UNIVERSIDAD MIGUEL HERNÁNDEZ

FACULTAD DE MEDICINA

TRABAJO FIN DE GRADO EN MEDICINA

PHARMACOGENETICS FOR PSYCHOTROPIC DRUGS AND A CROSS-SECTIONAL STUDY OF ADVERSE EVENTS IN AUTISM SPECTRUM DISORDER

AUTORA: DE MIGUEL LÓPEZ, LAURA

TUTORA: ANA MARÍA PEIRÓ PEIRÓ.

COTUTORA: PURA BALLESTER NAVARRO.

Departamento de Farmacología, Pediatría y Química Orgánica. Área de conocimiento: Farmacología.

Curso académico: 2022-2023

Convocatoria: Junio

AKNOWLEDGEMENTS

To my tutor, Ana, for letting me take part in an extraordinary journey.

To Mónica, Pura, Ana, Cecilia, Isidro, Enrique, Javier, Natalia, Irene; and especially to Laura Agulló for having patience and being a wonderful teacher. I have not only gained experience, but also friends.

To my parents and my sister, for making it possible (and coping with me). To Gill and Richard, for going through innumerable drafts without complaining.

To Natalia and Victor from St. Rafael, for being so collaborative and understanding.

And to all the patients involved in this project, for we must never forget they are in the purpose of everything we do.

"Do not be daunted by the enormity of the world and its problems. Do justly, now. Love mercy, now. You do not have to do something great. You are not obligated to complete the work, but neither are you free to abandon it".

Rabbi Tarfon

ABBREVIATIONS INDEX

ABCB1: adenosine triphosphate (ATP)-binding cassette (ABC) subfamily B member 1

AE: Adverse Event

ASD: Autism Spectrum Disorder

BMI: body max index

COMT: catechol-O-methyltransferase

CYP2D6: cytochrome P450 2D6

DSMV: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

EM: extensive metabolizer

HGUDrB: Hospital General Universitario Doctor Balmis

HTZ: heterozygous

IQ: Intelligence Quotient

MUT: mutant

PCR: Polymerase chain reaction

P-GP: P-glycoprotein

PGx: pharmacogenomics

PM: poor metabolizer

SD: standard deviation

SNP: Single nucleotide polymorphisms

UKU (Scale): Udvalg fur Kliniske Undersogelser Scale

UM: ultra-rapid metabolizer

UMH: *Universidad Miguel Hernández*

W/O: without

WT: wild type

yo: years old

INDEX

TABLES AND FIGURES INDEX

ABSTRACT

Introduction: Up to 73% of individuals with autism spectrum disorder (ASD) and intellectual disability (ID) currently have prescriptions for psychotropic drugs. This is explained by a higher prevalence of medical and psychiatric chronic comorbidities, which favors polypharmacy and increases the probability of appearance of adverse events (AE) that are a preventable cause of harm to patients and an unnecessary waste of healthcare resources.

Objective: To study the impact of pharmacogenetic markers on the appearance of AD in the population with ASD and ID.

Methods: This is a cross sectional, observational study (n=118) in ASD and ID population. Sociodemographic and pharmacological data was gathered. The UKU Scale was used to identify AEs secondary to the use of psychotropic medication. Finally, polymorphisms of *DOP2, ABCB1, COMT* and *CYP2D6* were genotyped, and correlated with the AE to find candidate genes.

Results: Most of the study population were men (75%) with multiple comorbidities and polypharmacy being the most frequently prescripted drug antipsychotics (69%) presenting nearly a third of the patients (21%) 4 or more AEs related to psychotropic drugs. The most common were “Neurological” and” Psychiatric” (both 41%). Statistical analysis results suggest a significant correlation between the neurological symptoms and *DOP2*, given that they are not equally distributed between the *DOP2* allelic variants. We found no other significant correlations.

Conclusion: A possible correlation between neurologic AE and polymorphisms of *DOP2* was observed that could contribute to the safety profile of this ASD and ID population´s prescriptions. Following studies are underway to maximise statistical power with a bigger sample size.

KEY WORDS: Autism Spectrum Disorder, Intellectual Disability, Pharmacogenetics, Adverse events, Polypharmacy, Dopaminergic System.

RESUMEN

Introducción: Hasta el 73% de los pacientes con Trastorno del Espectro Autista y Discapacidad intelectual tienen prescripciones activas para fármacos psicótropos. Esto se explica por la mayor prevalencia de comorbilidades crónicas, tanto médicas como psiquiátricas, que presenta esta población, favoreciendo la polifarmacia e incrementando la probabilidad de aparición de efectos adversos (EA) que son una causa prevenible de daño a los pacientes y un gasto de recursos sanitarios.

Objetivo: Estudiar el impacto de marcadores farmacogenéticos en la aparición de EA en población con TEA y DI.

Métodos: Se trata de un estudio transversal y observacional (n=118) en población con TEA e ID. Se recogió información farmacológica y sociodemográfica de los pacientes. La escala UKU fue utilizada para registrar eventos adversos secundarios al uso de medicamentos psicótropos. Finalmente, polimorfismos de *DOP2*, *ABCB1, COMT y CYP2D6* se genotiparon y correlacionaron con los EA.

Resultados: La mayor parte de los participantes (75% hombres) presentaron múltiples comorbilidades y polimedicación, siendo los fármacos más empleados los antipsicóticos (69%) presentando cerca de un tercio de los pacientes (21%), 4 o más EAs asociados a fármacos psicótropos. Los más comunes fueron neurológicos y psiquiátricos (41% ambos). Los análisis fueron significativos, y sugieren por tanto una correlación entre las diferentes variantes alélicas de *DOP2* y los EA Neurológicos. No encontramos otras asociaciones significativas.

Conclusión: Se observó una posible correlación entre EA neurológicos y polimorfismos *DOP2* que podría contribuir a comprometer la seguridad del perfil farmacológico de estos pacientes con TEA y DI. Se están realizando más estudios para maximizar el poder estadístico con un tamaño de muestra más grande.

PALABRAS CLAVE: Trastorno del Espectro Autista, Discapacidad Intelectual, Farmacogenética, Eventos Adversos, Polifarmacia, Sistema Dopaminérgico.

1- INTRODUCTION

ASD is a lifelong neurodevelopmental disorder that involves deficits in social interactions and repetitive/restricted behaviours. [1] The estimated global prevalence is 1-2%, varying widely among different countries and ethnicities. Numerous studies have reported an increasing tendency, that is expected to keep growing in the coming years, positioning this pathology as a focal point of public health. [2] ID is defined as a deficit in adaptive functioning. Both cause impairment in different areas and are often diagnosed during the developmental period. ID and ASD co-occur in up to 30% of the cases. [1, 3, 4]

These patients usually have prescriptions for psychotropic drugs, in the context of symptomatic treatment for irritability or behaviour disorders. [5] The concept of psychotropic drug refers to any substance capable of affecting the central nervous system and alter its functioning. Those prescriptions in this population increase with age and polypharmacy rates vary from 5 to 55%. [3,5] Both polimedication and the presence of several co-morbid conditions [6] are very common, which elevates the appearance of drug-drug interactions and AEs such as weight gain, motor disorders, hyperprolactinemia or similar. [7, 8]

Given the complexity of managing multiple drugs, increasing adherence to treatments and overall raising the quality of life of these patients; pharmacogenomics and pharmacogenetics are transpiring as a novel approach. [9]

Pharmacogenetic markers with potential clinical use

Pharmacogenetics intends to customize treatment according to the genetic profile of the patient. In the last decade, it has surfaced as an option for individualized medicine, having an effect in drug metabolism, efficacy and safety. [9] As to the candidate genes in this study, they are mostly related to the dopaminergic system. *DOP2* (that codifies for the dopamine receptor D2) is involved in the action mechanism of various psychotropic medications. [10] What´s more, *COMT* is an enzyme that

participates in the metabolism of dopamine (dopamine→COMT→3-Methoxytyramine) [11], and the phenotypes of *CYP2D6* (cytochrome of the P450 family) are involved in the metabolism of several drugs, as well as posing a risk for drug-drug interactions. [12] On the other side, *ABCB1*, also known as the multidrug resistance protein 1, codifies for P glycoprotein, which acts as one of the main transporters for these medications to the brain. [13] All of them can be seen at ***Figure 1***.

