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Letter to Editor

Molecular Genetics of Primary Microcephaly in Kashmiri Families from Pakistan: An Over view

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Letter to Editor

Microcephaly is an autosomal recessive neuro developmental disorder in which affected individual characterized by microcephaly present at birth and non-progressive mental retardation. In primary microcephaly, head circumference of the affected person shows variation from >3S D in normal population and in very rare cases non progressive mental retardation seen in affected individual [1-2]. Primary microcephaly is due to mutations in at least twelve lociat autosomal chromosome, which result in different phenotypes [3]. Persons with primary microcephaly have reduced skull consequently smaller brain but brain a architecture is quite normal as in normal person, the darker portion of brain (Gray matter)remain greatly preserved due to which no neurological abnormalities had seen such as abnormal muscle reflex, inability in speaking etc., but mild to severe mental retardation had been observed [4]. Recently it is identified that mutation in a new geneisal so involved in causing dominant microcephaly named as kinesine family member 11 (*KIF11*) which is reported in 16 families worldwide. It is firmly believed that due to mutations in the segenes ultimately lead to following consequences like in term it tent mitotic spindle fibers, transcriptional regulation, premature condensation, DNA aberration and many other problems which are not visible yet [5].

To date there are 12loci (MCPH1-MCPH12) have been identified in different populations and has following genes: *Microcephalin* (MCPH-1), *WDR62* (MCPH2), *CDK5RAP2* (MCPH3) *CASC5* (MCPH4), *ASPM* (MCPH5), *CENPJ* (MCPH6), *STIL* (MCPH7), *CEP135* (MCPH8), *CEP152* (MCPH9), *ZNF335* (MCPH10), *PHC1* (MCPH11), and *CDK6* (MCPH12) [3,9]. Role of *ASPM* and *WDR62* gene mutation in MCPH worldwide is slightly more than50 percent [6].

The Current Clinical Meaning of MCPH is as Per the Following:

A: A Head Boundary (HC) less than 3 SD underneath the age-and sex-coordinated means

B: Intellectual impairment that is not identified with a neurological finding, for example, spasticity or dynamic psychological decrease and

C: Most MCPH patients are of a typical tallness, weight and appearance and have ordinary chromosome investigation and brain scan results [7].

The one exception seen in patients with changes in the *microcephalin* gene that have a clinically characterized short stature and irregular chromosome investigation results [8]. In specific population event of autosomal recessive primary microcephaly is regular with approximations that ranges between 1:3 out of 10 000 and 1:2 out of 1000 000 yet in population the assessed prevalence is upto1:10 000 [10].

In the present study, two Kashmiri families with autosomal recessive primary microcephaly were found and contemplated by me (MCP-I and MCP-II). Both families were Hindko speaking and settled in remote areas of Muzaffarabad. In each family two to four affected members were included in the present study. Microsatellite markers were used in genotyping for these two families respectively. Family MCP-I showed linkage at *ASPM* gene with D1S3470 (204.51cM), D1S1614 (209.15 cM) and D1S3468 (205.40cM) markers. Family MCP-II showing no linkage on any known locus by using the homozygosity mapping tool. It might be possible any novel gene could be responsible for this phenotype. Current study shows the involvement of hereditary components in MCPH.

The identified locus in family-I, is a new target for mutation screening and gene finding, however the identified *ASPM* (Abnormal Spindle-Like Primary Microcephaly) is important

for the normal functioning of the mitotic spindle in embryonic neuroblasts harboringMCPH5 locus. The high odds of MCPH in Azad Jammu and Kashmir are because of exceptionally normal consanguineous relational unions. The most widely recognized reason for microcephaly in Azad Jammu and Kashmir is first cousin marriage. In Pakistan there is high rate (62.7%) of consanguinity and it is a significant burden of autosomal recessive disorders including primary microcephaly. Identification of inherited reasons of primary microcephaly in the studied families may allow genetic screening and genetic counseling to reduce the number of affected individuals born by the marriages among carriers of the same genes.

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