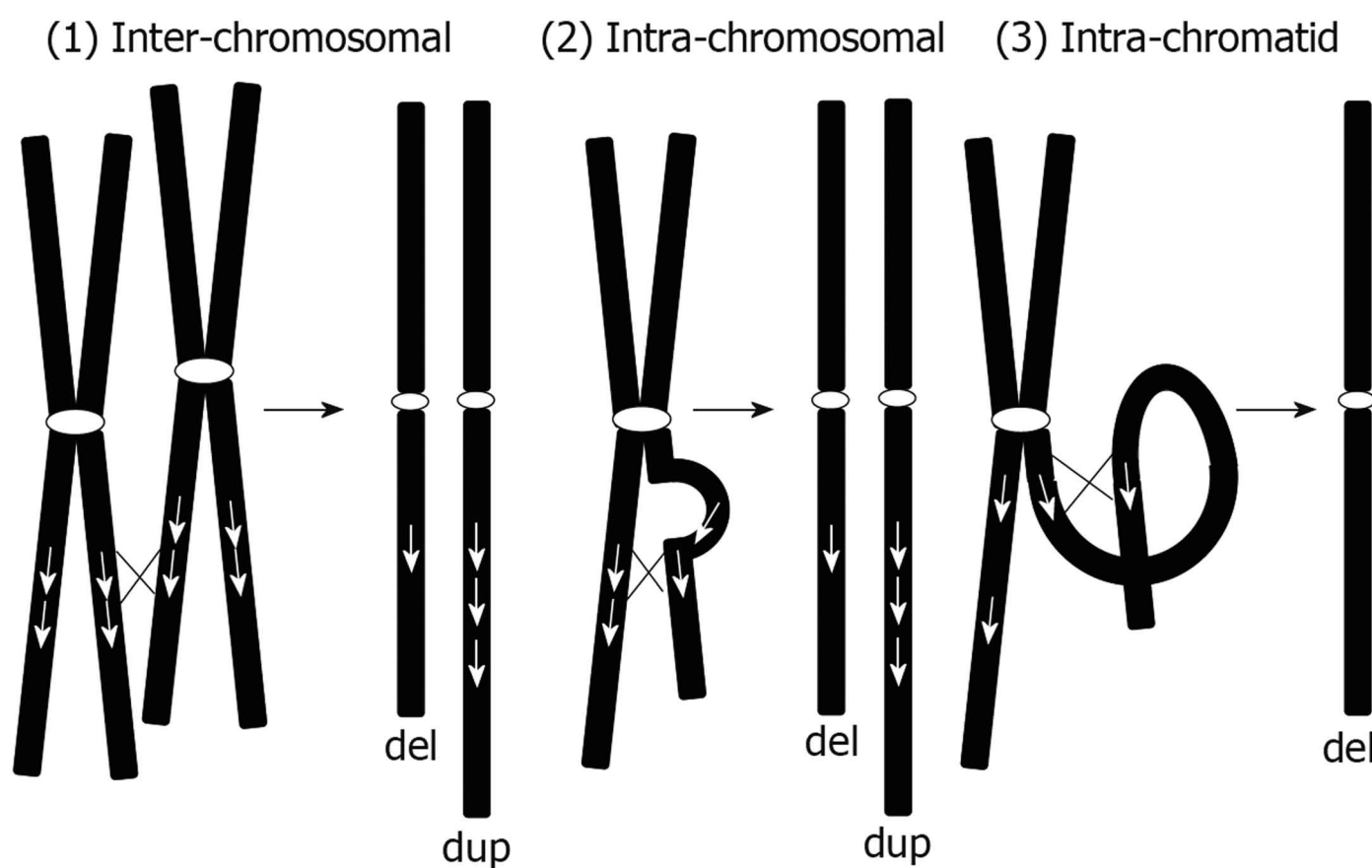


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Fiber-fluorescence *in situ* hybridization analyses as a diagnostic application  
for orientation of microduplications

*Yamamoto T, Shimada S, Shimojima K*

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## Fiber-fluorescence *in situ* hybridization analyses as a diagnostic application for orientation of microduplications

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and triplicated segments of chromosomes. Previously, we reported that interstitial duplications were aligned in tandem configurations, supporting the hypothesized mechanism of non-allelic homologous recombination; however, there were rare cases of inverted duplications. Further analysis is therefore required to fully elucidate the basic mechanisms underlying such duplications/triplications.