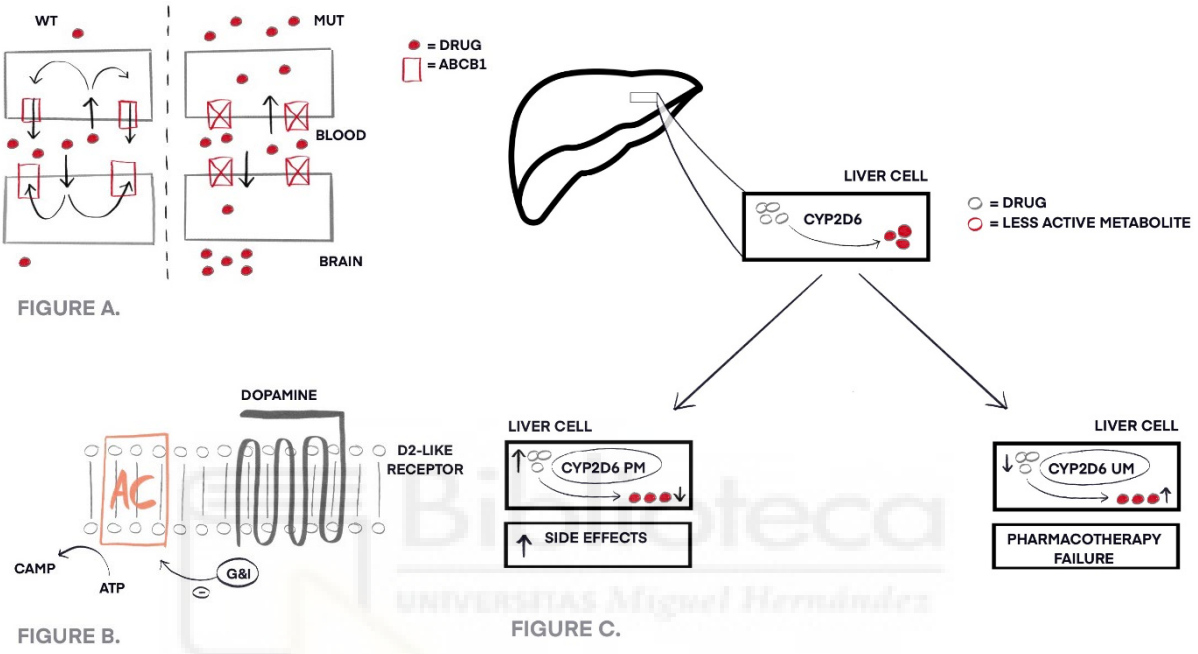


Figure 1. A) Function of ABCB1 both WT and MUT regarding drug transportation in the brain. B) Structure of D2-like dopamine receptor. C) CYP2D6 PM and UM intervention in drug metabolism with less active metabolites. WT:wild type. MUT: mutant. PM: poor metabolizer. UM: ultra-rapid metabolizer.

Given the distressing rates of comorbidity and polimedication in ASD and ID, not always resulting in effective treatments and often associating relevant AEs; more studies that aim to identify outcome and adverse events (AEs) deciding genetic variables are warranted, and could eventually transform into reliable methods for treatment selection. Here, pharmacogenetic markers could help to prevent AEs in vulnerable population.

This could improve drug tolerability pattern and cost to the Health System as seen at ***Figure 2***.

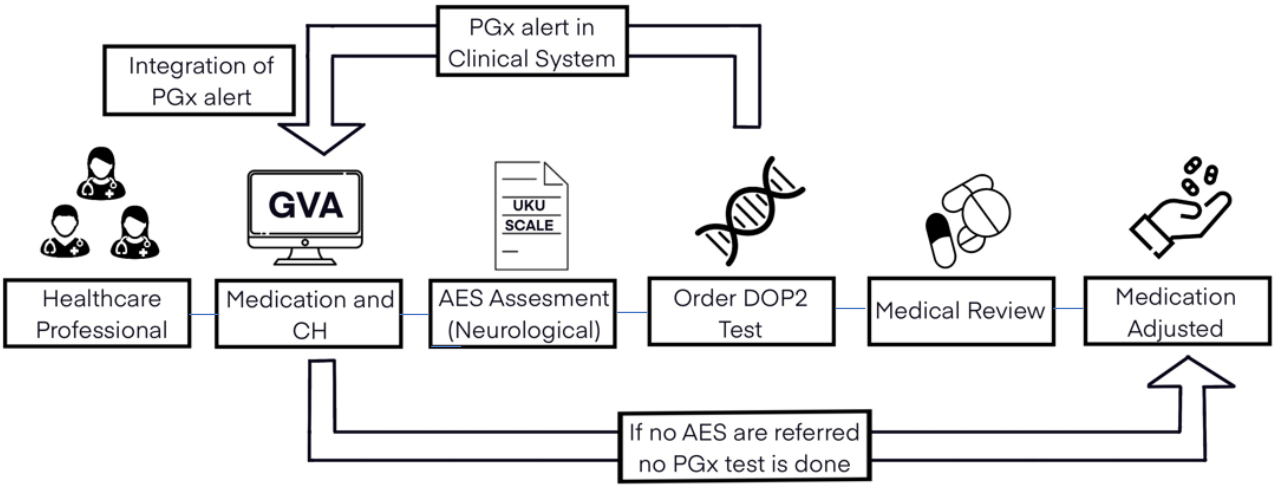


Figure 2. Theoretical implementation in clinical practice at Generalitat Valenciana (GVA) from Pharmacogenetic (PGx) Platform to using validated test as UKU scale in order to detect and prevent Adverse Events (AEs) [own creation figure].

Briefly, the implementation of pharmacogenetic interventions could have the potential to significantly improve the clinical outcomes in severe comorbid ASD populations with drug treatment resistance and poor prognosis.

2- HYPHOTESIS & OBJECTIVE

2.1. Hypothesis:

There is a wide interindividual variability in treatment outcome and safety when it comes to psychotropic medication. This can be explained by polypharmacy and drug-drug interactions, comorbidities and underlying illnesses, and pharmacogenetics. Certain genetic variants of genes involved in the pharmacokinetics and pharmacodynamics of psychotropic drugs could affect the safety of pharmacological profiles and predict the appearance of AEs.

2.2. Objective:

Main objective:

To study the impact of pharmacogenetic markers on the appearance of AEs in the population with ASD and ID.

Secondary objectives:

1. Describe the population characteristics and pharmacological profile.
2. Identify and register AEs in this ASD and ID population.
3. Define the impact of pharmacogenetics in AEs occurrence.

3- MATERIALS & METHODS

3.1- STUDY DESIGN

This is a cross sectional, observational study both descriptive and analytic in San Rafael Center (Santa Faz, Alicante) and Infanta Leonor Center. The study is divided according to two main objectives: to describe the characteristics of the study population, and to analyze a small sample of the group statistically in order to correlate the data. This is shown in ***Figure 3***.

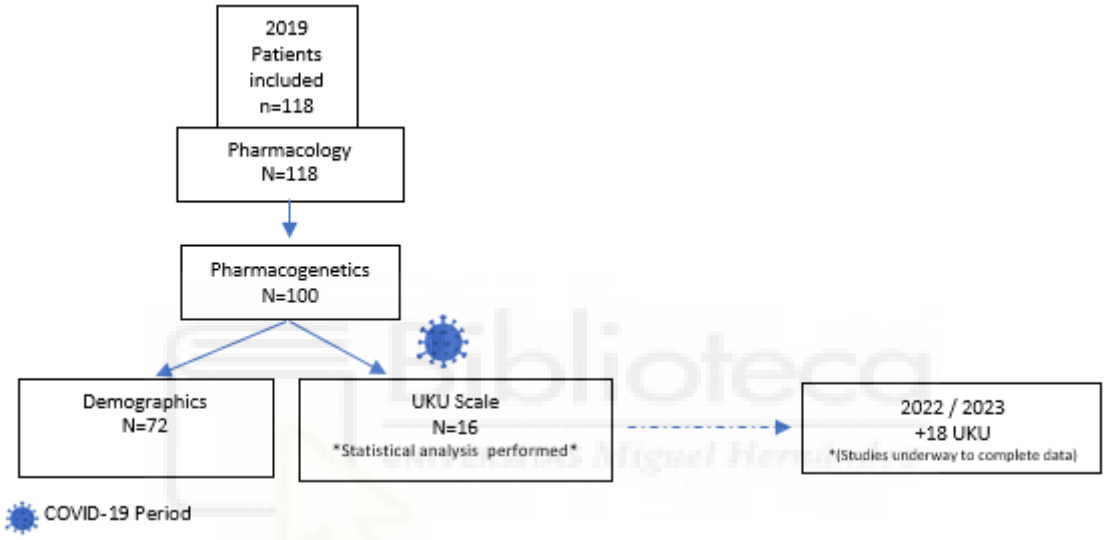


Figure 3. Flow diagram of the study design and population inclusion.

3.2- PARTICIPANTS

The subjects come from residential facilities located in Spain, and were selected following these criteria:

The inclusion criteria were:

-18 years old or above.

- Have a diagnosis of ASD as established by the DSM-5.

- Have a diagnosis of an intellectual disability (IQ <70 score).

- The patient/legal representative received, understood and signed the consent form.

The following exclusion criteria were applied:

- Patients with a medical condition or development of their pathology that made it difficult to participate.

- All participants could withdraw at any time.

To select the patients used for subsequent statistical analysis, they had to meet one additional criteria: have availability of all the data, that is, pharmacological, genetical, demographic and AE scale. A total of 16 patients were eligible candidates when these criteria were applied.

3.3- VARIABLES

(A) Sociodemographic and pharmacology data

Demographic data including age, sex, cardiovascular risk factors, medical comorbidities and toxic habits was obtained during routine clinical visits.

