MOLECULAR DIAGNOSIS OF RWANDAN CHILDREN WITH UNEXPLAINED INTELLECTUAL DISABILITY/NEURODEVELOPMENTAL DELAY BY a-CGH AND WHOLE EXOME SEQUENCING

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ABSTRACT

Background

Intellectual disability (ID) is described by significant limitations in both intellectual functioning and adaptive behavior that begin before the age of 18 years. The present study aimed at analyzing the potential pathogenic genomic imbalance in Rwandan children with unexplained intellectual disability (ID) and/or developmental delay (DD) and its association with phenotypes, and to investigate the value of array-CGH and whole exome sequencing (WES) in clinical genetic diagnosis.

Methods

Array CGH was performed in 50 rwandan patients with ID/DD associated with multiple congenital anomalies (MCA). Furthermore, whole exome sequencing using Hiseq2000 was performed in three families: two consanguineous and one non-consanguineous. Homozygosity mapping previously performed in consanguineous families, allowed to identify large regions of loss of heterozygoty.

Results

G-band karyotyping of peripheral blood cells showed no abnormalities in the 50 children. The results of the array-CGH revealed that 13 patients (26%) genomic CNVs. Six patients had CNVs associated with known syndromes including William-Beuren syndrome, deletion 22q11.21, duplication 7q23.11, deletion 8p23.1, and deletion 17q21.31; whereas 7 patients presented rare genomic imbalances. The WES allowed identifying mutation in the PEX13 gene responsible of a mild peroxisomal biogenesis disorder in a consanguineous family and a dominant mutation in EFTUD2 gene responsible of the mandibulofacial dysostosis syndrome Guion-Almeida type (MFDGA) in another family.

Conclusion

This research highlights the contribution of genetic factors in the etiology of DD/IDD and MCA, especially the implication of chromosomal abnormalities with an array-CGH detection high rate of 26%. The WES showed a great clinical utility in diagnosis of ultra-rare neurodevelopmental diseases. Applying WES to Rwandan families, a true genetic diagnosis was found in two families.

Nevertheless, as we are still facing the challenge that there are no available data about genomic studies in African population it seems possible that the identified novel variants could be commonly frequent in that population.

Key-words: Intellectual disability, Global development delay, Multiple congenital abnormalities, Array-CGH, Whole exome sequencing, PEX13, EFTUD2, mandibulofacial dysostosis syndrome Guion-Almeida type, Rwandan patients.