Legal Medicine 16 (2014) 61–69

Contents lists available at ScienceDirect

Legal Medicine

journal homepage: www.elsevier.com/locate/legalmed

# Forensic molecular pathology: Its impacts on routine work, education and training ☆

Hitoshi Maeda [a,b,*], Takaki Ishikawa [a,b,c], Tomomi Michiue [a,b]

[a] Department of Legal Medicine, Osaka City University Medical School, Asahi-machi 1-4-3, Abeno, 545-8585 Osaka, Japan
[b] Forensic Autopsy Section, Medico-legal Consultation and Postmortem Investigation Support Center (MLCPI-SC), c/o Osaka City University Medical School, Asahi-machi 1-4-3, Abeno, 545-8585 Osaka, Japan
[c] Division of Legal Medicine, Faculty of Medicine, Tottori University, 86 Nishi-cho, Yonago, 683-8503 Tottori, Japan

ARTICLE INFO

*Article history:*
Received 25 December 2013
Accepted 7 January 2014
Available online 17 January 2014

*Keywords:*
Forensic pathology
Omic science
Molecular biology
Pathophysiology of death
Violent death
Molecular autopsy

ABSTRACT

The major role of forensic pathology is the investigation of human death in relevance to social risk management to determine the cause and process of death, especially in violent and unexpected sudden deaths, which involve social and medicolegal issues of ultimate, personal and public concerns. In addition to the identification of victims and biological materials, forensic molecular pathology contributes to general explanation of the human death process and assessment of individual death on the basis of biological molecular evidence, visualizing dynamic functional changes involved in the dying process that cannot be detected by morphology (pathophysiological or molecular biological vital reactions); the genetic background (genomics), dynamics of gene expression (up-/down-regulation: transcriptomics) and vital phenomena, involving activated biological mediators and degenerative products (proteomics) as well as metabolic deterioration (metabolomics), are detected by DNA analysis, relative quantification of mRNA transcripts using real-time reverse transcription-PCR (RT-PCR), and immunohisto-/immunocytochemistry combined with biochemistry, respectively. Thus, forensic molecular pathology involves the application of omic medical sciences to investigate the genetic basis, and cause and process of death at the biological molecular level in the context of forensic pathology, that is, 'advanced molecular autopsy'. These procedures can be incorporated into routine death investigations as well as guidance, education and training programs in forensic pathology for 'dynamic assessment of the cause and process of death' on the basis of autopsy and laboratory data. Postmortem human data can also contribute to understanding patients' critical conditions in clinical management.



**Contents**



☆ Modified from an invited lecture presented in the session of the European Academy of Legal Medicine (EALM) at the 22nd Congress of the International Academy of Legal Medicine (IALM), 2012, Istanbul.

* Corresponding author at: Department of Legal Medicine, Osaka City University Medical School, Asahi-machi 1-4-3, Abeno, 545-8585 Osaka, Japan. Tel.: +81 6 6645 3765; fax: +81 6 6634 3871.
*E-mail address:* legalmed@med.osaka-cu.ac.jp (H. Maeda).

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http://dx.doi.org/10.1016/j.legalmed.2014.01.002