Information regarding the pharmacological treatment and active prescriptions of the patients between November 2019 and April 2020 were collected using the program "Abucasis"; this data was gathered coinciding with the moment where the UKU Scale **(ANNEX I)** was filled. Drugs were classified according to the main indication available in each technical data sheet. For this study, we considered antipsychotics, anxiolytics, antidepressants and anticonvulsants.

(B) Adverse events

The difficulties in communication and the introspection characteristic to these patients should be taking into consideration. Tveter, Bakken et al. [15] proposed an adjustment of this scale that classified the symptoms regarding observability and difficulty to score by the nurses and experts. Therefore, to evaluate the presence of AE, an adaptation to the UKU Scale for patients with intellectual disability was used.

This scale constitutes a measurement of the secondary events both physical and psychic that the intake of psychotropics drugs can produce. There are no cut-off points to this scale; the higher the mark, the more severe the AEs are. The modified scale focused on "The single symptom rating scale", covering four different areas: psychic, neurological, autonomic and other side effects. [(14)]

Each of the items were scored as follows: 0: not present, 1: very occasionally present, 2: present in a mild degree, 3: present twice a week, 4: present 4 times a week, 5: present every day, 99: not appropriate or relevant.

(C) Pharmacogenetics Variable

The analysis of the polymorphisms of dopaminergic receptor genes was performed, including *DOP, COMT, ABCB 1.1, ABCB1.2* and *CYP2D6* from samples donated to Biobank **(ANNEX IV).** The Kit for DNA extraction of blood samples was used, and the samples were analysed through TaqMan1, using a real-time PCR system (Thermo Fisher Scientific Inc). The phenotype of *CYP2D6* was calculated, obtaining three kinds of metabolizers: poor (PM), extensive (EM) or ultra-rapid (UM).

All was done at research group "Neuropharmacology applied to pain and functional diversity" Institute of Sanitary and Biomedical Research of Alicante (ISABIAL) located near Doctor Balmis General University Hospital (HGUDrB). This allows the clinical and biomolecular research, directing the Pharmacogenetics Platform. All the samples were donated to the Biobank who did support in genotyping.

3.4- STATISTICAL ANALYSIS

The optimal sample size has not been calculated due to the lack of accessibility to a larger number of patients; taking into consideration the features of the studied pathology.

The symptomatology scale (psychiatric, neurological, autonomic, or similar) has been categorized as a dichotomous variable (presents symptoms yes/no) for each symptomatic group. Each genes allele has been categorized as a qualitative variable of 3 categories (the heterozygous variable and two homozygous variables for the given allele). This gives us a resulting statistical analysis when combining each dichotomous variable of the symptomatic groups with qualitative variables (3 categories) of allele variants.

To prove if there are significant differences in a binary variable between more than 3 independent groups, it is common to use the Chi Square test, however in our model there is only n<30 subjects obtaining expected values lower than 5; therefore the Chi Square test is not viable (statistical significance could not be achieved complying with both conditions).

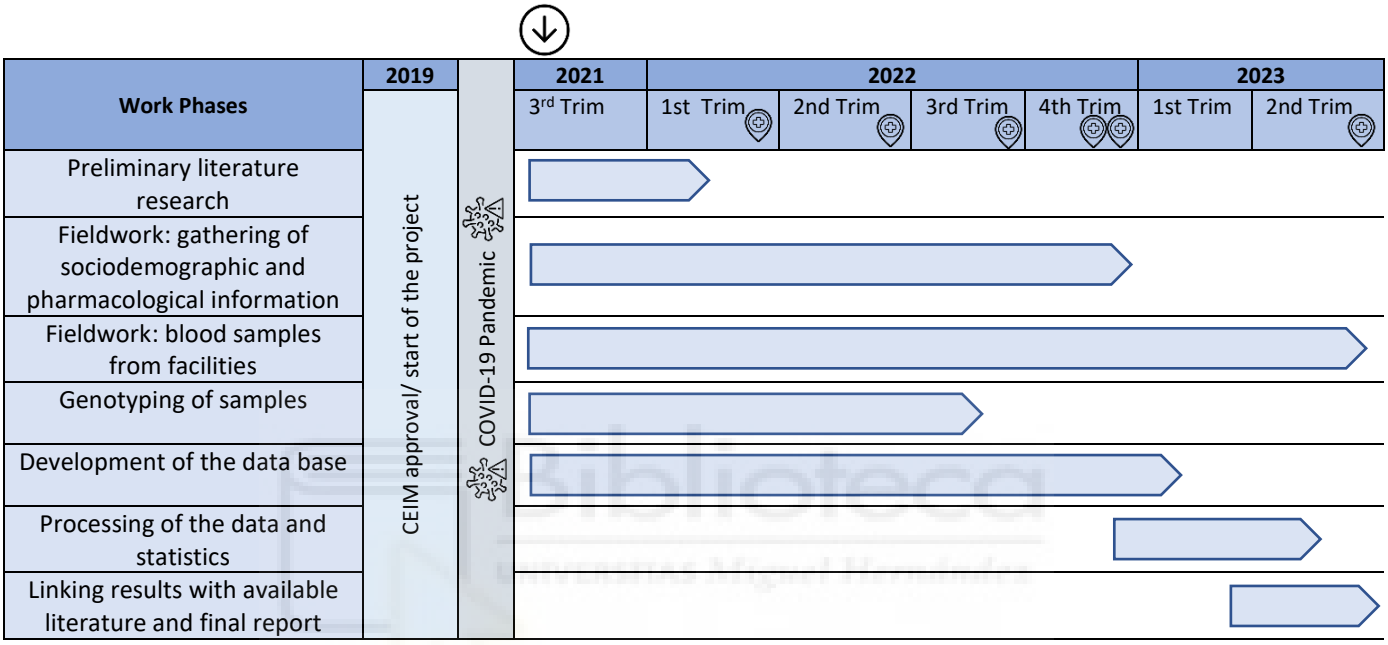
Given the above, the Freeman Halton extension of the Fishers Exact Test has been used to calculate the probability (two-tailed) to obtain a value distribution in a contingency table, given the observations on each cell.

This results in a series of statistical analysis (4 symptomatic groups yes/no) x 5 genes *(DOP2, ABCB1.1, ABCB1.2, COMT, CYP2D6)* =20 hypothesis contrasts with their associated p values which are presented as shown in the Table 5.

Finally, we used the software “R” to calculate a binary logistic regression model considering as dependent variable Neurological AEs (considered as a dichotomous variable), and as independent variables *DOP2* (TT) and pharmacological data.

3.5- CRONOGRAM

The following cronogram show all the activities developed in this project from 2021 until now. From literature research to the statistical analysis, Mrs. Laura de Miguel participated in all steps actively collaborating in the ISABIAL research group and personally going to the health care center for the study population inclusion, as shown in ***Figure 4***.



: *Visit to S.Rafael Centre*

: *First encounter and incorporation to the project (Oct)*

Figure 4. Cronogram of the activities carried out by the author of the present Final Degree Project.

3.6- ETHICS APPROVAL AND CONSENT

The Protocol has been approved by the Ethics Committee of HGUDrB **(ANNEX II)** and due the Responsible Investigation Office of the UMH **(ANNEX III)**; and it has been carried out following the current legislation. All patients and/or legal representatives signed the consent form. Laura de Miguel was incorporated as active collaborator researcher.

4- RESULTS

4.1. Demographic and Pharmacology data

Table 1. Demographic and pharmacology data (n = 72)		*N (%)*
Sex	Man	**54(75%)**
	Woman	18(25%)
Age average/standard dev		39,1 /±13,2
CVRF	Dyslipidemia	**15(21%)**
	Obesity	14(19%)
	Diabetes	4(5%)
	Hyperthension	4(5%)
Comorbidity	Without	4(5%)
	1	8(11%)
	2	9(12%)
	3	16(22%)
	4	14(19%)
	5 or more	**21(29%)**
Drug group	Antipsychotics	**81(69%)**
	Antidepressant	19(14%)
	Anticonvulsants	41(31%)
	Anxiolytics	19(9%)
	Without	15(13%)
Number of drugs	1 drug presc.	22(19%)
	2 drug presc.	**27(23%)**
	3 drug presc.	25(21%)
	4 drug presc.	13(11%)
	5 or more	16(14%)

Patients´ demographics are presented in ***Table 1.*** The majority of the study population were men, representing a 75% of the total (54 patients). Among the cardiovascular risk factors (CVRF), the most common was dyslipidaemia (21%). None of the patients referred toxic habits (including smoking, alcohol consumption and other drugs). Regarding their comorbidities, the most frequent was presenting five or more additional comorbidities, with a 29% representation over the total.

The most prescribed drugs were antipsychotics with a 69%, specifically risperidone (24%) being the most prescribed among them. The most frequently used anticonvulsant was valproic acid (15%); antidepressant was fluvoxamine (8%) and finally clonazepam stands out between the anxiolytics (12%).

4.2. Adverse events number

The most reiterated was the absence of AE (29%), followed by the occurrence of 4 or more AE (21%) as shown in ***Table 2***.