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### Abstract

Microduplications are normally invisible under microscopy and were not recognized before chromosomal microarray testing was available. Although it is difficult to confirm the orientation of duplicated segments by standard fluorescence *in situ* hybridization (FISH), our data indicates that fiber-FISH analysis has the potential to reveal the orientation of duplicated and triplicated segments of chromosomes. Recurrent microduplications reciprocal to microdeletions show tandem orientations of the duplicated segments, which is consistent with a non-allelic homologous recombination mechanism. Several random duplications showed tandem configurations and inverted duplications are rare. Further analysis is required to fully elucidate the basic mechanisms underlying such duplications/triplications.

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**Key words:** Chromosomal microarray testing; Copy number variation; Fiber-fluorescence *in situ* hybridization; Microduplication; Tandem orientation

**Core tip:** Fiber-fluorescence *in situ* hybridization analysis has the potential to reveal the orientation of duplicated

### COMMENTARY ON HOT TOPICS

#### Background

Chromosomal microduplication is a type of chromosomal anomaly. Although several chromosomal duplications have been reported previously, small microduplications that were invisible under the microscope were not recognized before chromosomal microarray testing was available. The only known microduplications were those involving specific genes, such as the peripheral myelin protein 22 gene (*PMP22*) and the proteolipid protein 1 gene (*PLP1*). Previously, we knew that patients with *PMP22* mutations manifest Charcot-Marie-Tooth disease [Mendelian Inheritance in Man (MIM) #118220] and patients with *PLP1* mutations show Pelizaeus-Merzbacher disease (PMD; MIM #312080); microduplications of these genes were revealed under the hypothesis that copy number gain of these genes may be related to disease occurrence<sup>[1]</sup>. Before the availability of chromosomal microarray testing, a targeting system was used to detect such duplications, including fluorescence *in situ* hybridization (FISH), quantitative polymerase chain reaction (PCR) and multiple ligation probe amplification (MLPA) (Table 1).



It is possible to detect the numbers of the targeted signals by FISH - whole subtelomeres can be analyzed in this manner<sup>[2]</sup>. Specific regions have already been analyzed previously using this method; *e.g.*, the 22q11.2 region for DiGeorge syndrome and the 7q11.2 region for Williams syndrome. Although FISH is a powerful tool for detecting deletions of targeted regions, the biggest disadvantage is that it is difficult to detect small duplications owing to overlapping signals.

Generally, PCR cannot be used to quantify amplified fragments owing to saturation of amplification. However, in cases of linear amplification, quantity can be estimated by using a real-time PCR monitoring system. The chief feature of this system is that the target is fixed at the start of analysis<sup>[3]</sup>. Although MLPA is based on a PCR system, the targets of amplification are fused probes included in the buffer. Because various sizes of the amplicons can be included in the same tube, multiplexed targets can be measured simultaneously<sup>[4]</sup> and whole subtelomeric regions can be analyzed comprehensively<sup>[5]</sup>.

At present, it is easier to detect genomic copy number aberrations by using chromosomal microarray testing as a comprehensive method. We subsequently realized that there are numerous microchromosomal duplications that are genetic causes for various diseases.

