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Postmortem Genetic Testing to Sudden and Unexpected Deaths Using the Next Generation Sequencing

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Abstract : Sudden and unexpected deaths from unknown causes occur in infants and youths. Recently, molecular links between a part of these deaths and several genetic diseases are examined in the postmortem. For instance, hereditary long QT syndrome and Burgada syndrome are occasionally fatal through critical ventricular tachyarrhythmia. There are a large number of target genes responsible for such diseases, the conventional analysis using the Sanger's method has been laborious. In this report, we attempted to analyze sudden deaths comprehensively using the next generation sequencing (NGS) technique. Multiplex PCR to subject's DNA was performed using Ion AmpliSeq Library Kits 2.0 and Ion AmpliSeq Inherited Disease Panel (Life Technologies). After the library was constructed by emulsion PCR, the amplicons were sequenced 500 flows on Ion Personal Genome Machine System (Life Technologies) according to the manufacture instruction. SNPs and indels were analyzed to the sequence reads that were mapped on hg19 of reference sequences. This project has been approved by the ethical committee of Tokai University School of Medicine. As a representative case, the molecular analysis to a 40 years old male who received a diagnosis of Brugada syndrome demonstrated a total of 584 SNPs or indels. Non-synonymous and frameshift nucleotide substitutions were selected in the coding region of heart disease related genes of ANK2, AKAP9, CACNA1C, DSC2, KCNQ1, MYLK, SCN1B, and STARD3. In particular, c.629T-C transition in exon 3 of the SCN1B gene, resulting in a leu210-to-pro (L210P) substitution is predicted "damaging" by the SIFT program. Because the mutation has not been reported, it was unclear if the substitution was pathogenic. Sudden death that failed in determining the cause of death constitutes one of the most important unsolved subjects in forensic pathology. The Ion AmpliSeq Inherited Disease Panel can amplify the exons of 328 genes at one time. We realized the difficulty in selection of the true source from a number of candidates, but postmortem genetic testing using NGS analysis deserves of a diagnostic to date. We now extend this analysis to SIDS suspected subjects and young sudden death victims.

Keywords : postmortem genetic testing, sudden death, SIDS, next generation sequencing
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