

Molecular aberration studies in cases of idiopathic mental retardation: An update

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Intellectual disability (ID), also known as mental retardation (MR) is a multifactorial disorder. It can be caused by prenatal, perinatal, and postnatal factors. Prenatal causes account for approximately 60-80% of the etiological factors, may be genetic or nongenetic, and rest 20-40% may be environmental factors. Genetic causes which include chromosomal and nonchromosomal account for 17.4-47.1% of cases, with reported frequencies varying even on the basis of the different techniques used for the analysis. Chromosomal disorders include Down syndrome, various forms of trisomy, deletion syndromes (Cat-cry, Prader-Willi, Angelman) and single gene disorders (fragile X syndrome and Rett syndrome). Nonchromosomal genetic conditions include inborn errors of metabolism (IEMs) and some structural brain abnormalities.

In the present issue of the journal, Neetha *et al.*,^[1] have reported the detection of submicroscopic chromosomal abnormalities in 122 cases of mental retardation using multiple ligation-dependent probe amplification (MLPA) methods in their cohort of patients. Authors have successfully identified six chromosomal imbalances altogether. Even though the results are encouraging, detecting only the known aberrations is a major technical limiting factor.

Although the study title indicates the focus on

idiopathic mental retardation, they have included mixed population of syndromic and idiopathic cases with/without congenital anomalies. It is already well documented that the chromosomal abnormalities are higher in cases of MR associated with congenital anomalies and dysmorphic features. Authors have used conventional karyotyping in the samples of their study group. However, conventional karyotyping is unable to detect imbalances smaller than 3-5 Mb. It would be appropriate to use high resolution karyotyping. Authors have also carried out fragile X screening by analyzing CGG repeat size for exclusion fragile X syndrome cases. However, there exists a possibility that their cohort may have some cases of Rett syndrome which is the second most common cause of MR in females. Rett syndrome is a single gene disorder having mutations in MECP2 and CDKL5 genes. Our group has published the spectrum of mutations in MECP2 gene^[2] and various novel and known mutations in CDKL5 gene^[3] reported for first time in India.

Of the 122 cases, only 11 patients (9%) were found to be positive using MLPA by the authors. This low frequency can be attributed to the use of MLPA which detects only known aberrations. There exists a likelihood of the presence of imbalances in the regions, other than those investigated by the authors. Another flaw of the study is that authors did not confirm whether the aberrations detected were *de novo* or inherited. A clinically relevant aberration need to be confirmed through testing in the parents of the affected patients. Authors should have validated their observations by polymerase chain reaction (PCR) or fluorescent *in situ* hybridization (FISH). Further deletions reported appear to be heterozygous; however, authors have failed to mention it.

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There is a need to validate heterozygosity of these deletions by FISH. Genotype-phenotype correlations especially with reference to head circumference is important in MR.

Molecular abnormalities including those reported by Neetha *et al.*, may arise either due to copy number variation (CNV) or due to copy number polymorphism (CNP). These CNPs may not have effect on phenotype. To rule out that the genetic imbalances were not CNPs, statistically valid number of control population should have been genotyped or compared the clinical features of previously reported patients with similar rearrangements.

The authors have rightly mentioned in their concluding remark that the advent of microarray technology heralded identification of cryptic and interstitial chromosome imbalances. Microarrays techniques such as array-comparative genomic hybridization (array-CGH) revealed submicroscopic aberrations in 5-17% of MR patients which appeared normal as per conventional cytogenetic testing. Higher-density platforms (such as single nucleotide polymorphism array (SNP array) enable more sensitive diagnosis by detecting additional 6% of cases.^[4]

In conclusion, detection of molecular abnormalities requires a combination of strategies. A variety of robust high throughput and sensitive techniques need to be

used to unravel the contribution of genetic factors to its pathology. In future, identification of the major players and the pathways mediated by those will help in understanding the disease pathogenesis and progression of mental retardation.

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