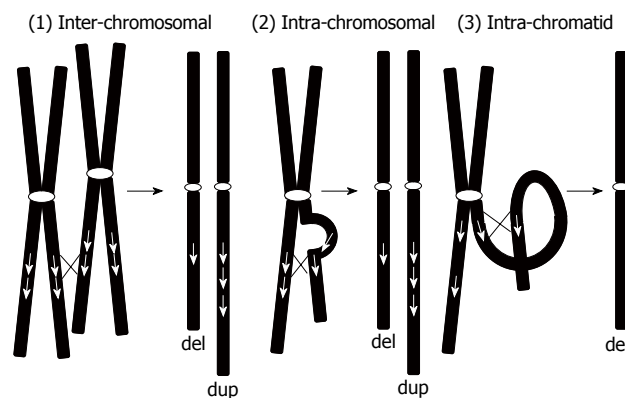
### Mechanism of microduplications

We can classify duplications into 2 types: recurrent microduplications and random microduplications (Table 2). Recurrent microduplications are caused by non-allelic homologous recombination (NAHR) mediated by low-copy repeats. Consequently, such microduplications are reciprocal to the microdeletions caused by the NAHR mechanism. According to this mechanism, chromosomal aberrations can occur in 3 ways<sup>[6]</sup>: (1) inter-chromosomal; (2) intra-chromosomal; and (3) intra-chromatid (Figure 1). As shown in Figure 1, inter-chromosomal and intra-chromosomal exchanges can create both deletions and duplications equally. However, intra-chromatid exchange only creates microdeletion and not microduplication. Thus, microduplications created by NAHR are definitely a consequence of inter-chromosomal or intra-chromosomal exchange. Both processes create duplications in tandem orientation. However, few studies have confirmed the hypothesized tandem configurations of the duplication.

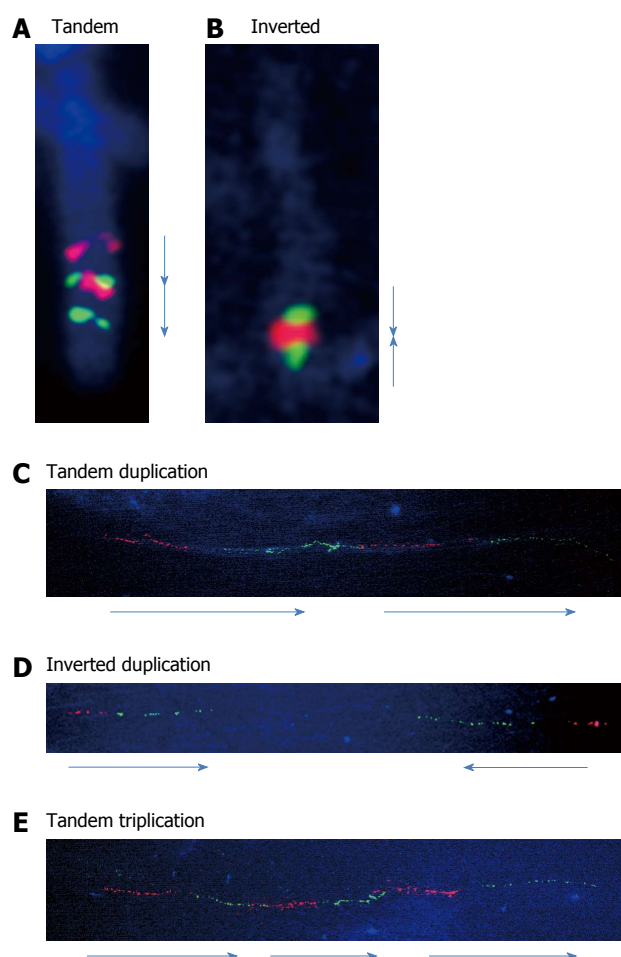
### Standard FISH

Previously, many efforts have been made to detect orientations of the duplication by FISH. The combined use of 2 different colored probes can detect the orientations of the duplicated segments. We analyzed the orientations of the duplicated segments and many showed tandem configurations. As shown in Figure 2A, an interstitial duplication of 2q32.1-q33.3 was inserted in a contiguous tandem configuration<sup>[7]</sup>.

Compared to such interstitial duplications, subtelomere duplications are different because they are most commonly a result of U-type exchange between the sister chromatids during the meiotic process<sup>[8]</sup>. We observed



**Figure 1 Schematic representation of the mechanism of non-allelic homologous recombination.** The mechanism can occur in 3 ways. Chromosomal duplications can be created by (1) inter-chromosomal exchange; (2) intra-chromosomal exchange; and (3) intra-chromatid exchange. Although inter-chromosomal and intra-chromosomal exchanges can lead to deletions and duplications equally, intra-chromatid exchange only creates microdeletions and not microduplications. Microduplications created by non-allelic homologous recombination invariably show tandem orientations. White arrows indicate the directions of the segments. This figure is referring the report by Gu *et al.*<sup>[6]</sup>.