Table 2. Number of Adverse Events (AE,n= 34) from the UKU scale results.		*N (%)*
Number of AE´s	Without AE	10(29%)
	1 AE	6(18%)
	2 AE	6(18%)
	3 AE	5(15%)
	4 or more	7(21%)
Number of AE by AE group	Psychiatric	14(41%)
	Neurological	14(41%)
	Autonomic	12(35%)
	Other	12(35%)

The most usual were the Neurological AE, especially the epileptic seizures (41% of them) and the Psychiatric AE, being the most common of them the appearance of tension/restlessness with a 48% of the cases. Regarding the Autonomic AE, constipation stands out with a 55% of the cases.

4.3. Pharmacogenetics data

Most of the study population was heterozygous for the *DOP2* gene (39%) as well as for the *ABCB 1.2* (42%). On the other hand, the majority of the subjects were classified as Wild Type for the *ABCB 1.1* gene (79%). As for the results for *COMT,* the most common was mutant with a 25% over the total. Finally, 65% of the total presented an Extensive metabolizer classification in the *CYP2D6* Activity Score. All can be seen at ***Table 3***.

As explained previously, once the descriptive of our data was completed, we selected a subgroup of the population. The data analysis performed in those 16 subjects is presented below. To see more details, please see **ANNEX V and VI.**

Table 3. Descriptive of the population´s genotyping results (n= 100).

DOP2 rs6277	WT(CC)	37	37%
	MUT (TT)	16	16%
	HTZ (CT)	39	39%
	W/O data	8	8%
Alleles	C	113	143%
	T	71	39%
COMT rs4680	WT(GG)	21	21%
	MUT (AA)	25	25%
	HTZ (GA)	5	5%
	W/O data	49	49%
Alleles	G	47	46%
	A	55	54%
ABCB1.1 rs2032582	WT(GG)	79	79%
	MUT(TT)	0	0%
	HTZ(GT)	2	2%
	W/O data	19	19%
Alleles	G	160	99%
	T	2	1%
ABCB1.2 rs1045642	WT(CC)	20	20%
	MUT(TT)	20	20%
	HTZ(CT)	42	42%
	W/O data	18	18%
Alleles	C	82	50%
	T	82	50%
CYP2D6	PM	5	5%
	EM	71	65%
	UM	4	4%
	W/o data	20	26%

When correlating the sociodemographic information with the registered AE, we found that the people that were being administrated between 1 and 3 drugs simultaneously showed more AE. Even so, none of the related facts showed a significative statistical difference. The correlated data is shown in **ANNEX VI.** We also established the relation between the genotype and the registered AEs, and did the statistical analysis as described previously. The results (p values) are presented in ***Table 4.***

*Table 4. P-values obtained when correlating genotype and AEs expanding DOP*2 information*

p-vaue	**DOP*2**	**COMT**	**ABCB1.1**	**ABCB1.2**	**CYP2D6**
Psyquiatric AE	1	0,3	1	0,4	1
Neurological AE	0,01	0,06	1	0,8	1
Autonomic AE	0,3	0,3	1	1	1
Other AE	0,8	0,3	1	0,8	1

Alleles of DOP*2 (p-value)			
	CT	**TT**	**CC**
Neurological AE	1,00	0,02	0,04

The probability of finding the given results in this study, assuming that the null hypothesis is true (that is, the psychiatric symptoms are equally distributed between the 3 different alleles of the *DOP2, ABCB1.1, ABCB1.2, COMT AND CYP2D6* genes in our sample) it's presented in the table. Given that p is >0, 05 in all those cases, we found no statistical significance for these associations and therefore we assume that these results could be explained by chance (random error).

The same occurs when interpreting the results obtained for Neurological, Autonomic and Other AEs in all the analysed genes, with the exception of *DOP2* when correlated to Neurological AEs, as explained hereafter. Given that p<=0, 05 (5% possibilities of Ho being true in our sample), the relation between neurological symptoms and *DOP2* alleles is statistically significant, that is, the neurological symptoms are not equally distributed between the *DOP2* alleles, which will require further analysis to establish

where exactly these differences are found (in which allele, the higher probability of presenting a Neurological symptom).

Finally, ***Table 5*** displays the result of the binary logistic regression model where no significant correlations were found between the studied variables.

Table 5. Binary regression model. Neurological AEs: dependent variable. DOP2, prescriptions and medication group as independent variables (n=16).

		Estimate	**P-value**
Neurological AEs (dependent variable)	*DOP2* (MUT)	-19.48758	1
	≥ 3 Coprescriptions	1.83638	0,8
	Anticonvulsant	0.31493	0,2
	DOP2 (MUT)	-38.222	1
	≥3 Coprescriptions	2.079	0,2
	Antipsychotic	-20.181	1
	DOP2 (MUT)	-1.926	1
	≥3 Coprescriptions	9.163	0,5
	Antidepressive	1.369	1
	DOP2 (MUT)	-1.957	1
	≥3 Coprescriptions	1.099	0,5
	Ansiolytic	1.910	1

5- DISCUSSION

The majority of the ASD and ID population presented multiple comorbidities and polypharmacy mostly due to antipsychotics. Nearly a third of the patients showed 4 or more AEs related to psychotropic drugs where *DOP2* allelic variants could influence on Neurologic AEs. A pharmacoeconomic study could be carried out from the perspective of the National Health System to assess the clinical translation of an anticipate dopaminergic genotyping in this vulnerable population.

We should consider that literature concerning general health conditions of adults with ASD are scarce. In this study, the mean age was 39 yo, being higher than most published studies with a predominantly masculine population, in a similar way of prior data. ASD is more prevalent in males than females. Previous research indicates females camouflage ASD symptoms more than males, potentially contributing to the difference in prevalence. [6, 11, 16] This should be carefully analysed through a sex and gender perspective analysis.

Though the study population resided in facilities and therefore no substance abuse was reported, it has been stated that the risk of tobacco/alcohol/drug abuse is lower in ASD adults. Croen et al. found a significant increase in the prevalence of notable chronic conditions in ASD subjects compared with controls, being comorbidity the general rule. The number of comorbidities was consistent with our results, nonetheless the order of importance amongst cardiovascular risk factors differed, being dyslipidaemia the most common in comparison with other studies that positioned obesity and hypertension as the primary factors. [6, 16]

Regarding the pharmacological profile of our population, we found consistent results with other studies, where the most commonly prescribed medication were antipsychotics, standing out between them risperidone. Nevertheless, those studies reported the use of 3 or more drugs simultaneously in approximately 10% of the patients, whereas in our project the amount of patients in this situation rose up to 46%. [2, 17]

Adverse events and Pharmacogenetic data

The AE results of this analysis are along the lines of prior cases such as those of Puagnpecht et al., were they established neurological AEs as the most common, though in the present analysis they are matched by psychiatric AEs. However, they stated that the most usual amongst them was tremor instead of seizures. Between the psychiatric AEs, somnolence was the most frequent whereas for us it was restlessness. [8] In respect to the results of CYP2D6 genotyping, the proportion of PM, EM and UM was similar to other studies. [17] When analysing these phenotypes and the AE we found no significant relation, as opposed to previous studies. Correia et al. reported higher weight gain when comparing EM with UM subjects, with a 4,8% lower BMI in the latter. [18]

In respect to other AE, there are several studies in prolactin elevation related to prescription of psychotropic drugs (which effects we have included under "Other AE"). Sukasem et al. did not find significant differences in prolactin levels when comparing *CYP2D6* genotypes, which supports our results. However, Roke et al. concluded that ultra-rapid metabolizers had lower serum prolactin levels than the other fenotypes; and Ngamsamut et al. inferred that patients with poor *CYP2D6* activity had greater levels of risperidone rather than 9 hydoxirisperidone, and therefore higher prolactin levels, translating those levels into the previously appointed AEs. [17]

Neurological AEs (such as hypokinesia, akathisia or other movement disorders) have not been significantly correlated with *CYP2D6* phenotypes in most studies, which is consistent with our results. Cabaleiro et al., Dodgen et al., Bozina et al. and Novalbos et al. reported no association, though the studies were conducted in healthy volunteers or risperidone-taking patients with a different diagnosis than ASD. A single study by De Leon et al. showed significant results when correlating neurological and extrapyramidal AE, though the results must be carefully interpreted due to the reduced sample size. Altogether, having a decrease activity of this enzyme is related to elevated plasma levels of some psychotropic drugs, higher incidence of side effects as weight gain or hyperprolactinemia, and may result in discontinuation of treatment. [8]

The genotype frequencies of *ABCB1* were similar to previous studies located in Spain [13]. T allele of *ABCB1.2* has been associated with a lower expression of P-gp (present in the blood brain barrier), resulting in higher concentrations of medications that constitute a substrate to this protein, as several antidepressants and antipsychotics. These increased drug levels in plasma, and expecially in the brain surpassing the recommended range could be associated with more side effects. However, other studies have failed to establish a clear association. Mutant (TT) polymorphism patients showed more insomnia and fatigue than C allele carriers, as reported by Lin et al.; though these results have not been replicated. [19] The wild type and heterozygous variants of *ABCB1.1* has been associated with higher antidepressant plasma levels, though they did not reach a significant result in appearance of AE or treatment response. [20] These results match our own, having found no significant associations between *ABCB1* genotypes and AE, taking into consideration that we found no studies with a similar population whose aim was to correlate these two variables.

