GeNeDit

NGS – From the Womb to the Tomb

Editorial

Deoxyribonucleic acid (DNA) molecules inside each nucleus of a living cell are the musical instruments of the orchestra of life. The loss of any key of an accordion or breaking of a string of a sitar can disturb the melody of life. Now we have the technology to detect defects in any of the 3 billion keys as easily as looking at the facial features or palmar dermatoglyphics. Repairing the defective keys by gene therapy also has become possible. Next-generation sequencing (NGS)-based diagnostics for monogenic disorders has revolutionized the field of medicine. The contribution of monogenic causes to diseases in human beings is becoming clearer and the list of monogenic disorders is increasing every month. These disorders manifesting at any age have varied presentations and accurate genetic diagnosis is of utmost importance due to the possibility of targeted therapy and implications for the family. NGS-based testing is the first-tier test for many clinical presentations.

One dramatic presentation of monogenic disorders is sudden death, which may be in utero or in a child or an adult. Intrauterine fetal demise of a well supervised pregnancy is a shock to the family and a nightmare for the obstetrician. Genetic arrhythmias have been documented to be the causes in some cases of intrauterine fetal deaths bringing relief to the obstetrician and closure to the family. Sudden death of an adult or a child is not only an unbearable grief for the family but brings a wave of anxiety about the uncertainty of life. Everyone in the family will be worried whether this can be the fate of some more family members including self. The causes of sudden death, especially cardiomyopathies, arrhythmias and connective tissue disorders leading to rupture of aorta can be investigated by NGS-based testing, and identification of the causative genetic variant is useful for screening of family members and timely actions. The GenExpress in this issue mentions a study which has done NGS-based testing by a panel for channelopathies and cardiomyopathies on cases of unexplained sudden deaths. The diagnostic yield for definitely causative variants was less and many variations of uncertain significance were identified. The utility of diagnosis for the family by molecular autopsy is beyond doubt and guidelines for incorporation and interpretation of molecular testing in autopsy are needed.

NGS-based testing of fetal disorders, and carrier detection have been incorporated in reproductive genetics. NGS-based testing for newborn screening is being investigated under research mode. Though screening of all genes for serious disorders in one go is possible, the issues are the disorders to be chosen and variations of uncertain significance. It has been shown that NGS-based testing along with traditional newborn screening can be complementary to each other by reducing false positives and improving interpretation. Thus, in addition to diagnostics, NGS based testing is getting expanded to cover the whole length of life, from the womb to the tomb!

Dr. Shubha Phadke
1st April, 2022