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ORIGINAL ARTICLE

Prevalence of Epilepsy with Autosomal Recessive Intellectual Disability in Consanguineous Families

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ABSTRACT

Background: Intellectual disability (I.D) is the limitation of cognitive impairment and decreased ability of learning of a person. It is a type of neurological genetic disease, which results in incomplete or retarded/ arrested development of the brain. I.D is one of the most common health problem worldwide. These patients have decreased intellectual functions and at least limitation in their two adoptive skills such as writing or reading abilities, communication ability and self-care etc.

While epilepsy is a neurodevelopment disease presented as abrupt & episodic recurrence of sensory disturbance, loss of consciousness or convulsions,

related with the abnormality of electrical activities in the brain. Epilepsy is an illness of CNS that result in abnormal brain activity, causing periods of unusual behavior or seizures, loss of awareness, and sometimes sensations.

Methods: This study was done from April 2014 to February 2016. The inclusion criteria for these patients were consanguineous families with two or more than two effected persons. All the I.D patients and their families were interviewed one by one. Blood samples were collected under hygienic method. Each patient were examined thoroughly and noted the points with the help of different proformas. Collected blood collection were stored in laboratory. After DNA extraction ,PCR was done. After extraction exome sequencing process used to find the pathogenic /effected variants. CATCH used for the analyzed of data. Sanger Sequencing was applied to note the segregation.

Results: In ID-family1 the variant of AP4B1 was segregated with the disease phenotype. Mutation in AP4B1 is known to cause intellectual disability. In ID-family2 the variants of WDR62, EML2 and KCNK6 were co-segregated with diseased phenotype. But only changes in WDR62 which is known as a cause of intellectual disability. These patients also have symptoms of epilepsy. In ID-family3 exome sequencing data reveal no putative variants.

Conclusion: This study was done in three consanguineous families to determine the responsible mutant genes for the disorder of intellectual disability. Their Exome sequencing showed putative mutations in AP4B1 and WDR62 in two out of three families. In third family we could not locate any putative mutation.

Keywords: Epilepsy, Intellectual disability, Autosomal recessive disorders, Autosomal recessive nonsyndromic intellectual disability, Seizures, Neurological, Behavioral Abnormality, Central Nervous System, Electroencephalogram.

INTRODUCTION

Intellectual disability or (ID) is described as a patient has certain limitations in their cognitive functioning and social skills, that include communication skills, social and self-care skills. These limitations of skills can affect the development of a child to learn slowly or differently as compare to a typically and normal developing child[1-2].Intellectual disability [3] (ID) has involvement with general mental health /abilities that affect functions in two angles: Intellectual functioning (such as judgment, learning and problem solving,). Adaptive functions such as (daily life activities such as communication in society and independent living) [4].Epilepsy can be defined as the tendency of seizures that's beginning in the brain[5]. As our brain using electrical signals to transfer messages among brain cells. If these electrical signals are disturbs, it can cause seizure. For the diagnosis of epilepsy the patient will have history of recurrent and more than one abrupt attacks of seizures[6].These seizures are due to a disruption of electrical signals in the cells of brain, which temporarily and for a period of time disturbs the messaging transforming systems between brain cells[7].According to research that Epilepsy is a neurological conditions, having an incidence ratio of approximately fifty new cases per 100,000 population per year[8]. (Hauser and Hersdorffer 1990). About 1% of world wide population are suffering from epilepsy, Approximately seventy five percent of epilepsy started during childhood, which reflecting a heightened susceptibility of the developing brain to seizures[9-10].

This study was conducted in highly consanguineous families to identify causative genes of intellectual disability (ID) with the symptoms of epilepsy.

MATERIALS AND METHODS

This study was conducted from April 2014 to February 2016at KPK Kohat. ID patients were related from 03 ID families under the following criteria.

