
Karyotype	.90(*)	-.43
Gene(a)	.28(*)	-.12
Multi-type(a)	-.11(*)	-.08
Schizoid-type(a)	-.10(*)	-.07
Family-multi(a)	.10(*)	-.06
Family- autism(a)	-.08(*)	.00
Family-organic(a)	.04(*)	.00
Organic-type(a)	.02(*)	-.00
Diagnosis	.46	.88(*)
Age(a)	.24	.44(*)
Center(a)	.10	.17(*)
Sex(a)	-.06	.13(*)
Family-schizoid(a)	-.09	-.10(*)
Family-multi(a)	-.08	-.09(*)
Location(a)	-.06	.09(*)
Family-type-depressive(a)	.00	-.08(*)
Autism-type(a)	-.05	-.06(*)
Anxidety-type(a)	.00	-.04(*)

The variable "gene" is incorporated in structure matrix within 1 function: "karyotype". Indeed, this variable stand out by presence of following genes over diagnosis reports: 1) the 15q-11.2 gene (13 situations, 6.8%), 2) the q13 gene (3 times, 1.6%), 3) the fragile X gene (3 times, 1.6%), 4) gene/s combined (3 times, 1.6%), and 5) others genes: 45XY, P16, TCF3, ETV6 (27 times, 14.1%).

Also, the "age" variable correlates with high score with 2 function: "diagnosis" ("diagnosis" + "karyotype"), that conforms, then, an essential element of diagnostic process. In this sense, diagnosis process is more effective if earlier the diagnosis age.

Comparative analysis

Finally, centroids analysis conclude that clearly differentiated statistic means are observed for 1-2 functions, which allows delimit evident differences for the three ASD levels. Thereby, 1-2 functions are clearly differentiated to group ASD, thus, ASD1 level: 1 function= .32; 2 function= .05 in relation to ASD2:

1 function= -.20; 2 function= -.43 and, also, in relation to ASD3 variable level (1 function= -.58; 2 function= .15) (see Table 6).

Tabla 6: Canonical Discriminant Function Coefficients.

	Function	
	1	2
diagnosis	.52	1.08
karyotype	1.90	-.99
(constant)	-1.13	-.29

ASD	Function	
	1	2
ASD1	.32	.05
ASD2	-.20	-.43
ASD3	-.58	.15

CONCLUSIONS

Although, factors collected for discriminant analysis initially contribute to explaining the explanatory variance of the disorder diagnosis: "ASD", all variables accumulated along two axes selected by discriminant analysis contribute to forming the explicative components of VD variance: "ASD".

Thus, effectiveness of action protocol for ASD diagnosis and, therefore, the prognosis to effective and efficient intervention proposal is directly related, firstly, to the development of corresponding genetic karyotype and specification of possible existence of responsible genes: “gene” variable (see Table 5), which must carried out early possible, especially, if there´re high-risk family factors related to presence of significant symptomatic alterations, related with "type-autism" variable (see Table 1). Secondly, also, participants age when this diagnostic process is carried out: "diagnosis" constitutes basic axis of the 2 function of discriminant analysis, which allows deduce that effectiveness of this protocol correlates with the age at diagnostic process is carried out and, also, extent, also, with age of diagnosed people: “age” (see Table 5).

Likewise, early detection of diagnostic process makes possible establish the intervention measures more adjusted to particular perceptual-cognitive processes of people with ASD, who, in situations of absence of specific diagnosis and, mainly, of a misdiagnosis, may lead to measures of support or reinforcement contradictory with shape of information processing of people with ASD. Particular procedural functioning of coding and memory system of these people require a specific adaptation of differential socio-educational and clinical action method regarding others diagnoses, e.g., related to lexical difficulties, emotional disturbances, attention deficits and hyperactivity or other symptoms, which initially can be confused if there´s no clearly specific diagnosis of ASD disorder.

DISCUSSION

According this research results, the US Department of Health and Human Services, Interagency Autism Coordinating Committee; National Institute of Mental Health (NIMH) (DHHS/NIH), Office of Autism Research Coordination (OARC)- (2017) confirm, throughout different studies, that fundamental causes of ASD are genetic type, however, the presence of single genetic variations doesn´t seem sufficient to cause ASD disorder, therefore, posterior researchs refer to variations over gene/s and its modifications associated as responsables of ASD highest risk. Studies conclude that genetic variations can lead to alteration of DNA methylation, which constitutes a type of genetic modification that can change the gene expression without altering the DNA sequence. These variations, called methylation, can indirectly affect the expression of one or more highest risk genes regarding this disorder.

For this reason, the researchers scope that, along different studies, show empirical conclusions regarding karyotype analysis that provide clarification on specific etiology is essential.

Napoli et al. (2018), likewise, conduct a study with 133 children with ASD phenotype by means of comparative genomic hybridization analysis, whose results show that 12 children have variants of causal genetic copies number associated with the disorder susceptibility, 29 children had non-causal variants and 92 didn´t present. This data indicate the analysis documented that none participant was affected by Fragile X, 41 tested positive for genetic copy variations, 33 showed only 1 variation, 7 showed 2 and only one participant showed 3 or more; in one participant 50 desequilibrium were detected with 19 deletions and 31 duplications, hence for 26 desequilibrium was possible verify the parents inherited origin, 11 by maternal and 8 by paternal via, while 7 new emerged. Two duplications involved chromosomes 4 and 15, regarding 4p16.3p15.1 gene and 15q11.2q13.1 gene, which emerged new and were classified as pathogenic in 4%, ten showed 6 duplications and 4 deletions, were potentially causal and 38 presented 23 duplicacoines and 15 deletions, that were considered potential in 76%.

