综 述

基因拷贝数异常的研究进展

程玉强 郭卫星 程树群*

(第二军医大学东方肝胆外科医院, 上海 200438)

摘要 基因拷贝数异常(copy number variations, CNVs)是广泛存在于人体基因组的一种结构变异现象，主要包括拷贝数的缺失、插入、重组以及多位点的复杂变异等。最初是在病人的基因组中发现，后来的研究表明在正常人体中也普遍存在。有关CNVs的研究将随机个体之间的基因组差异估计值大大提高，极大的改变了人们的认识。目前，关于CNVs的研究多处在初步探索阶段，CNVs如何导致疾病，以及如何引起基因等的改变而诱发疾病的机理也需更进一步的研究加以验证和证实。该文主要就近年来关于CNVs的研究进展作一综述。

关键词 基因拷贝数异常; 肿瘤; 单核苷酸多态性; 基因组杂交芯片技术

拷贝数异常(copy number variations, CNVs)是广泛存在于人体基因组的一种结构变异现象, 也称为拷贝数多态性(copy number polymorphisms, CNPs), 异常片段大小从1 Kb到数Mb范围不等, 主要包括拷贝数的缺失、插入、重组以及多位点的复杂变异等[1-4]。CNVs最初是在病人的基因组中发现[5-6], 但后来的研究表明在正常人体中也普遍存在[1-2], 有统计显示, 目前共发现CNVs约57 829个(图1, 已发现的CNVs与染色体位置关系, http://projects.tcag.ca/variation/), 其中染色体倒位847; 100 bp~1 Kb的插入缺失为30 748个; 倒置断裂位点约14 478个。此外, 据Hurles[7]研究估计, CNVs至少占到基因组的12%, 已成为基因组多态性的又一重要来源[8]。

有关CNVs的研究将随机个体之间的基因组差异估计值提高到大于1%, 大大改变了人们先前的认识, 有学者甚至认为这一发现将改变人类对遗传学领域的认知[3,9]。与一直以来研究较多的单核苷酸多态性(SNPs)相比, CNVs发生的频率虽然较低, 但累及的序列长度却明显超过了前者, 因此对人类健康和疾病的影响更为显著。本文主要就近年来关于CNVs的研究进展作一综述。

1 基因拷贝数异常的检测方法

鉴于CNVs在基因层面研究疾病的巨大作用, 如何更好的检测CNVs便成了首要解决的问题。随着生物技术的发展, CNVs的检测分析技术也在不断更新。目前的检测方法主要包括: 基于芯片和DNA测序的高通量分析方法的比较基因组杂交技术(array-CGH)[10-12]、BAC芯片技术[13]、SNP分型芯片[14-15]和寡核苷酸芯片技术(oaCGH)[23,26]等; 基于PCR技术的靶向分析的多重扩增探针杂交技术(MAPH)[27]和依赖于连接的多重探针扩增技术(MLPA)[28]以及高分辨率TILING芯片[19]及基于芯片技术的MAPH(microarray MAPH)方法[29]等。近年来, 随着下一代测序技术(next generation sequencing)的逐步开展, CNVs的相关检测也正变得更加高效、准确。虽然关于CNVs的检测方法仍在不断改进, 但每种方法都有各自的优点和不足之处, 实际工作中还要根据具体情况选择最佳检测方法(表1, 不同CNVs检测方法及适用情况)。

2 基因拷贝数异常的形成、作用机制

Shaw-Smith等[30]利用比较基因组杂交芯片技术(array-CGH)所做的研究显示, CNVs多发生在同源重复序列或DNA重复片段区域; 另据类似分析显示, 非同源重组和DNA结构中的非βDNA结构(包括左旋Z型DNA和十字型DNA)在CNVs的形成过程中也有很大的促进作用[31-32]。虽然CNVs的形成机制尚未完全探明, 但随着相关检测技术的发展和研究的

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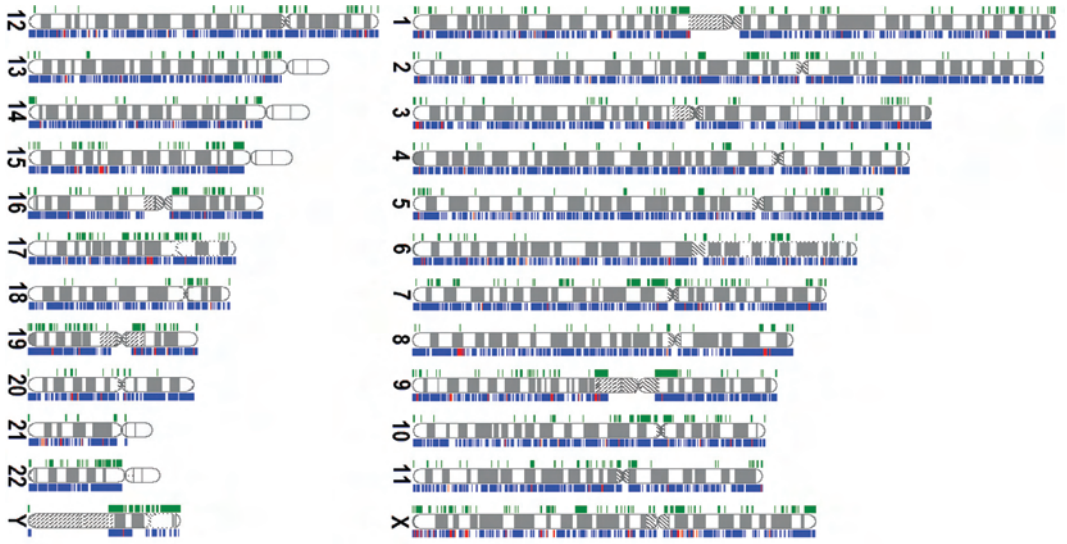
*通讯作者。Tel: 021-81875251, Fax: 021-65562400, E-mail: chengshuqun@yahoo.com.cn



