Diagnostic yield of Whole Exome and Whole Genome Sequencing in pediatric neurological disorders. A UAE Tertiary hospital experience

Bushra **Alattas**[1] , Majid **Aziz**[2]

[1] Department of Pediatrics and [2] Department of Pediatric Neurology, Sheikh Khalifa Medical City, Abu Dhabi, UAE

ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY | OCTOBER 3-7, 2022

INTRODUCTION

Neurological disorders in children can pose diagnostic challenge. Whole exome (WES) and Whole genome (WGS) sequencing is becoming part of routine clinical and diagnostic practice in children with neurological disorders.

High consanguinity rates in middle east population increases the risk of genetic disorders.

The yield depends on the characteristics of the patient population. Little is known about the diagnostic yield of WES and WGS in non-Caucasian populations.

OBJECTIVES

1. Diagnostic yield of WES in native Arab population
2. Additional detection rate of WGS
3. Chances of positive results on reanalysing WES
4. Predictors of positive result

MATERIALS & METHODS

We retrospectively and prospectively studied the utility of WES and WGS in neurogenetic diagnosis of Emirati children (age 0-18 years) following in SKMC, Abu Dhabi, between January 1st 2020 to December2021, with undiagnosed neurological disorders where conventional genetic (microarray / gene panels) and metabolic testing were inconclusive. Clinical presentations were classified into five categories: isolated developmental impairment, epileptic encephalopathy, movement disorder, CNS malformation, and miscellaneous.

RESULTS

Table 1 : Demographic	
Total number of patients (n)	85
Age in months, Median	19 (2 weeks – 18 years)
Gender (Male), % (n)	55 (47)
Ethnicity (UAE), %(n)	90 (70)
Consanguinity, %(n)	61 (52)
Family history , %(n)	40 (34)

Table 2: Neurological presentation	% (n)
Developmental Impairment	43 (36)
Epileptic encephalopathy	22 (19)
CNS malformation	18 (15)
Movement disorder	9 (8)
Miscellaneous	8 (7)

Table 3: Investigations

	Normal	Abnormal
Metabolic Screen	76	9
Microarray	29	7 (Nonspecific)
MRI	46	39

Figure 1: WES and WGS diagnostic yield

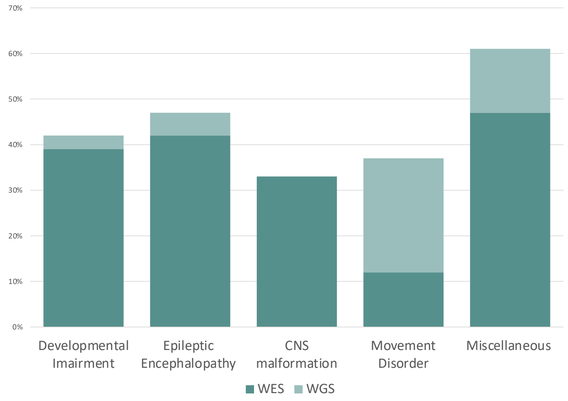

Figure 2:

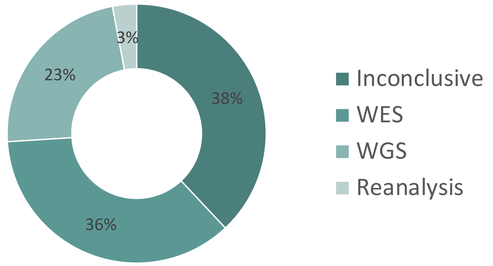

Table 4: Predictors for positive test

	P-Value
Gender	0.096
Consanguinity	0.060
MRI Finding	0.067

DISCUSSION

In our cohort of 85 children WES diagnostic sensitivity was 36% and additional yield with WGS was 23%. VUS of pathogenic significance were seen in 27% of the cohort. WES retesting added genetic diagnosis in 3% cases. Median time to diagnosis was 8 months. Consanguinity rate was high up to 61%, and 40% of them had positive family history of similar presentation. In our cohort we identified 6 novel genes.

Most positive cases in clinical whole-exome studies in Emiratis were in consanguineous populations with AR disorders.

Cases where the clinical diagnosis is associated with a high level of genetic heterogeneity exome/genome sequencing as first-tier test for children with intellectual disability, epileptic encephalopathy, developmental impairment, and multiple congenital anomalies is a more cost-effective approach.

CONCLUSION

Our study shows that WGS hit rate was nearly 23% over WES and reanalysing WES data had additional, but limited, clinical utility. Additionally, variants of pathogenic relevance from middle east population will allow to integrate new genomic data.

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