MENTAL RETARDATION AS A MAIN INDICATOR OF PATOLOGIC GENETIC VARIANTS IN EXOME STUDIES. STRATIFIED ANALYSIS IN A REFERENCE POPULATION.

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Introduction

Among the most relevant complementary studies currently carried out for etiological diagnosis in neurodevelopmental disorders and in neuropediatric pathology in general, the clinical exome has become a fundamental piece. The reason why this type of genetic studies is used more is neurodevelopmental disorders followed by the presence of dysmorphological traits (1).

Because the demographic distribution of healthcare populations can have a significant influence on the type of genetic variants detectable by these techniques, we believe the analysis of the data accumulated in the regular healthcare of a reference population with population significance is justified (2).

On the other hand, given that the debut of neurodevelopmental disorders can be paucisymptomatic for a long time, we consider the value of analysing genetic variants of uncertain significance present in the patient and who have developed few or no symptoms of that variant at the beginning of follow-up of these patients (3).

Objectives

Identify the best indicator to detect genetic pathologic variants (PV) in clinical exome studies, in a referral population with developmental problems.

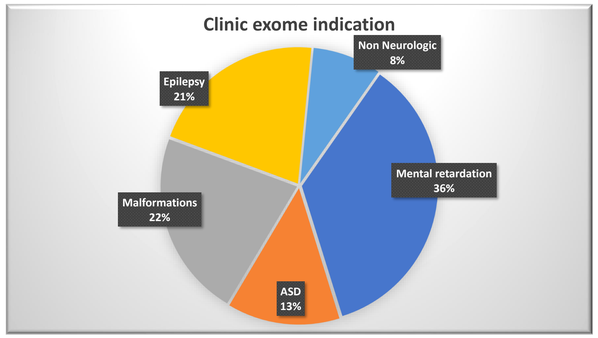
Table 1.- Demographic data of the study setting

Spanish Population	48.592.909 inh.	100,00%
Valencian Community Population	5.316.478 inh	10,94%
Alicante Province Population	1.964.651 inh.	36,95%
17th Department Population	235.062 inh.	11,96%
17th Department Population under 15 y.o.	32.230 Inh.	13,71%

Patients and Methods

A two years 2021-22 ambispective cohort study on 100 patients referred to our health area of the Valencian Public Health System (Reference for 32230 children < 15 y-o)(Table 1), for different developmental disorders who have the indication for an exome study due to presenting disorders of the neurodevelopment among which the following indication factors (IF) emerge (Figure1): Mental Retardation (MR), ASD, Motor Delay (MD), Epilepsy (EP), Physical Malformations (PHM) and other reasons different from neurological ones (Non-IF) . The presence of PV is assessed and the number of Variants of Uncertain Significance (VUS) is compared between those who present an IF and those who do not. The relative risk (RR) of presenting or not presenting PV is analyzed, as well as the differences in the mean total number of VUS between those who present or not one of the IF (student-t).

Figure 1.- different developmental disorders who have the indication for an exome study due to presenting disorders of the neurodevelopment among which the following indication factors (IF)



Results

In 61 cases of the 100, PV were found. Patients with MR presented an RR = 1.56 (1.1-2.3) compared to patients who did not have it Figure 2). In patients with MR the mean number was VUS=33±-13.6, significantly higher (p=0.04) than those without Non_MR VUS=27±12.7. ASD, MD, and PHM did not show significant risk values either in frequency of VP or VUS.

Figure 2.- Presence of Pathogenic Variants (PV) in Patients Diagnosed as: Mental Retardation

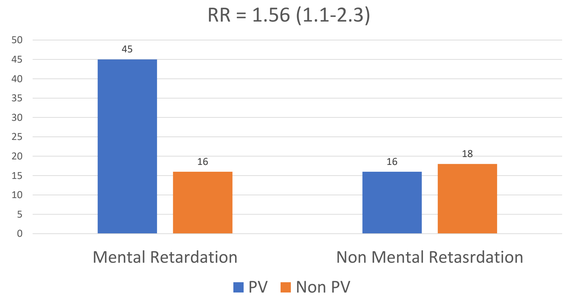
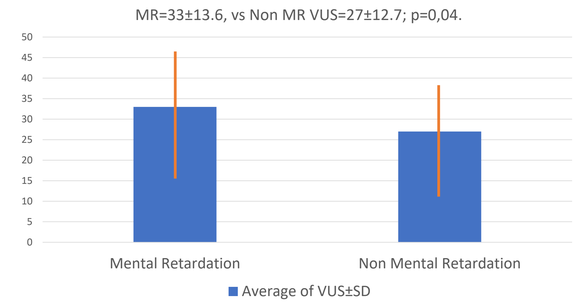


Figure 3.- Presence of Variants of Uncertain Significance in Patients Diagnosed as: Mental Retardation



Conclusions

1) MR is the main individual indicator of risk of PV in the exome in our healthcare reference area.

2) The other recommended exome study indicators, individually, did not represent a significant increase in the risk of PV or VUS over those who did not present them.

3) Knowledge of variants of uncertain significance can be an important guide for the follow-up of patients with neurodevelopmental disorders because they are significantly more present in patients who present MR or psychomotor delay as main symptoms.

References

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