NEWS

Committee presents guidelines for variant reporting

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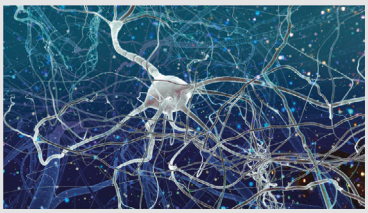
Accurately documenting genomic variation is central to genetics research and clinical care. However, not all published variants conform to the same standard for description. In response, the Human Variome Project assembled a committee to address the issue. In a recent article in *Human Mutation* (https://doi.org/10.1002/humu.24144), Higgins and colleagues outlined a set of guidelines for reporting sequence variants. The guidelines recommend that variants adhere to current criteria developed by the Human Genome Variation Society (HGVS), that nomenclature should be verified with tools such as Mutalyzer or VariantValidator, that authors should provide documentation demonstrating compliance with recommendations, and that editorial staff will review submissions for compliance, but that authors will be responsible for the accuracy of variant descriptions in their manuscripts. To determine the burden nomenclature requirements would place on authors and editorial staff, the team conducted a pilot project with *Human Mutation* and *Genetics in Medicine* (*GIM*). The committee found that more than half of initial submissions to *Human Mutation* over a 6-month period in 2019 that contained variant data included the validation file, as did nearly all manuscripts under revision (87%) that reported variants. At *GIM*, only 18% of revised manuscripts received over a 3-month period in 2019 had variant data (35/193), but all included a variant file. The pilot project determined that most editorial office staff were unable to assist authors when nomenclature errors were found. Instead, the database administrators, who were part of the committee, suggested that editorial office staff should direct authors to their websites FAQ to resolve common warning messages and that if further clarification was needed, the authors should contact the database administrators directly. Finally, in an effort to correct existing nomenclature errors in an ongoing manner, the committee decided that all variants in a manuscript should be verified, regardless of whether they have been reported previously. Altogether, the committee found that the requirements should not place excessive burden on editorial staff or authors. They indicate that the minor bump in workload is a reasonable step toward standardizing the global inventory of human variation, where increased accuracy makes up for the additional effort. The committee concluded that adopting these minimal requirements across journals that often report disease-related variants will greatly improve the quality of variant description in the molecular and medical genetics literature. —*V. L. Dengler, News Editor*

Calcium signaling deficit may point to new therapies for 22q11.2 deletion syndrome



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Patients with 22q11.2 deletion syndrome (22q11DS), the most common genetic deletion in humans, are at increased risk for autism spectrum disorder and schizophrenia. Although rodent models have provided insights into circuit dysfunction, human neuronal phenotypes are less well described. In a recent article published in *Nature Medicine* (https://doi.org/10.1038/s41591-020-1043-9), Khan and colleagues show that defects in calcium signaling lead to spontaneous neuronal activity in cells derived from 22q11DS patients and that antipsychotic drugs rescue the defect, pointing toward potential therapeutic avenues. The researchers first generated human induced pluripotent stem (hiPS) cells from 15 22q11DS patients and 15 controls and then derived three-dimensional human cortical spheroids (hCSs) on which they performed transcriptional profiling over 100 days of differentiation. The analysis uncovered enrichment for genes involved in neuronal excitability, calcium signaling, and resting membrane potential (RMP). The results prompted the researchers to investigate the electrophysiological properties of cortical neurons. They performed cell-attached and whole-cell patch-clamp recordings in dissociated hCS neurons and found that 22q11DS cells were about four times more likely to spontaneously fire action potentials than control cells. When the team examined intracellular calcium levels in dissociated 22q11DS hCS neurons, they saw that following depolarization, intracellular calcium levels did not rise to the same amplitude as that in controls. A follow-up measurement of RMP revealed that patient-derived neurons were more depolarized. The researchers next assessed a role for *DGCR8*, a gene that is deleted in 22q11DS and associated with neuronal defects in rodent models of the disease. The team found that, compared with controls, *DGCR8*$^{+/-}$ neurons were also more likely to fire action potentials, had intracellular calcium levels that did not rise to the same amplitude after depolarization, and were more depolarized. Overexpressing *DGCR8* increased the amplitude of intracellular calcium rise following depolarization in hCS neurons differentiated from 22q11DS patients and hyperpolarized the membrane potential of 22q11DS neurons by approximately 7 mA. Finally, the researchers exposed 22q11DS cells to raclopride, a high-affinity dopamine D2 receptor blocker and antipsychotic. The treatment restored the intracellular calcium-rise deficit following depolarization and reduced the fraction of spontaneously firing 22q11DS neurons. The researchers confirmed the effects with two other antipsychotic drugs. Altogether, the work uncovers significant neuronal phenotypes in 22q11DS, according to the authors, and identifies potential therapeutic approaches. —*V. L. Dengler, News Editor*

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