## 1. Background

As part of forensic/legal medicine, the major role of forensic pathology is investigating human death in relevance to social risk management to determine the cause and process of death, especially in violent and unexpected sudden deaths, which involve social and medicolegal issues of ultimate, personal and public concerns. Forensic pathologists have the task to respond to social requests through reliable interpretation of these issues in routine casework on the basis of research activities to develop, improve and sophisticate the procedures as well as to establish an autopsy database within the framework of social and legal systems. While classical morphology remains a core procedure to investigate deaths, updated forensic pathology involves the application of medical sciences. Making full use of the available procedures, systematic investigations are needed for comprehensive assessment of pathological findings; thus, a spectrum of ancillary procedures have been developed and incorporated to detail the pathology (Table 1) [1–30]. DNA and RNA analyses contribute to the identification of victims and biological materials as well as diagnosis of genetic disorders and microbiological investigation of infectious diseases, and can be applied to the identification of foreign biological substances in drowning and aspiration; genetic analysis is referred to as 'molecular autopsy' [12,13]. Furthermore, in addition to postmortem biochemistry, experimental and practical investigations using molecular biological procedures in the context of forensic pathology (molecular forensic pathology) have suggested the potential usefulness of detecting dynamic functional changes involved in the dying process that cannot be detected by morphology, which may be termed pathophysiological or molecular pathological vital reactions, demonstrated by 'advanced molecular autopsy' [6,13]. These updated procedures, namely, forensic molecular pathology, may effectively be included in routine casework as part of forensic laboratory investigations in combination with postmortem diagnostic imaging procedures to detect morphological changes *in situ* before or at autopsy alongside conventional morphological and chemical procedures for comprehensive assessment; coordination of the autopsy system is needed in relevance to social situations and legal systems [6,13,30,31]. The background and present state of casework and research work exhibit substantial variation globally; however, international exchanges of these updated procedures are important to ensure an innovative future for forensic medicine all over the world to meet existing social requirements.

## 2. Concept

Fatal insults cause: (a) immediate damage to tissues/viscera and/or (b) serial functional changes involving alterations in mRNA transcription under genetic controls, followed by synthesis of biological mediators and modification of cell/tissue components, leading to deterioration of cellular, local tissue/visceral and systemic structures. Major procedures of forensic pathology include: (a) macropathology and histology/cytology to examine structural alterations, and (b) molecular pathology to detect alterations of the components. Forensic molecular pathology involves laboratory work to investigate the genetic basis, causes and process of death at a biological molecular level in the context of forensic pathology for increased sophistication of analyses of postmortem evidence as part of forensic laboratory systems. This consists of: (a) local molecular pathology at the site of insult, and (b) systemic molecular pathology to analyze whole-body pathophysiology leading to death (Table 2) [13]. The purpose is to visualize molecular evidence, which represents dynamic functional/structural changes in major viscera/tissues after insults, (a) for a general explanation of the human death process involving forensic issues as well as (b) for the assessment of individual death. This is a new challenge in forensic research toward innovation of forensic pathology in the coming decades, for which cooperative developments in guidance, routine work, research, education and training through international exchanges should be considered.

## 3. Methodology

In forensic molecular pathology to investigate the cause and process of death, (a) the genetic background (genomics; conventional 'static' molecular biology), (b) dynamics of gene expression (up-/down-regulation: transcriptomics; 'dynamic' molecular biology) and (c) vital phenomena, involving activated biological mediators and degenerative products (proteomics) as well as metabolic deterioration (metabolomics), are detected by means of (a) DNA analysis, (b) relative quantification of mRNA transcripts using real-time reverse transcription-PCR (RT-PCR), and (c) immunohisto-/immunocytochemistry combined with biochemistry, respectively. These procedures are used in cases in the early postmortem period without evident decomposition; however, the status of forensic materials available at autopsy involves (a) preexisting pathology before insults, (b) alterations in the death process (agony) after insults, including specific findings and unspecific changes, and (c) postmortem changes or artifacts (Fig. 1) [6,13]. Thus, various antemortem and postmortem factors can interfere with the analytical data, in terms of characterizing biochemical and molecular biological profiles at autopsy [6,13]. These conditions are not specific to molecular pathology but are inevitable and partly unpredictable in all postmortem procedures; the interference should be assessed by comprehensive data analysis, including histology and biochemistry. These procedures may also contribute to estimating the time of death or the time since death, which is another major interest in forensic pathology.

**Table 1**
Updated ancillary procedures in forensic pathology.

| |
|---|
| Radiology before autopsy |
| Laboratory investigation and data analyses, following autopsy and sample collection: |
| microbiology, serology, |
| immunohisto-/immunocytochemistry, |
| biochemistry, molecular biology, |
| CT/radiological data analysis, and genetics |