Inclusion Criteria

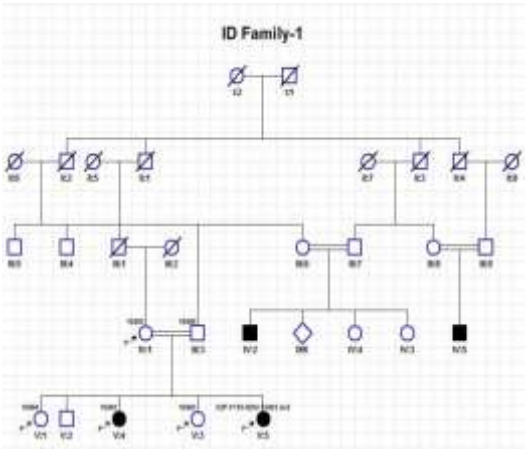
1. Those families which have2 or more than 2patients of congenital ID.
2. ID patients which have history of disease either from their birth or before the age of 18 years of age.
3. ID patients were brothers or sisters.
4. The parents of all the selected ID patients were close cousins, either from maternal side or from paternal side of relation.

Exclusion Criteria

1. Those families of ID disorder whose already have been given their blood samples for the purpose of research to someone else.
2. ID patients whose onset of disease was after the age of 18 years.
3. Those ID families which were not willing for the informed consent or for the blood samples extraction.

All the ID patients with or without epilepsy were individually interviewed in friendly atmosphere. Blood samples were taken by aseptic method. All the ID patients were properly physically examined. And their blood samples sent to processed in laboratory. DNA extraction and polymerase chain reaction was done. Then the exome sequencing was applied to find out the mutant variants. CATCH was used to analyze data. Sanger Sequencing was applied to see the segregation. The sampling technique used was non probability consecutive sampling technique. Five cc samples of blood were collected from each ID patients, and from their parents and normal siblings.

RESULTS



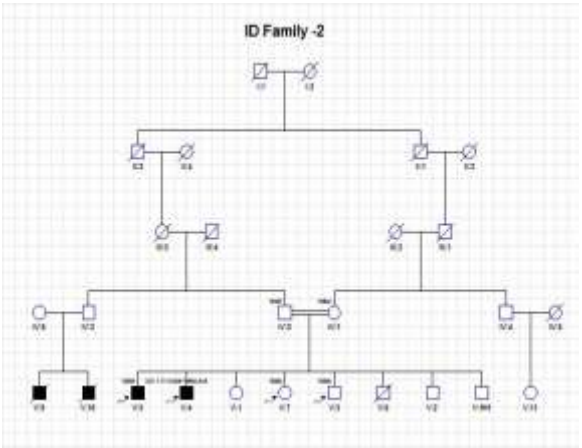
Family-1 Intellectual Disability

In all the three ID families' pedigrees or family trees I, II, III, roman numbers were used for the identification of the number of generations. While 1, 2, 3, of English numbers were used to indicate the numbers of members in the family. The circular boxes are for the female sex and quadrangle box for the male sex in each family. The blacked colored boxes are for the infected members of the family.

Segregation analysis of family-1: The AP4B1mutation was the only known mutation segregating with disease phenotype. V:3normal sibling was carrier, while V:1 was absolutely normal for ID disease variant.

AP4B1exon5:c.968dupC:p.S323fs **(M1)**

AP4B1 (adaptor-related protein complex 4, beta 1 subunit): This gene has encodes a subunit of a heterotetrameric adapter-like complex 4.Mutations in AP4B1gene are linked with cerebral palsy spastic quadriplegic type 5 (CPSQ5) disorder.



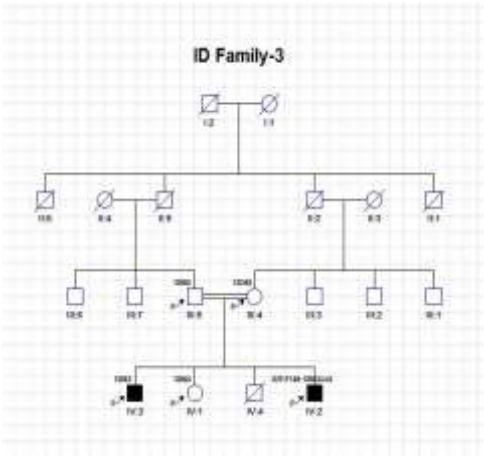
Family-2 Intellectual Disability

In the ID family II all the patients having same phenotype characteristics as of family-1. Their associated problems in all these 4 patients having the same signs symptoms, that are the Intellectual disability, short stature and spastic paraplegia. All the marked individuals with arrows and P symbols were rechecked for segregation after the exome sequencing.