**Figure 2 Results of fluorescence *in situ* hybridization in metaphase and fiber-fluorescence *in situ* hybridization.** A: Tandem duplication aligned in red-green-red-green is shown; B: Inverted duplication aligned in green-red-red-green is shown; C: Tandem duplication aligned in red-green-red-green is shown in a single DNA fiber; D: Inverted duplication aligned in red-green-green-red is shown; E: Tandem triplication with 3 repeats of red-green units. Arrows indicate the directions of the segments.

**Table 1 Characters of the methods to detect genomic copy number variations**

Characters	Advantages	Disadvantages
Fluorescence <i>in situ</i> hybridization	Numbers of the signals correspond to the genomic copy numbers	Small duplications cannot be detected
Quantitative polymerase chain reaction	Wide dynamic range Many samples can be analyzed at once	Primer designs are required for each targets
Multiple ligation probe amplification	Multiple targets can be analyzed at once	Original primer designs are required for specific regions
Chromosomal microarray testing	Accurate and high resolution Comprehensive	Chromosomal structures including balanced translocations cannot be analyzed

**Table 2 Characteristics of microduplications**

Characteristic	Recurrent microduplications	Random microduplications
Mechanism	Non-allelic homologous recombination Mediated by locus control regions	Random
Characteristics	Reciprocal to common deletions Uniformed size	Random

inverted duplication and deletion in the 10q26 region<sup>[9]</sup>. Inverted orientation was confirmed by FISH in this case (Figure 2B).

As mentioned above, in the cases of large duplications it is possible to determine the orientations of the duplicated segments; however, it is difficult to determine orientation for small duplications owing to overlapping signals in metaphase spreads. Consequently, interphase nuclei were used as an alternative to determine the alignments of the signals. Lee *et al.*<sup>[10]</sup> analyzed the orientations of the duplications involving *PLP1* in patients with PMD using interphase nuclei. They confirmed that many duplications of this region were aligned in tandem orientations. However, there is the limitation that directions cannot be detected accurately. To compensate for this, several nuclei from the same patients have to be checked.

### Methods of fiber-FISH

Chromosomes are composed of 3-dimensional structures that consist of DNA and histones. Thus, targeted signals can be overlapped. In such cases, fiber-FISH analysis has the advantage of being able to detect the orientations of the duplicated segments accurately<sup>[11-13]</sup> ("fiber" means DNA fibers).

DNA fiber specimens can be prepared after separating chromatin structures by surfactants. To perform fiber-FISH analysis, traditional Carnoy fixation can be used. The method is as follows: Carnoy-fixed samples should be mounted on the surface of the glass slides and the slides should be immediately dipped into sodium dodecyl sulfate solution and then slowly pulled out. Consequently, the separated DNA fibers can be fixed onto the surface of the glass slides.

The same probes used for standard FISH can be used for fiber-FISH. Compared to standard FISH, targeted signal intensity is extremely weak. Because live signals are not visible by microscopy, long exposure time is required

for signal capture. To capture standard FISH pictures, interphase nucleus or metaphase labeled by DAPI can be used as landmarks; however, there are no interphase nucleus and metaphase in fiber-FISH specimens. Thus, it is necessary to search the entire surface of the slide to detect signals.

Not all fibers show the same rate of extension on the same slide. This is dependent on the duration of the dip into the surfactants solution. If the length of the targeted fiber was too long to be captured in a single field of view, not all the target signals can be captured in the same field of view. It also depends on the size of the targeted duplications. If signals can be successfully captured, the directions of the fragments can be determined.

In terms of the clinical point of view, detection of microduplication orientation is not a suitable strategy for clinical analyses. Thus, fiber-FISH analysis is a specialized method for research work.

### Orientations of the duplicated segments

Previously, we analyzed the directions of the duplicated segments of the 22q11.2 region. The 4 duplications of the 22q11.2 region, identified by chromosomal microarray testing, showed tandem configurations of the duplicated segments, supporting the hypothesized mechanism of NAHR<sup>[11]</sup>. We analyzed 7 and 4 samples with the duplications in the region of *PLP1* and the methyl CpG binding protein 2 gene, respectively<sup>[12-14]</sup>, and all of the duplications showed tandem configurations as seen in the 22q11.2 region (Figure 2C), although the duplications in the region of *PLP1* are considered to be created by fork stalling and template switching and not by NAHR<sup>[15]</sup>.