When analysing the *COMT* gene, we found that 25% of our population was mutant (AA), as opposed to previous studies, at the expense of heterozygous subjects. [11, 21] *COMT* has been associated with elevated proportions of tension/restlessness, anxiety and depression in individuals not diagnosed with ASD. However, this was not supported when performing studies in ASD polimedicated patients, which is consistent with our result, having found no significant correlation between psychiatric symptoms and *COMT* polymorphisms. [22] Esmaiel et al. reported the mutant variant of *COMT* being associated with increased levels of dopamine and abnormalities in EEG, suggesting a significantly elevated prevalence of epilepsy as well as a decreased seizure threshold which could result in more motor and neurological AE. However, more analysis are needed; and these results are not coherent with our own.

Finally, in respect to *DOP2,* there are very few studies despite it being a crucial candidate gene. [23] It has been associated with motor disorders and pathophysiology of ASD; but to this date there aren´t studies aiming to correlate AE with allelic variants, except two studies with inconclusive results on hyperprolactinemia when treated with risperidone. [3, 23, 10] To the present day, we have not found studies correlating autonomic AEs with patient´s genotype. [17]

6- LIMITATIONS AND FUTURE RESEARCH

6.1- LIMITATIONS

The main limitations were the sample size of the statistically analysed group that translated into lower statistical power. Also, the difficulties of separating symptoms due to the underlying illness to those caused by medications; as well as identifying some of the items of the UKU Scale that were categorized as "not easily observable" by the healthcare professionals.

Concerning the application of a pharmacogenetics testing approach to daily clinical practice, several studies have assessed the acceptability and feasibility of this practice. [24, 25, 12] The identification of genetic variants of enzymes, receptors and transporters may provide useful information for dosage and duration of treatment; as well as predictions on therapy outcomes and side effects. Currently, specific factors or AE are being targeted to estimate relevance of certain genes, though in the future we can expect the development of panels addressing general characteristics, faster screening methods and protocols for applying these findings. [25, 26, 27]

6.2- FUTURE RESEARCH

The ISABIAL Pharmacogenetics Platform applied to Research was created through prior investigation projects also concerning pharmacogenomics of ASD and ID population, and is currently offering support to projects working with genetic markers associated with medications; such as the testing of PGx in chronic pain in ASD population or the continuation of this project itself. The creation of platforms such as this one provides infrastructure and resources in the process of implementing this practice. To sum up, the study of pharmacogenetics in ASD and ID population is booming, emerging as an innovative perspective for personalized medicine. A pharmacoeconomic study could be carried out from the perspective of the National Health System to assess the clinical translation of an anticipate dopaminergic genotyping. *Upon next conclusion, we intend to send it to Autism (IF: 6.68), for publishing consideration.*

7- CONCLUSIONS

1. The majority of the study population were men with multiple comorbidities, amongst which the most prevalent was dyslipidaemia. Most of them took 2 or 3 medications simultaneously, and the most frequently prescribed were antipsychotics. These findings are supported by previous studies with similar results and should analysed through a sex/gender perspective.

2. The highest percentage of a third of the subjects had no AE but near a quarter presented 4 or more, mostly related to Neurological and Psychiatric areas, specifically epileptic seizures and restlessness. This different safety profile should be deeper analysed through Personalized Medicine.

3. Statistical analysis results suggest a significant correlation between the neurological symptoms and *DOP2*, given that they are not equally distributed between the *DOP2* alleles. Following studies are underway to maximise statistical power with a bigger sample size, which we expect will corroborate these results or suggest new hypothesis.

BIBLIOGRAPHY

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. Arlington: American Psychiatric Association, 2013.
2. Eissa N, Al-Houqani M, Sadeq A, Ojha SK, Sasse A, Sadek B. Current Enlightenment About Etiology and Pharmacological Treatment of Autism Spectrum Disorder. Front Neurosci. 2018 May 16;12:304. doi: 10.3389/fnins.2018.00304.
3. Yoshida K, Koyama E, Zai CC, Beitchman JH, Kennedy JL, Lunsky Y, Desarkar P, Müller DJ. Pharmacogenomic Studies in Intellectual Disabilities and Autism Spectrum Disorder: A Systematic Review. Can J Psychiatry. 2021 Dec;66(12):1019-1041. doi: 10.1177/0706743720971950.
4. Espadas C, Ballester P, Londoño AC, Almenara S, Aguilar V, Belda C, Pérez E, Peiró AM. Multimorbidity and psychotropic polypharmacy among participants with autism spectrum disorder with intellectual disability. Psychiatry Res. 2020 Oct;292:113321. doi: 10.1016/j.psychres.2020.113321.
5. Costello A, Hudson E, Morrissey S, Sharma D, Kelly D, Doody O. Management of psychotropic medications in adults with intellectual disability: a scoping review. Ann Med. 2022 Dec;54(1):2486-2499. doi: 10.1080/07853890.2022.2121853.
6. Croen LA, Zerbo O, Qian Y, Massolo ML, Rich S, Sidney S, Kripke C. The health status of adults on the autism spectrum. Autism. 2015 Oct;19(7):814-23. doi: 10.1177/1362361315577517.
7. Khanzada NS, Butler MG, Manzardo AM. GeneAnalytics Pathway Analysis and Genetic Overlap among Autism Spectrum Disorder, Bipolar Disorder and Schizophrenia. Int J Mol Sci. 2017 Feb 28;18(3):527. doi: 10.3390/ijms18030527.
8. Puangpetch A, Vanwong N, Nuntamool N, Hongkaew Y, Chamnanphon M, Sukasem C. CYP2D6 polymorphisms and their influence on risperidone treatment. Pharmgenomics Pers Med. 2016 Dec 1;9:131-147. doi: 10.2147/PGPM.S107772.
9. Cecchin E, Stocco G. Pharmacogenomics and Personalized Medicine. Genes (Basel). 2020 Jun 22;11(6):679. doi: 10.3390/genes11060679.
10. Mandic-Maravic V, Grujicic R, Milutinovic L, Munjiza-Jovanovic A, Pejovic-Milovancevic M. Dopamine in Autism Spectrum Disorders-Focus on D2/D3 Partial Agonists and Their Possible Use in Treatment. Front Psychiatry. 2022 Feb 3;12:787097. doi: 10.3389/fpsyt.2021.787097.
11. Esmaiel NN, Ashaat EA, Mosaad R, Fayez A, Ibrahim M, Abdallah ZY, Issa MY, Salem S, Ramadan A, El Wakeel MA, Ashaat NA, Zaki MS, Ismail S. The potential impact of COMT gene variants on dopamine regulation and phenotypic traits of ASD patients. Behav Brain Res. 2020 Jan 27;378:112272. doi: 10.1016/j.bbr.2019.112272.

12. Biswas M, Vanwong N, Sukasem C. Pharmacogenomics in clinical practice to prevent risperidone-induced hyperprolactinemia in autism spectrum disorder. Pharmacogenomics. 2022 Jun;23(8):493-503. doi: 10.2217/pgs-2022-0016.
13. Saiz-Rodríguez M, Belmonte C, Román M, Ochoa D, Jiang-Zheng C, Koller D, Mejía G, Zubiaur P, Wojnicz A, Abad-Santos F. Effect of ABCB1 C3435T Polymorphism on Pharmacokinetics of Antipsychotics and Antidepressants. Basic Clin Pharmacol Toxicol. 2018 Oct;123(4):474-485. doi: 10.1111/bcpt.13031.
14. Lingjaerde, O; Ahlfors, U G; Bech, P; Dencker, S J; Elgen, K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. ACTA PSYCHIATRICA SCANDINAVICA. 1987;334:1-100.
15. Louise Tveter, A., Lise Bakken, T., G. Bramness, J. and Ivar Røssberg, J. (2014), "Adjustment of the UKU Side Effect Rating Scale for adults with intellectual disabilities. A pilot study", Advances in Mental Health and Intellectual Disabilities, Vol. 8 No. 4, pp. 260-267. https://doi.org/10.1108/AMHID-11-2013-0064
16. Al Dera H. Cellular and molecular mechanisms underlying autism spectrum disorders and associated comorbidities: A pathophysiological review. Biomed Pharmacother. 2022 Apr;148:112688. doi: 10.1016/j.biopha.2022.112688.
17. Brown JT, Eum S, Cook EH, Bishop JR. Pharmacogenomics of autism spectrum disorder. Pharmacogenomics. 2017 Mar;18(4):403-414. doi: 10.2217/pgs-2016-0167.
18. Correia CT, Almeida JP, Santos PE, Sequeira AF, Marques CE, Miguel TS, Abreu RL, Oliveira GG, Vicente AM. Pharmacogenetics of risperidone therapy in autism: association analysis of eight candidate genes with drug efficacy and adverse drug reactions. Pharmacogenomics J. 2010 Oct;10(5):418-30. doi: 10.1038/tpj.2009.63.
19. Breitenstein B, Scheuer S, Brückl TM, Meyer J, Ising M, Uhr M, Holsboer F. Association of ABCB1 gene variants, plasma antidepressant concentration, and treatment response: Results from a randomized clinical study. J Psychiatr Res. 2016 Feb;73:86-95. doi: 10.1016/j.jpsychires.2015.11.010.
20. Kalla P, Namerow LB, Walker SA, Ruaño G, Malik S. Contrasting ABCB1 pharmacogenetics and psychotropic responses in child and adolescent psychiatry: a case comparison. Pharmacogenomics. 2023 Feb;24(3):131-139. doi: 10.2217/pgs-2022-0120.
21. Planelles B, Margarit C, Inda MD, Ballester P, Muriel J, Barrachina J, Ajo R, Esteban MD, Peiró AM. Gender based differences, pharmacogenetics and adverse events in chronic pain management. Pharmacogenomics J. 2020 Apr;20(2):320-328. doi: 10.1038/s41397-019-0118-9.