蓝色表示已报道的CNVs, 红色表示已报道的倒置断裂位点, 绿色表示扩增片段。

Blue bars indicate reported CNVs, red bars indicate reported inversion breakpoints, green bars to the left indicate segmental duplications.

图1　CNVs在染色体上的位置

Fig.1　The distribution of CNVs in human genome

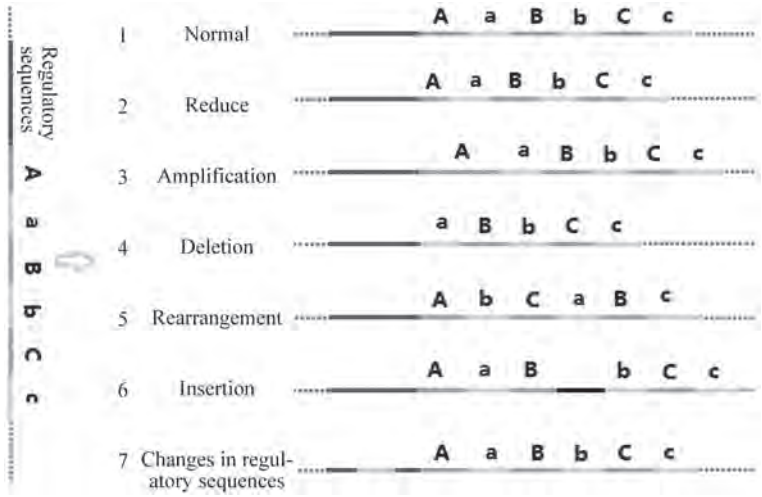
表1　不同CNVs检测方法及适用情况

Table 1　CNVs detection methods and applications

检测方法 Detection method	适用范围 Applications	参考文献 References
Fluorescence *in situ* hybridization, FISH	Chromosomal mapping of repeat DNA sequences and multiple-copied gene families Identification of hybrid parental chromosomes; structural analysis and physical mapping of chromosome Detection of exogenous chromatin Species evolution and phylogenetic study	Halling, *et al.*[16]
Comparative genomic hybridization, CGH	Using small sample size tumor DNA to identify whole genome copy number variations Researches on samples from peripheral blood, cultured cells, fresh tissue and fixed tissue Small amount DNA samples after PCR amplification	Sharp, *et al.*[10]
High resolution comparative genomic hybridization, HR-CGH	Genetic diagnosis of abnormal phenotypes with “normal” or “balanced translocation” karyotyping results Sources identification of marker chromosomes Diagnosis of complex chromosomal abnormalities	Huang, *et al.*[17-18]
Bacterial artificial chromosomes, BAC	Analysis of poor-quality DNA samples; CNVs detection with high sensitivity and reproducibility, including single copy gain and loss, homozygous deletion and high level amplification, conducive to cancer gene identification and genetic research	Jonsson, *et al.*[19-20]
cDNA aCGH	Detection of CNVs in the exon region, and its results represent relations between high level amplification or deletion and changes in gene expression	Pollack, *et al.*[21]
Oligonucleotide array CGH, oaCGH	Chip of the highest resolution, for high-resolution scanning of genome wide CNVs with accurately identification of CNVs number and breakpoints, analysisng a syndrome, providing favorable results for diagnosis, prognosis, genetic counseling and clinical management of unbalanced cytogenetic imbalances	Borze, *et al.*[22-23]
Multiplex amplifiable Probe hybridization, MAPH	Detecting CNVs of multiple exons at a time	Armour, *et al.*[24]
Next-generation sequencing	Whole-genome resequencing or more targeted sequencing for discovery of mutations or polymorphisms Large-scale analysis of DNA methylation	Zhou, *et al.*[25]

不断深入, 其形成机制和遗传模式将逐渐明朗。

伴随CNVs的形成而出现的便是基因表达的异常和表型的改变(图2, CNVs形成方式图示)。CNVs影响基因最常见的方式是基因的微量删除和重复[30,33-34]或破坏某一基因的编码蛋白的部分而影响其活性[13]; 也可以通过破坏基因的调控区域[7], 或者扰乱和改变基因的剂量使基因发生重排影响其作用的发挥[6,35-37]。此外, CNVs还可通过改变基因的位置等促使其向易感疾病的方向改变, 甚至可通过在染色体的进化过程中为其改变提供必要的条件而使相关基因的某些功能发生异常[8,34,38-39]。当然, CNVs影响基因方式并不是仅限于一种或某几种, 多数情况下可能是集中方式



“A、B、C…”表示某段基因的不同编码区域; “a、b、c…”表示不同的非编码区域; “1~7”分别表示基因复制过程中可能出现的异常情况。
“A、B、C…”mean different coding fragments; “a、b、c…” mean different non-coding fragments; “1~7” mean the abnormalities of genes happened in its duplicating processes.