Almost all duplications analyzed previously showed tandem configurations, as seen in cases of large duplications visible by general FISH analysis. The only exception was a benign copy number gain identified at the Xp22.31 region that included the steroid sulfatase gene (Figure 2D)<sup>[12]</sup>. This may indicate that the mechanism of the copy number gain in the benign region may be different from that of the pathological CNV.

### Triplications

Triplications are rare chromosomal aberrations which can be classified into 2 types: (1) triplication embedded into duplicated segments; and (2) triplications not embedded into duplicated segments<sup>[16]</sup>. Because sufficient data are not available owing to the scarcity of these triplications,

the mechanisms underlying them have seldom been analyzed. The clearest evidence is that some of the triplications embedded into duplicated segments are caused by the duplication-inverted triplication-duplication mechanism revealed by Carvalho *et al.*<sup>[17]</sup> and Shimojima *et al.*<sup>[18]</sup>. Compared to this, a tandem triplication was confirmed in another case involving the platelet-activating factor acetylhydrolase 1b regulatory subunit gene (Figure 2E)<sup>[19]</sup>.

In conclusion, as a result of the wider adoption of chromosomal microarray testing as a diagnostic tool, many genomic copy number gains were found to cause multiple congenital anomalies and intellectual impairments. Thus, this is just a starting point to understanding the mechanism of such genomic copy number gains. For this purpose, we should accumulate more cases of duplications and triplications and analyze the orientations of the segments.

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An informative, structured abstract should accompany each manuscript. Abstracts of original contributions should be structured into the following sections: AIM (no more than 20 words; Only the purpose of the study should be included. Please write the Aim in the form of "To investigate/study/..."), METHODS (no less than 140 words for Original Articles; and no less than 80 words for Brief Articles), RESULTS (no less than 150 words for Original Articles and no less than 120 words for Brief Articles; You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, *e.g.*,  $6.92 \pm 3.86$  vs  $3.61 \pm 1.67$ ,  $P < 0.001$ ), and CONCLUSION (no more than 26 words).

### Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

### Core tip

Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

### Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both.

### Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ... *etc.* It is our principle to publish high resolution-figures for the E-versions.

### Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

### Notes in tables and illustrations

Data that are not statistically significant should not be noted. \**P* <



## Instructions to authors

0.05, <sup>b</sup> $P < 0.01$  should be noted ( $P > 0.05$  should not be noted). If there are other series of  $P$  values, <sup>c</sup> $P < 0.05$  and <sup>d</sup> $P < 0.01$  are used. A third series of  $P$  values can be expressed as <sup>e</sup> $P < 0.05$  and <sup>f</sup> $P < 0.01$ . Other notes in tables or under illustrations should be expressed as <sup>1</sup>F, <sup>2</sup>F, <sup>3</sup>F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, etc., in a certain sequence.

### Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

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Please provide PubMed citation numbers to the reference list, e.g., PMID and DOI, which can be found at <http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed> and <http://www.crossref.org/SimpleTextQuery/>, respectively. The numbers will be used in E-version of this journal.

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### Format

#### Journals

English journal article (list all authors and include the PMID where applicable)

- 1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature

of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

### Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

### Statistical data

Write as mean  $\pm$  SD or mean  $\pm$  SE.



### Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as  $\chi^2$  (in Greek), related coefficient as *r* (in italics), degree of freedom as *ν* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

### Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h; blood glucose concentration, *c* (glucose)  $6.4 \pm 2.1$  mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 24.5 μg/L; CO<sub>2</sub> volume fraction, 50 mL/L CO<sub>2</sub>, not 5% CO<sub>2</sub>; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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### Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, *etc.*

Restriction enzymes: *EcoRI*, *HindI*, *BamHI*, *Kho I*, *Kpn I*, *etc.*

Biology: *H. pylori*, *E. coli*, *etc.*

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