Rubenstein et al. (2019) replicate these studies through analysis of sample of 707 people with ASD and conclude the infant phenotype in autism is related to broader phenotypic forms derived from multiple developmental measures. In this investigation find that phenotype existing, at least, regarding one of their parents and seems associated with greater probability the child present a symptomatology related this disorder.

Demily et al. (2018) find that duplication of 22q11.2 gene is variant of penetrating copy number associated with a broad spectrum of clinical manifestations that include ASD and epilepsy and report over presence of pathogenic genetic mutations "HUWE1" and "KIF1A" in two ASD participants with duplication of the 22q11.2 gene, which leads conclude to recommend an urgent action protocol in families that carry this pathogenic mutation.

Artemios et al. (2019) associate the ASD clinical characteristics with presence of Myhre syndrome, which constitutes a connective tissue disorder with multisitemic involvement, which decisively influences over information transmission, requiring greater deepening this research pathway.

STUDY LIMITATIONS

Indeed, a greater depth is needed to investigate the relationship of responsibles genes of ASD diagnosis, as well as increasae the surveys number obtained, which was slightly lower to purposes of this study.

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ANNEX 1

ETIOLOGICAL STUDY OF AUTISTIC SPECTRUM DISORDER (ASD)

1. **DIAGNOSIS TYPE ***

( ) ASD 1
( ) ASD 2
( ) ASD 3
( ) Anothers:

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2. **CURRENT AGE OF DIAGNOSED PEOPLE ***

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3. **AGE WHEN DIAGNOSTIC PROCESS HAS BEEN CARRIED OUT SEXO DE LA PERSONA CON DIAGNÓSTICO DEL TEA ***

4. **SEX**

( ) MAN
( ) WOMAN

5. **LOCATION (indicate location):**

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6. **DIAGNOSTIC CENTER ***

( ) EDUCATIONAL SERVICE
( ) MEDICAL SERVICE
( ) SOCIAL SERVICE
( ) ASSOCIATION/ FEDERARATION SERVICE
( ) Another:

7. **WAS A GENETIC ANALYSIS REALIZED DURING THE DIAGNOSIS PROCESS: KARYOTYPE ANALYSIS?***

( ) YES
( ) NO
( ) Another:

- **IF AFFIRMATIVE, KARYOTYPE STUDY INDICATES THE PRESENCE OF GENE?**

( ) YES
( ) NO
( ) Another:

- **IF AFFIRMATIVE, WRITE NAME OF RESPONSIBLE GEN / GENES:**

- **OTHERS CONSIDERATIONS INDICATED IN KARYOTYPE ANALYSIS:**

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8. IN DIAGNOSTIC PROCESS, ARE VARIOUS CAUSES INDICATED?

( ) ENVIRONMENTAL CAUSES ( ) PSYCHOLOGICAL CAUSES ( ) EDUCATIONAL CAUSES
( ) OTHER CAUSES ( ) NO INDICATED

- **IF AFFIRMATIVE, WRITE BRIEFLY:**

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9. FAMILY BACKGROUND: PRESENCE OF AUTISTIC DISORDER:
( ) FATHER/ MATHER ( ) BROTHER ( ) GRANDFATHER/ GRANDMOTHER
( ) UNCLE/COUSIN ( ) OTHERS ( ) NO INDICATED

- **IF AFFIRMATIVE, INDICATE AUTISM TYPE:**

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10. FAMILY BACKGROUND: PRESENCE OF NEUROLOGICAL-ORGANIC DISORDER
( ) FATHER/ MATHER ( ) BROTHER ( ) GRANDFATHER/ GRANDMOTHER
( ) UNCLE/COUSIN ( ) OTHERS ( ) NO INDICATED

- **IF AFFIRMATIVE, INDICATE DISORDER TYPE:**

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11. FAMILY BACKGROUND: PRESENCE OF SCHIZOID DISORDER
( ) FATHER/ MATHER ( ) BROTHER ( ) GRANDFATHER/ GRANDMOTHER
( ) UNCLE/COUSIN ( )OTHERS ( )NO INDICATED

- **IF AFFIRMATIVE, INDICATE SCHIZOID TYPE:**

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12. FAMILY BACKGROUND: PRESENCE OF DEPRESSIVE TYPE:
( ) FATHER/ MATHER ( ) BROTHER ( ) GRANDFATHER/ GRANDMOTHER
( ) UNCLE/COUSIN ( ) OTHERS ( ) NO INDICATED

13. FAMILY BACKGROUND: PRESENCE OF ANXIETY- EMOTIONAL DISTURBANCE:

( ) FATHER/ MATHER ( ) BROTHER ( ) GRANDFATHER/ GRANDMOTHER
( ) UNCLE/COUSIN ( ) OTHERS ( ) NO INDICATED

- **IF AFFIRMATIVE, INDICATE EMOTIONAL DISTRUBANCE TYPE:**

*****Answer is obligatory.

THANK YOU FOR YOUR COOPERATION