22. Gadow KD, Roohi J, DeVincent CJ, Kirsch S, Hatchwell E. Association of COMT (Val158Met) and BDNF (Val66Met) gene polymorphisms with anxiety, ADHD and tics in children with autism spectrum disorder. J Autism Dev Disord. 2009 Nov;39(11):1542-51. doi: 10.1007/s10803-009-0794-4.
23. Zhang JP, Lencz T, Malhotra AK. D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. Am J Psychiatry. 2010 Jul;167(7):763-72. doi: 10.1176/appi.ajp.2009.09040598.
24. de Leon J, Spina E. What is needed to incorporate clinical pharmacogenetic tests into the practice of psychopharmacotherapy? Expert Rev Clin Pharmacol. 2016;9(3):351-4. doi: 10.1586/17512433.2016.1112737.
25. Staddon S, Arranz MJ, Mancama D, Mata I, Kerwin RW. Clinical applications of pharmacogenetics in psychiatry. Psychopharmacology (Berl). 2002 Jun;162(1):18-23. doi: 10.1007/s00213-002-1084-4.
26. Filaković P, Petek A. Personalized pharmacotherapy in psychiatry. Psychiatr Danub. 2009 Sep;21(3):341-6.
27. Claudio-Campos K, Padrón A, Jerkins G, Nainaparampil J, Nelson R, Martin A, Wiisanen K, Smith DM, Strekalova Y, Marsiske M, Cicali EJ, Cavallari LH, Mathews CA. Acceptability, Feasibility, and Utility of Integrating Pharmacogenetic Testing into a Child Psychiatry Clinic. Clin Transl Sci. 2021 Mar;14(2):589-598. doi: 10.1111/cts.12914.

ANNEXES

ANNEX 1. UKU SCALE

GUIA DE VALORACIÓN DE EFECTOS SECUNDARIOS DE MEDICACIÓN

Servicio de Psiquiatría

Fecha:
NOMBRE:
SIP:

Efectos secundarios	***Puntuación según gravedad***						***Observaciones***
EFECTOS PSÍQUICOS	**0**	**1**	**2**	**3**	**4**	**5**	
Dificultad de concentración							
Astenia/lasitud/fatigabilidad							
Alteraciones mnésicas							
Somnolencia /sedación							
Depresión							
Tensión/inquietud							
Aumento de la duración del sueño							
Aumento de los sueños							
Indiferencia emocional							
EFECTOS NEUROLÓGICOS							
Distonía							
Convulsiones epilépticas							
Parestesias							
Hipocinesia/acinesia							
Hipercinesia							
Temblor							
Acatisia							
Rigidez							
EFECTOS AUTONÓMICOS							
Trastorno de la acomodación							
Aumentos de la salivación							
Disminución de la salivación							
Náusea/vómito							
Diarrea							
Estreñimiento							
Alteración de la micción							
Vértigo ortostático							
Poliuria/polidipsia							
Palpitaciones /taquicardia							
Aumento de la sudoración							
OTROS EFECTOS							
Exantema							
Prurito							
Fotosensibilidad							

Aumento de la pigmentación							
Aumento de peso							
Pérdida de peso							
Amenorrea							
Galactorrea							
Ginecomastía							
Disfunción eréctil							
Disfunción eyaculatoria							
Disfunción orgásmica							
Alteración del deseo sexual							
Disfunción de la lubricación vaginal							
Cefalea							
Dependencia física							
Dependencia psíquica							
Tensión Arterial							

N/P: no procede. 0: No presenta. 1: Muy ocasionalmente. 2: Ocasionalmente 3: 2 veces por semana 4: 4 veces por semana 5: Todos los días.

ANNEX 2. ETHICAL APPROVAL

GENERALITAT VALENCIANA

ALACANT HOSPITAL GENERAL
DEPARTAMENT DE SALUT

C COMITÉ ÉTICO DE INVESTIGACIÓN CON MEDICAMENTOS DEL DEPARTAMENTO DE SALUD DE ALICANTE – HOSPITAL GENERAL
C/. Pintor Baeza, 12 – 03010 Alicante
http://www.dep19.san.gva.es
Teléfono: 965-913-952
Correo electrónico: isabial@gva.es

Ref. CEIm: 2019/008 Ref. ISABIAL: 190273

DICTAMEN DE ESTUDIO OBSERVACIONAL

D. Luis Manuel Hernández Blasco, titular de la Secretaría Técnica del Comité Ético de Investigación con Medicamentos del Departamento de Salud de Alicante - Hospital General.

CERTIFICA

Que este Comité en su reunión del día 31 de julio de 2019 (acta 2019/07) ha evaluado la propuesta del promotor e investigador principal Dña. Cecilia Magdalena Egoavil Rojas, para que se realice el Estudio Posautorización con otros diseños diferentes al de seguimiento prospectivo (EPA-OD)

TÍTULO	**FARMACOGENETICA APLICADA A PRESCRIPCION DE ANTIPSICÓTICOS EN POBLACION CON DIVERSIDAD FUNCIONAL –VIGITEADOP**
PROMOTOR	**Dña. Cecilia Magdalena Egoavil Rojas**
CÓDIGO DEL PROTOCOLO	**CME-HAL-2019-01**
VERSION DEL PROTOCOLO	**versión 2.0**
FECHA DEL PROTOCOLO	**8 de mayo de 2019**

Y tomando en consideración las siguientes cuestiones:

- La pertinencia del estudio, teniendo en cuenta el conocimiento disponible, así como los preceptos éticos formulados en la Orden SAS/3470/2009, de 16 de diciembre, por la que se publican las directrices sobre estudios postautorización de tipo observacional para medicamentos de uso humano y la Declaración de Helsinki de la Asociación Médica mundial sobre principios éticos para las investigaciones médicas en seres humanos y en sus posteriores revisiones, así como aquellos exigidos por la normativa aplicable en función de las características del estudio.

- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto, teniendo en cuenta los beneficios esperados.

- El plan de reclutamiento de sujetos previstos son adecuados, así como las compensaciones previstas para los sujetos por daños que pudieran derivarse de su participación en el estudio.

GENERALITAT VALENCIANA · DPTO. DE SALUD DE ALICANTE · COMITÉ DE ÉTICA PARA LA INVESTIGACIÓN CON MEDICAMENTOS · HOSPITAL GENERAL

GENERALITAT VALENCIANA

ALACANT HOSPITAL GENERAL DEPARTAMENT DE SALUT

- La capacidad del investigador y sus colaboradores son apropiados para llevar a cabo el estudio.

- Las instalaciones y medios disponibles son apropiados para llevar a cabo el estudio.

- El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.

Por tanto, este Comité emite un **DICTAMEN FAVORABLE** para la realización de dicho estudio en el Hospital General Universitario de Alicante.

Que el Comité tanto en su composición con en los PNT cumple con las normas de BPC (CPMP/ICH/135/95) y con el Real Decreto 1090/2015, y que en el supuesto que algún miembro de CEIm sea investigador principal o colaborador del estudio evaluado, éste se ausentará de la reunión durante la deliberación y toma de decisión y su composición actual es la siguiente:

Presidente:
Dra. Caridad Tapia Collados, Jefe de Sección de Pediatría en el Hospital General Universitario de Alicante

Vicepresidente:
Dra. Sofía Lorenzo García, Facultativo Especialista en Análisis Clínicos en el Hospital General Universitario de Alicante

Secretario Técnico:
Dr. Luis Manuel Hernández Blasco, Facultativo Especialista en Neumología en el Hospital General Universitario de Alicante

Vocales:

