Editorial: Sub-molecular mechanism of genetic epilepsy

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Proteins are the essential functional molecule in living organisms. A protein is featured by finely structured domains, which are encoded by genetic sequences. Variants in a gene potentially result in functional alteration of the protein and thus cause diseases. From the perspective of molecular structure, the different domains of a protein play distinct roles. Variants of different locations are thus potentially associated with various damaging effects and subsequently lead to phenotypical variation. Similarly, the bio-physical feature of the substituted amino acids caused by variants is also a determinant of the damaging effect. Such submolecular implication would be a critical factor in determining the pathogenicity of variants.

More than 4,000 genes have been associated with human diseases (https://omim.org/). A gene could be associated with a distinct phenotype, but in the majority of circumstances, it is associated with a spectrum of phenotypes that are varied in severity or other aspects, for which the underlying mechanism is mostly unknown. Previously, sub-molecular implications have been demonstrated to be a determinant of phenotypical variation in several molecules, such as sodium channel Nav1.1 (SCN1A) (Meng et al., 2015; Tang et al., 2020), tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein gamma (YWHAG) (Ye et al., 2021), and disheveled Egl-10 and pleckstrin domain-containing protein 5 (DEPDC5) (Liu et al., 2020).

The present Research Topic is dedicated to exploring the Sub-molecular Mechanism of Genetic Epilepsy and providing novel perspectives to understanding of the mechanisms underlying the phenotypical variation of genetic diseases. The sub-molecular implications of genetic variants are disclosed in terms of six aspects in this collection.
Functional domain and sub-molecular implication

Shu et al. identified four de novo missense MAST3 variants from four patients with heterotopic neurodevelopmental disorders (NDD), including two with intellectual disability (ID) and epilepsy and two with ID and autism spectrum disorders (ASD). They created a mast3a/b knockout zebrafish model and observed abnormal morphology of the central nervous system. The results support the possibility that MAST3 is a novel gene associated with NDD. Additionally, ASD-related missense variants presented higher frequencies in the DUF domain, while epilepsy-related variants exhibited higher frequencies in the STK domain, suggesting a sub-regional effect.

Bian et al. identified six hemizygous missense SHROOM4 variants from six cases with epilepsy without ID. The SHROOM4 gene was previously reported in patients with the Stocco dos Santos type X-linked syndromic intellectual developmental disorder (SDSX) (Hagens et al., 2006). The SDSX-related variants reported were mostly destructive or duplicative variants, while the epilepsy-related variants were all missense variants located around the N-terminal PDZ domain and the C-terminal ASD2 domain, indicating a molecular sub-regional effect.

Zou et al. identified five hemizygous missense AFF2 mutations from five males with partial epilepsy and antecedent febrile seizures without intellectual disability or other developmental abnormalities. The AFF2 gene is previously reported to be associated with X-linked intellectual developmental disorder 109 and ASD (Stettner et al., 2011). The ID-associated AFF2 mutations were mostly genomic rearrangements and CCG repeats expansion mutations that caused gene silencing, whereas the mutations associated with epilepsy or ASD were all missense, suggesting the correlation between the phenotype and variant type. Furthermore, epilepsy-relative AFF2 variants fell into the regions from N-terminal to the nuclear localization signal 1 (NLS1), while ASD-associated missense mutations were located in the regions from NLS1 to C-terminal, suggesting a sub-region effect.

Li et al. identified 12 CACNA1A variants and analyzed the correlation between genotype and phenotype. This study suggested that CACNA1A mutations were potentially associated with a spectrum of epileptic phenotypes, ranging from mild absence epilepsy to severe developmental and epileptic encephalopathy (DEE). Further analysis revealed that: 1) episodic ataxic type 2 had a tendency of higher frequency of null variants than epilepsies; 2) the missense variants in severe epileptic phenotypes were more frequently located in the pore region than those in milder epileptic phenotypes; and 3) de novo variants in epilepsy were more frequently associated with ID.