KCNK1: Potassium channel involved in coordination disorder: In this table homozygous region matching's are shown. For the exome sequencing the parents must be heterozygous. Family information about the variant/ candidate genes KCNK6, EML2, WDR62 are shown in pedigree. This family was analyzed manually.

Segregation analysis of ID family-2: All the putative mutations (**KCNK6,EML2**) showing co-segregation of ID with diseased phenotype. V:7sibling found normal while the disease genotype was found in V:3 as carrier.

WDR62, chr19.exon11:c.G1531C:p.D511H **(M3)**



Family-3 Intellectual Disability

In case of ID family III both of the ID patients having the similar characteristics, phenotype of ID with epilepsy. These patients having no other related abnormalities ie short stature or spastic paraplegia. In ID family III no putative mutation gens was found there for segregation analysis was avoided.

DISCUSSION

Intellectual disability (ID) is a neuro-developmental disorders which results in arrested or incomplete development of mind. Around 1to 3 percent of the world wide population are suffers from adaptive incapacities and learning because of ID which causes a severe lifelong load on the daily life activities of the ID patients, as will as on their families[11] . In 2002 Modell and Darr described from their research that recessively inherited congenital diseases are highly present in consanguineous families[12].There is an increased probability rate of recessive disorder causing alleles (variants) being inherited from both maternal and paternal lineages in the off springs of consanguineous families[13].Consanguineous families ratio is high in Pakistan have high prevalence of congenital ID[14]. Upto now only 4 loci has been identified in Pakistani peoples for ARNSID, these are (MRT13/TRAPPC9) on chromosome 8th, (MRT14) on chromosome 2nd, (MRT15) and(MRT16) on Chromosome 9th. On the bases of these facts we needed more work to illustrate ID and epilepsy in Pakistani peoples. This study was done on three ID families having consanguinity among parents and their selection was done under a define criteria. All the Intellectual disable infamily-1 having the characteristics of same phenotype with the presence of epileptic attacks of seizures, In this family exome sequencing was done for V:5 which is denoted by IDP.F110-ID03-10491.Av5. After exome sequencing different qualities of mutations were obtained. Mutation in AP4B1 gene was found to be responsible for intellectual disability in this family.

In ID family-2 all the patients had the same phenotype characteristics without epilepsy history as of ID family-1. In this family there were four ID patients, all were male. Exome sequencing was done for V:4 which is denoted by IDP.F111-ID04-10499.Av5.Exome sequencing by manual method revealed different qualities of mutations. On sequencing analysis the involved gene on chromosome 19 of individual V: 4 was WDR62

its function was exonic. Amino acid changes were found on exon11. In different studies WDR62 gene was matched with the gene responsible for intellectual disability and was identified in mutation analysis of patients with microcephaly and cortical abnormalities[15].

In case of ID family-3 the patients were two males having the same characteristics phenotypically i.e. ID associated with epilepsy. There were no other symptoms of associated abnormalities like short stature or spastic paraplegia. In ID family-3 we didn't find any putative mutation gene. The design of this study was to identified the mutant genes which responsible in causing intellectual disability in KPK Pakistani families affected with ARNSID and prevalence of epilepsy with Autosomal recessive intellectual disability. The study of exome sequencing of the families having Intellectual disability have allot of benefits. It will helps in identification of the disease responsible regions on genome and cloning of the localized genome segments. This will helpful in the controlling of the disorder transmission in to the offspring's by genetic counseling & information's about the carrier status of their normal members in the ID families. It will also help in maintain the genotype-phenotype correlations.

CONCLUSION

This study was conducted in 3 consanguineous ID families for the identification of the responsible mutant genes for ID disorder. In which two families patients were positive for epilepsy, ie ID family1 and ID family2.Exome sequencing showed mutations in (AP4B1) and (WDR62) in two out of three families. In third family we could not locate any putative mutation. The prevalence of epilepsy indentified in this study was slightly higher in ID patients compare with other population, Wide range of testing offers should be provided to find out the carrier status before marriage and also preconception counseling should be provided, this can guides the people in making their positive decisions since we know that consanguineous marriages are favored in a substantial number of people in this region, as well as the proper and early treatment for the ID and epileptic children's.

