De novo paradigm: the ultimate answer to the paradox in mental retardation?

K Huang

The Centre for Molecular Medicine and Therapeutics, 980 28th Avenue West, Vancouver, BC V5Z 4H4, Canada.
e-mail: khuang@cmmt.ubc.ca

A de novo paradigm for mental retardation
Vissers et al. (2010)
Nature Genetics 42:1109−1112

Almost 3% of the general population suffers from mental retardation (MR) which represents one of the most difficult challenges faced today by clinicians, geneticists as well as our social system (1). Apparently, large genetic contribution to the etiology of mental retardation presents a formidable puzzle. Unlike common physical disorders, mental retardation is associated with substantial reproductive disadvantage. Therefore, genetic variants associated with susceptibility to mental retardation should be diminished in the genetic pool through strong negative selection (2). However, mental retardation is still common in the population.

Several theories have been proposed to explain the paradox of high heritability and reproductive disadvantage associated with the same common phenotype, but none provides a satisfactory explanation for all types of neurodevelopmental and neuropsychiatric illnesses (3−7). One emerging hypothesis is spontaneous germline mutations, which may affect functionally important bases and cause serious phenotypic consequences (2, 7). In agreement with this idea, de novo copy number variations are a known cause of schizophrenia, autism and mental retardation (8−10). This hypothesis is appealing because humans have exceptionally high per-generation mutation rate. De novo mutations can occur at any point from germline stem cell stage to postnatal growth (11) (Fig. 3). An average newborn is estimated to acquire 50−100 new mutations in his or her genome (12, 13). The occurrence of spontaneous mutations may explain why diseases with a severely reduced fecundity such as severe mental retardation remain frequent in the population.

How do we know which genes are mutated de novo in mental retardation? The power of traditional positional cloning to identify disease gene is limited (14). The emergence of next-generation sequencing techniques (i.e. whole-genome, whole-exome and whole-transcriptome sequencing) allows substantial advances in identifying genetic alterations. In theory, whole-genome sequencing of all human genes for discovery of genetic variants could potentially identify the gene underlying any given monogenic disease. However, the cost associated with sequencing the whole genome in many is still significant. An alternative approach, exome sequencing, involves the targeted resequencing of all protein-coding regions, which only requires approximately 5% as much sequencing as a whole-human genome (15−17).

To investigate the genetic basis for unexplained mental retardation, Vessers et al. used a family-based exome sequencing approach to identify de novo mutations in children with otherwise normal karyotype and array-based genome profiling. Whole-exome sequencing was performed on 10 children with unexplained mental retardation and on their parents. An average of 21,755 genetic variants was found per individual, which was reduced to 5640 by exclusion of all non-genic, intronic and synonymous variants. These variants were further filtered by excluding known and likely benign ones, firstly by comparing with SNP databases to exclude common variants, and secondly by comparing with the parents’ genomes to exclude inherited variants. Following this process and validation by Sanger sequencing, nine candidate-causal mutations remained and were assessed for their likely biological function and impact (Fig. 4).

A comprehensive literature review and bioinformatics analysis was carried out on these
nine candidate-dominant mutations. All de novo mutations occurred in different genes, including RAB39B and SYNGAP1, the two genes recently implicated in mental retardation (18, 19). Another identified variant in a known X-linked mental retardation gene, JARID1C (20), was inherited from the mother of this proband. However, such mutation had occurred de novo in the mother as the maternal grandparents do not have this variant. On the basis of gene function, evolutionary conservation and likely mutational impact, a final of six variants were proposed to be pathogenic. These findings provide strong experimental support for the importance of novel genetic variants arising de novo in the etiology of severe mental retardation.

This study also provides an excellent example of the application of whole-exome sequencing to identify genetic alterations that may underlie diseases. The analysis pipeline described in Ref (21) and Fig. 4 has implications for both preventive screening and diagnostic approaches in diseases with a strong heritable component. As more and more comprehensive databases of genomic variation and functional assays are developed, exome sequencing is likely to be increasingly fruitful and applicable in medicine.

References