A functional molecular unit may be a single molecule encoded by a gene or a molecular complex consisting of several proteins encoded by different genes. Previously, the A subunit of the V1 domain of V-ATPase encoded by ATP6V1A was associated with DEE-93 (Fassio et al., 2018). The ATP6V1C gene encoded the C subunit of the V0 domain of V-ATPase. Tian Y. et al. identified ATP6V1C as a novel causative gene for febrile seizures (FS) and epilepsy with febrile seizures plus (EFS+), providing a novel perspective of the functional domain and sub-molecular implication.

Substituted amino acid and sub-molecular implication

Su et al. focus on the relationship between the nature of substituted amino acids and functional alteration. They identified a novel missense SCN1A variant (c.4868A>C/p.E1613A) in the extracellular S3-S4 loop of Nav.1.1 from two cases with epilepsy. Functional studies were conducted on six mutants with all possible substitutions in the residue E1623. This study suggested the critical role of the S3–S4 loop in sodium channel function. Analysis of the correlation between the residue properties and electrophysiological alterations demonstrated that hydrophilicity of the side-chain at E1623 was potentially a crucial contributor to voltage-dependent kinetics, whereas the contributor to the channel conductance, which is closely associated with epileptogenesis, remains undetermined.

Isoforms and sub-molecular implication

Zhou et al. identified 12 ADGRV1 variants in nine unrelated cases with FS or EFS+. Previously, the ADGRV1 gene was reported to be associated with Usher syndrome (Weston et al., 2004). The authors reviewed all ADGRV1 variants and analyzed the genotype-phenotype correlations of the ADGRV1 variants in epilepsy and audio-visual disorders. This study showed that the epilepsy-related variants were monoallelic, missense, and mainly located at the CalX-β domain. Furthermore, the epilepsy-related variants mostly affected isoforms VLGR1b/1c, while the audio-visual-related variants were mainly affected isoforms VLGR1a, suggesting a potential role of isoform in phenotype variation.

Monoallelic and biallelic variants

Wang et al. identified eight pairs of compound heterozygous missense PKD1 variants in eight patients with FS or EFS+. Dominant PKD1 variants were reported to be associated with polycystic kidney disease (Roelfsema et al., 1997). Further analysis suggested that monoallelic mutations with haploinsufficiency of
PKD1 were potentially associated with kidney disease, compound heterozygotes with superimposed effects of two missense mutations were associated with epilepsy; whereas the homozygotes with complete loss of PKD1 would be embryonically lethal, suggesting monoallelic variant/biallelic variant was potentially a factor in determining phenotypical variation.

Locations of the two variants in a pair of compound heterozygous variant

Luo et al. identified six pairs of compound heterozygous missense LAMA5 variants in six unrelated infants with partial epilepsy and spasms. This article identified LAMA5 as a novel potential epilepsy gene. Interestingly, among the biallelic variants in cases with mild phenotype, two variants of each pair were located in different structural domains or domains/links, whereas in the cases with spasms (the severer phenotype), the biallelic variants were constituted by two variants in the identical functional domains, potentially suggesting a novel perspective on sub-molecular mechanisms.

Specific genotype and sub-molecular implication

Wang et al. identified six in-frame deletion variants in SCN1A and performed further functional analysis. The experiments showed the complete loss of function caused by the six in-frame deletion variants, emphasizing the damaging effect of in-frame deletion variants.

Truncated C-terminal region MN1 variants caused MN1 C-terminal truncation (MCTT) syndrome (Mak et al., 2020). Tian Q. et al. reported a novel C-terminal null MN1 variant (p.L1245fs) in a patient with mild developmental delay without structural brain abnormalities, expanding the clinical and genetic spectrum of MCTT.

In conclusion, this Research Topic provides novel perspectives on the mechanisms underlying phenotypical variation. Phenotypical heterogeneity is common in genetic disorders. We advocate further studies on the submolecular mechanism of genetic diseases beyond epilepsy, toward setting a submolecular stage of medicine.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

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