REFERENCES

1. C. Bowley, M. Kerr,Epilepsy and intellectual disability
J Intellect Disabil Res, 44 (5) (2000), pp. 529-543
View Record in ScopusGoogle Scholar,
2. J. Corbett, Epilepsy and mental retardation
E.R. Reyonds, M.R. Trimble (Eds.), Epilepsy and psychiatry, Churchill Livingstone, Edinburgh (1981)p. 138–46,Google Scholar
3. S.A. Richardson, H. Koller, M. Katz, A functional classification of seizures and its distribution in a mentally retarded population
Am J MentDefic, 85 (1981), pp. 457-466, View Record in ScopusGoogle Scholar
4. L. Forsgren, S.-
O. Edvinsson, H.K. Blomquist, J. Heijbel, R. Sidenvall. Epilepsy in a population of mentally retarded children and adults
Epilepsy Res, 6 (1990), pp. 234-238, View Record in ScopusGoogle Scholar
5. S.D. Lhatoo, J.W.A.S. Sander
The epidemiology of epilepsy and learning disability, Epilepsia, 42 (Suppl. 1) (2001), pp. 6-9
View Record in ScopusGoogle Scholar
6. Organization WH. Geneva: World Health Organization; 1992. International Classification of Diseases, 10th Revision. 1994;1.
7. Leonard R, Alison L. Critical incident stress debriefing and its effects on coping strategies and anger in a sample of Australian police officers involved in shooting incidents. Work & Stress. 1999;13(2):144-61.
8. Beirne-Smith M. Mental Retardation: An Introduction to Intellectual Disability Author: Mary Beirne-Smith, James R. Patton, Sh. 2015.
9 Prasher, VP, Kerr MP. (2008). Epilepsy and Intellectual Disabilities. Springer
10 Doran Z, Shankar R, Keezer M, Dale C, McLean B, Kerr M et al. Managing anti-epileptic drug treatment in adult patients with intellectual disability: a serious conundrum European Journal of Neurology 2016;23: 1152–1157 doi: 10.1111/ene.13016 [PubMed] [Google Scholar]
11 Sangani M, Shahid A, Amina S, et al. Improvement of myoclonic epilepsy in Down syndrome treated with levetiracetam. Epileptic Disord 2010;12:151–154. [PubMed] [Google Scholar]
12 Lefter S, Costello DJ, McNamara B, et al. Clinical and EEG features of seizures in adults with down syndrome. J Clin Neurophysiol 2011;28:469–473. [PubMed] [Google Scholar]
13 Shankar R, Cox D, Jalihal V, Brown S, Hanna J, McLean B (2013) Sudden unexpected death in epilepsy (SUDEP): Development of a safety checklist. Seizure 22:812–817.
14 Bowley C, Kerr M. (2000). Epilepsy and intellectual disability. J Intellect Disabil Res 44(Pt 5):529-543.
15 Rothner AD. (1989). 'Not everything that shakes is epilepsy'. The differential diagnosis of paroxysmal nonepileptiform disorders. [Review]. Cleveland Clinic Journal of Medicine, 56 Suppl Pt 2:S206-S213.
16 Lawyer, Liz (2010-11-26). "Rosa's Law to remove stigmatized language from law books". Ithaca, New York: The Ithaca Journal. Retrieved 2010-12-04. The resolution ... urges a change from the old term to "developmental disability"
17 Hussain R, Bittles A. The prevalence and demographic characteristics of consanguineous marriages in Pakistan.Journal of biosocial science. 1998;30(02)
18 Global Burden of Disease Study 2013, Collaborators (5 June 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". Lancet (London, England).PMID 26063472.
19 Cooney G, Jahoda A, Gumley A, Knott F (June 2006). "Young people with intellectual disabilities attending mainstream and segregated schooling: perceived stigma, social comparison and future aspirations". J Intellect Disabil Res 50 (Pt 6): 432–44.doi:10.1111/j.1365-2788.2006.00789.x. PMID 16672037.