- Dra. Cristina Alenda González, Jefe de Sección de Anatomía Patológica y Directora Científica de Biobanco en el Hospital General Universitario de Alicante y miembro de la Comisión de Investigación.
- Dra. Amparo Burgos San José, Facultativo Especialista en Farmacia en el Hospital General Universitario de Alicante
- Dr. Vicente Climent Payá, Facultativo Especialista en Cardiología en el Hospital General Universitario de Alicante
- Dr. Mariano Esteban Fontecha, Facultativo Especialista y Jefe de Sección de UCI en el Hospital General Universitario de Alicante
- D. Óscar Fuentes Coso, Licenciado en Derecho y Técnico de la Función Administrativa en el Hospital General Universitario de Alicante
- Dra. Edith Danielle Leutscher Vasen, Facultativo Especialista en Medicina Preventiva en el Hospital General Universitario de Alicante
- Dña. Sonia Balboa Esteve, Enfermera en el Servicio de Medicina Preventiva en el Hospital General Universitario de Alicante
- Dña. María Gazapo Martínez, Licenciada en Psicología y trabajadora autónoma.
- Dr. José Antonio Monge Argiles, Facultativo Especialista en Neurología en el Hospital General Universitario de Alicante
- Dra. Elena Lorda Barraguer, Facultativo Especialista en Cirugía y miembro del Comité de Ética Asistencial
- Dra. Mª Asunción Quijada Cazorla, Facultativo Especialista en Obstetricia y Ginecología en el Hospital General Universitario de Alicante
- D. Alberto Pastor Campos, Licenciado en Veterinaria y Responsable de la Oficina Evaluadora de Proyectos UMH
- Dr. Mª Ángeles Pena Pardo, Facultativo Especialista en Farmacología Clínica en el

GENERALITAT VALENCIANA CONSELLERIA DE SANITAT UNIVERSAL I SALUT PÚBLICA DEPARTAMENT DE SALUT ALACANT COMITÉ DE ÉTICA PARA LA INVESTIGACIÓN CON MEDICAMENTOS HOSPITAL GENERAL

GENERALITAT VALENCIANA

ALACANT HOSPITAL GENERAL DEPARTAMENT DE SALUT

Hospital General Universitario de Alicante

- D. José Miguel Sempere Ortells, Catedrático y Director del Departamento de Biotecnología de la Universidad de Alicante

Lo que firmo en Alicante, a 31 de julio de 2019

LA SECRETARIA TÉCNICA DEL CEIm,

GENERALITAT VALENCIANA DPTO. DE SALUD DE ALICANTE COMITÉ DE ÉTICA PARA LA INVESTIGACIÓN CON MEDICAMENTOS HOSPITAL GENERAL Conselleria de Sanitat Universal i Salut Pública

Fdo.: D. Luis Manuel Hernández Blasco

ANNEX 3. COIR REGISTRATION

INFORME DE EVALUACIÓN DE INVESTIGACIÓN RESPONSABLE DE 1. TFG (Trabajo Fin de Grado)

Elche, a 12/12/2022

Nombre del tutor/a	Ana María Peiró Peiró
Nombre del alumno/a	Laura de Miguel López
Tipo de actividad	1. Adherido a un proyecto autorizado
Título del 1. TFG (Trabajo Fin de Grado)	Pharmacogenetics for psychotropic drugs and a cross-sectional study of side effects in autism spectrum disorder
Evaluación Riesgos Laborales	No procede
Evaluación Ética	No procede
Registro provisional	221205112451
Código de Investigación Responsable	**TFG.GME.AMPP.LDML.221205**
Caducidad	2 años

Se considera que la presente actividad no supone riesgos laborales adicionales a los ya evaluados en el proyecto de investigación al que se adhiere. No obstante, es responsabilidad del tutor/a informar y/o formar al estudiante de los posibles riesgos laborales de la presente actividad.

La necesidad de evaluación ética del trabajo titulado: **Pharmacogenetics for psychotropic drugs and a cross-sectional study of side effects in autism spectrum disorder** ha sido realizada en base a la información aportada en el formulario online: "TFG/TFM: Solicitud Código de Investigación Responsable (COIR)", habiéndose determinado que no requiere ninguna evaluación adicional. Es importante destacar que si la información aportada en dicho formulario no es correcta este informe no tiene validez.

Por todo lo anterior, **se autoriza** la realización de la presente actividad.

Atentamente,

Alberto Pastor Campos
Secretario del CEII
Vicerrectorado de Investigación

Domingo L. Orozco Beltrán
Presidente del CEII
Vicerrectorado de Investigación

Información adicional:

- En caso de que la presente actividad se desarrolle total o parcialmente en otras instituciones es responsabilidad del investigador principal solicitar cuantas autorizaciones sean pertinentes, de manera que se garantice, al menos, que los responsables de las mismas están informados.
- Le recordamos que durante la realización de este trabajo debe cumplir con las exigencias en materia de prevención de riesgos laborales. En concreto: las recogidas en el plan de prevención de la UMH y en las planificaciones preventivas de las unidades en las que se integra la investigación. Igualmente, debe promover la realización de reconocimientos médicos periódicos entre su personal; cumplir con los procedimientos sobre coordinación de actividades empresariales en el caso de que trabaje en el centro de trabajo de otra empresa o que personal de otra empresa se desplace a las instalaciones de la UMH; y atender a las obligaciones formativas del personal en materia de

COMITÉ DE ÉTICA E INTEGRIDAD EN LA INVESTIGACIÓN
VICERRECTORADO DE INVESTIGACIÓN
UNIVERSIDAD MIGUEL HERNÁNDEZ DE ELCHE

prevención de riesgos laborales. Le indicamos que tiene a su disposición al Servicio de Prevención de la UMH para asesorarle en esta materia.

ANNEX 4. CONSENT FORM BIOBANK SAMPLES

GENERALITAT VALENCIANA
CONSELLERIA DE SANITAT
AGÈNCIA VALENCIANA DE SALUT
RVB

Consentimiento informado para la donación voluntaria de muestras biológicas para investigación obtenidas en el curso de procedimientos quirúrgicos, terapéuticos o diagnósticos Biobanco ISABIAL

(1 de 6)

RED VALENCIANA DE BIOBANCOS

1. Identificación y descripción del procedimiento

Durante la intervención quirúrgica o la prueba diagnóstica a la que va a ser sometido se podrán tomar muestras de sus tejidos, sangre, así como fluidos (orina, esputo, saliva, etc) o microorganismos. El procedimiento que se le propone consiste en donar voluntariamente cualquier muestra biológica sobrante de la intervención o prueba a la que va a ser sometido a un biobanco de muestras biológicas, sin que ello suponga ningún riesgo añadido para su salud ni comprometa el correcto diagnóstico y tratamiento de su enfermedad. Dichas muestras biológicas excedentes podrán ser utilizados en proyectos de investigación biomédica que previamente sean aprobados por los comités externos, ético y científico, a los que está adscrito el biobanco.

Las muestras seguirán almacenadas en el biobanco hasta el fin de las existencias si no existe una revocación del presente consentimiento.

2. Objetivo

La finalidad del biobanco es recoger y almacenar muestras biológicas humanas para realizar proyectos de investigación biomédica o diagnósticos. Los resultados de dichos proyectos de investigación pueden derivar en el descubrimiento de nuevos métodos para el mejor diagnóstico de las enfermedades y de nuevas medicinas para tratarlas.

3. Condiciones de la donación

Usted no recibirá ninguna compensación económica ni otros beneficios materiales por donar sus muestras. Sin embargo, si las investigaciones que se realicen tuvieran éxito, podrán ayudar en el futuro a pacientes que tienen su misma enfermedad o padecen otras enfermedades similares.

Las muestras que usted dona no serán vendidas o distribuidas a terceros con fines comerciales, pero los costes de obtención, conservación y envío de las muestras se repercutirán, sin ánimo de lucro, a quienes las utilicen.

La donación de muestras no impedirá que usted o su familia puedan hacer uso de ellas siempre que estén disponibles, cuando así lo requieran. Debe saber que será prioritario el uso diagnóstico de la muestra que dona y que se garantizará un remanente de las muestras para este fin.

En caso de producirse un eventual cierre del biobanco o revocación de la autorización para su constitución y funcionamiento, la información sobre el destino de las muestras estará a disposición en el registro nacional de biobancos para investigación biomédica, con el fin de que pueda manifestar su conformidad o disconformidad con el destino previsto de las muestras.

4. Consecuencias previsibles de su realización

Se podría dar la circunstancia de ser contactado/a con el fin de recabar nueva información sobre su situación o de tomar una nueva muestra que pudiera ser interesante en el desarrollo de la investigación biomédica, en cuyo caso volverá a ser informado/a de la situación y tendrá la libertad de participar o rechazar dicha participación. Por tal motivo, es importante que comunique al Servicio de Admisión del centro FUTUROS CAMBIOS DE DIRECCIÓN y números de TELÉFONO, ya que es la única vía para poder contactar con usted.

Es posible que se obtenga información relativa a su salud derivada del desarrollo de los proyectos de investigación y, en particular, datos genéticos con relevancia clínica. En este sentido, puede solicitar la información relativa a su salud derivada del estudio de las muestras donadas. Para ejercer este derecho, tiene a su disposición en el biobanco el correspondiente formulario de solicitud.

La información que se obtenga puede ser relevante también para sus familiares biológicos. Es decisión suya informarles – algo que nosotros le aconsejamos - con el fin de que, si ellos lo desean, puedan ser estudiados y valorar así cual es el riesgo personal y sus opciones de salud en un futuro.

Cuando esta información, según criterio médico, sea necesaria para evitar un grave perjuicio a la salud de sus familiares biológicos, previa consulta del comité asistencial, se les informará de ello.

GENERALITAT VALENCIANA
CONSELLERIA DE SANITAT
AGÈNCIA VALENCIANA DE SALUT
RVB

Consentimiento informado para la donación voluntaria de muestras biológicas para investigación obtenidas en el curso de procedimientos quirúrgicos, terapéuticos o diagnósticos Biobanco ISABIAL

(2 de 6)

5. Derecho de revocación del consentimiento

La decisión de donar sus muestras es totalmente voluntaria. Usted puede negarse a donarlas e incluso puede revocar su consentimiento en cualquier momento, sin tener que dar ninguna explicación y sin que ello tenga ninguna repercusión en la atención médica que recibe en el Centro.

Si revoca el consentimiento que ahora presta, la parte de las muestras que no se hayan utilizado en la investigación, podrá decidir que sean destruidas o anonimizadas. Tales efectos no se extenderán a los datos resultantes de las investigaciones que ya se hayan llevado a cabo antes de la revocación de su consentimiento.

6. Riesgos

El procedimiento que se le propone no supone ningún riesgo añadido para su salud ni compromete el correcto diagnóstico y tratamiento de su enfermedad, puesto que se trata de muestra sobrante de la intervención.

La donación de sangre apenas tiene efectos secundarios; lo más frecuente es la aparición de pequeños hematomas en las zonas de punción que desaparecen transcurridos 1 ó 2 días.

7. Protección de datos personales y confidencialidad

Los datos personales y de salud obtenidos de su historia clínica o equivalente serán incorporados y tratados en una base de datos que cumple con las garantías que establece la legislación sanitaria y sobre protección de datos de carácter personal.

La cesión a otros centros de investigación, públicos o privados, de sus muestras o de sus derivados, así como de la información contenida en las bases de datos vinculada a las mismas y a su estado de salud, se realizará mediante un procedimiento de disociación, esto es, suprimiendo la información personal que la identifica y sustituyéndola por un código.

Es posible que en el desarrollo de un proyecto de investigación se genere mucha información genética de sus muestras. Si los resultados fueran relevantes desde el punto de vista científico, la información obtenida, desligada de cualquier dato que pueda permitir su identificación por medios razonables, podría ser remitida para su inclusión en bases científicas y demás medios de difusión de contenido científico a los que tendrán acceso, con carácter restringido, investigadores científicos.

El biobanco en el que se custodiarán sus muestras forma parte de la Red Valenciana de Biobancos cuya coordinación es llevada a cabo por el Centro Superior de Investigación de Salud Pública de la Comunitat Valenciana.

Como consecuencia de lo anterior, el ente coordinador de la Red Valenciana de Biobancos, esto es, el Centro Superior de Investigación en Salud Pública de la Comunitat Valenciana, tendrá acceso a sus datos personales y a la información clínica asociada a la muestra donada voluntariamente, con el único fin de cumplir con las labores atribuidas a la Red Valenciana de Biobancos en virtud de la legislación vigente. En particular, el eventual acceso a sus datos personales por parte de la Red Valenciana de Biobancos tendrá como finalidad poder coordinar de la manera más eficiente posible desde el punto de vista científico la información obtenida por los biobancos adscritos a la Red Valenciana de Biobancos, mediante la gestión y coordinación del Sistema de Gestión de la Información de la Red Valenciana de Biobancos, así como la coordinación de las actividades desarrolladas por los biobancos, todo ello de acuerdo con la normativa aplicable.

Podrá ejercitar sus derechos de acceso, rectificación, cancelación y oposición, para lo cual tiene en el biobanco el correspondiente formulario de solicitud. En dicho escrito, deberá adjuntar copia de su DNI para que el Centro responsable de sus datos pueda comprobar su identidad.

GENERALITAT VALENCIANA
CONSELLERIA DE SANITAT
AGÈNCIA VALENCIANA DE SALUT
RVB

Consentimiento informado para la donación voluntaria de muestras biológicas para investigación obtenidas en el curso de procedimientos quirúrgicos, terapéuticos o diagnósticos Biobanco ISABIAL

(3 de 6)

Declaración de consentimiento

EJEMPLAR PARA EL DONANTE

D./Dª ..... de ..... .años de edad, con domicilio en.....,

DNI ..... y nº de SIP .....

D./Dª ..... de ..... años de edad, con domicilio en .....,

DNI ..... en calidad de representante (en caso de minoría legal o incapacidad)

del paciente con DNI ..... y nº de SIP ..... .

DECLARO

He leído la hoja de información que se me ha entregado.

He sido informado por el profesional de salud abajo mencionado sobre la donación de muestras a un biobanco.

He comprendido las explicaciones que se me han facilitado en un lenguaje claro y sencillo.

He podido realizar observaciones y me han sido aclaradas todas las dudas que he planteado.

He comprendido que la donación de muestras a un biobanco es voluntaria y puedo revocar mi consentimiento en cualquier momento, sin tener que dar explicaciones y sin que esto repercuta en mis cuidados médicos.

Que libre y voluntariamente acepto la realización de la donación voluntaria de:

Una/s muestra/s de saliva .....

.....

Que puedo incluir restricciones sobre el uso de las mismas:

.....

CONSIENTO

Que el Hospital u otros centros de investigación, públicos o privados, utilicen mis datos y las muestras donadas en las condiciones establecidas en la hoja de información.

Que el ente coordinador de la Red Valenciana de Biobancos pueda acceder a mis datos, en la medida en que sea necesario y manteniendo siempre su confidencialidad.

A completar por el donante:

Fdo.: D./Dª .....
DNI: .....

A completar por el profesional de salud:

Fdo.: D./Dª .....
DNI: .....
Colegiado Nº: .....

En condición de: .....

En Alicante .....a ..... de ..... de 20.....

RED VALENCIANA DE BIOBANCOS

ANNEX 5. GENETIC ANALYSIS INFORMATION. CYP2D6 PHENOTYPE.

SNP		**Nº Casos**	**%**
rs1080985	CYP2D6*2		
	WT(CC)	55	55%
	MUT(GG)	9	9%
	HTZ(CG)	32	32%
	Sin Info (vacias)	4	4%
Alelos	C	142	
	G	50	
rs35742686	CYP2D6*3		
	WT(Del)	0	0%
	MUT(AA)	84	84%
	HTZ(DelA)	2	2%
	Sin Info (vacias)	11	11%
Alelos	Del	2	
	A	170	
rs3892097	CYP2D6*4		
	WT(GG)	57	57%
	MUT(AA)	5	5%
	HTZ(GA)	32	32%
	Sin Info (vacias)	6	6%
Alelos	G	146	78%
	A	42	22%
rs5030655	CYP2D6*6		
	WT(TT)	94	94%
	MUT(Del)	0	0%
	HTZ(TDel)	0	0%
	Sin Info (vacias)	6	6%
Alelos	T	188	100%
	Del	0	0%
rs1065852	CYP2D6*10		
	WT(CC)	53	53%
	MUT(TT)	10	10%
	HTZ(CT)	29	29%
	Sin Info (vacias)	5	5%
Alelos	C	135	73%
	T	49	27%

SNP		Nº Casos	%
rs28371706	CYP2D6*17		
	WT(CC)	89	89%
	MUT(TT)	0	0%
	HTZ(CT)	2	2%
	Sin Info (vacias)	9	9%
Alelos	C	180	99%
	T	2	1%
rs59421388	CYP2D6*29		
	WT(GG)	91	91%
	MUT(AA)	0	0%
	HTZ(GA)	1	1%
	Sin Info (vacias)	8	8%
Alelos	G	183	99%
	A	1	1%
rs769258	CYP2D6*35		
	WT(GG)	87	87%
	MUT(AA)	0	0%
	HTZ(GA)	8	8%
	Sin Info (vacias)	5	5%
Alelos	G	182	96%
	A	8	4%
rs28371725	CYP2D6*41		
	WT(GG)	81	81%
	MUT(AA)	3	3%
	HTZ(GA)	8	8%
	Sin Info (vacias)	8	8%
Alelos	G	170	92%
	A	14	8%

ANNEX 6. CORRELATION BETWEEN SOCIODEMOGRAPHIC AND ADVERSE EVENTS DATA

		EA Total		**EA Psíquicos**		**EA Neurológicos**		**EA Autonómicos**		**Otros EA**	
		Con	*Sin*	*Con*	*Sin*	*Con*	*Sin*	*Con*	*Sin*	*Con*	*Sin*
Edad Media		46,43 / 12,13	56 / 11,36	46,5 / 7,33	51,17 / 14,96	54,14 / 9,96	46,69 / 13,22	46,11 / 11,87	51,91 / 12,74	42,4 / 10,25	51,6 / 12,59
Sexo	*Mujer*	*5*	3	4	4	2	6	3	5	3	5
	Hombre	9	3	4	8	5	7	6	6	2	10
Nº Farmacos	*Sin fármacos*	1	1	1	1	0	2	0	2	0	2
	de 1 a 3	16	8	7	17	9	15	10	14	4	20
	4 o más	4	0	3	1	2	2	3	1	2	2
Comorbilidades	*Sin comor*	1	0	1	0	1	0	1	0	1	0
	de 1 a 3	4	2	1	5	2	4	3	3	1	5
	4 o más	8	2	5	5	4	6	5	5	2	8

Relation between Aes and demographic/pharmacologycal data. (n=16)