图2 CNVs形成方式示意图

Fig.2 Schematic representation of the formation of CNVs

共同存在, 甚至一个片段存在多种变异方式, 由此也更增加了CNVs的表现形式及作用方式。

3 基因拷贝数异常与疾病

随着人体CNV图谱的逐步精确, 众多频发及相似的基因结构改变和断裂位置被定位, 某些与疾病相关的特殊CNV位点被确定, 同时还发现, 致病性CNVs在不同疾病中影响基因的数目也不尽相同(表2, 部分疾病与其相关的CNVs)。例如, 与22q11.2缺失有关的DiGeorge/Velocardiofacial综合征累及的基因就包括T盒转录因子1和儿茶酚邻甲基转移酶等相关的基因[40-41]; 与7q11.23缺失有关的Williams-Beuren综合征累及的基因达28个以上[42-44]; 而与15q11-13缺失有关的Prader-Willi综合征则是通过影响更多基因而发生[45]。除直接引起基因改变致病外, CNVs还可以作为某些复杂疾病的危险因素而发挥作用, 如使感染HIV的易感性增加[46]和提高患肾小球肾炎的风险等[47]; 另外, 对于如Charge综合征[48]、阿尔茨海默病(Alzheimer’s disease)[49-51] 、帕金森氏症(Parkinson’s disease)[52-53]等某些等位基因突变引起的特殊疾病也可以做出一定的解释。

除以上提及的一些疾病外, 在一些肿瘤的相关研究中也发现, CNVs与许多肿瘤的发生发展有很密切的关系。Cybulski等[54]做的一项包括4 454例乳腺癌病人与5 496例正常女性的研究表明, 许多乳腺癌病人中存在CHEK2序列多达5 359个碱基的缺失; Horvath等[55]在Carney综合征的研究中则发现*PRKAR1A*基因的大片段缺失与其有关。另外, 在一些具有家族聚集性发病的肿瘤中CNVs现象更明显。Hattem等[56]的研究发现*SMAD4*、*BMPR1A*和*PTEN*基因的缺失和改变可能是幼年性息肉病(Juvenile polyposis, JPS)的主要原因, Cerqueira等[57]的进一步研究中则发现, JPS病人中存在*SMAD4*和*BMPR1A*基因改变的比例高达40%~60%; 而Preudhomme等[58]的研究

表2 与CNVs有关的疾病及其相关的基因

Table 2 Diseases relating with CNVs and related genes

疾病名称 Diseases	存在拷贝数异常的基因 Genes	参考文献 References
Progressive muscula dystrophy, PMD	*PLP1*	Lee *et al*.[9]
Acquired Immune Deficiency Syndrome, AIDS	*CCL3L1*	Gonzalez *et al*.[46,61]
Mammary cancer*CHEK2*	Cybulski [54]	
Carney syndrome	*PRKAR1A*	Horvath *et al*.[55]
Familial juvenile polyposis, FJP	*SMAD4*,*BMPR1A*	Calva *et al*.[57]
Acute myelogenous leukemia, AML	*RUNX1*	Preudhomme *et al*.[58-59]
Familial gastric carcinoma	*CDH1*	Oliveira *et al*.[60]
Parkinson's disease	*Alpha-Synuclein*	Ibanez *et al*.[62]
Charcot-Marie-Tooth, CMT	*PMP22*	Passage *et al*.[63]
Colon cancer *Ets2*	Sussan *et al*.[64]	
Schizophrenia*NRXN1, ASTN2*	Kirov *et al*.[65-66]	
Osteoporosis*UGT2B17*	Yang *et al*.[67]	
Subarachnoid aneurysmal hemorrhage	*SEL1L*	Bae *et al*.[68]
Glomerulonephritis	*FCGR3B*	Ouahchi *et al*.[69]

发现, 在血小板异常的家族中存在*RUNX1*基因的频繁突变的病人发生急性髓性白血病的风险将大大增加, Jongmans等[59]的研究也进一步证明了该结果; 在家族型胃癌的研究中Oliveira等[60]发现30%~50%的家族存在有*CDH1*基因的点突变或小片段变化。由此可见, CNVs很有可能是另一种致使疾病尤其是某些基因病发生的重要原因。

4 展望

CNVs是近年来被广泛关注的焦点之一。虽然, 各项关于CNVs的研究多处在初步探索阶段, 但均显示了CNVs与人类疾病之间的潜在关系。随着基因芯片等生物技术的逐步成熟和应用, 关于CNVs的认识将会逐渐清楚, CNVs与SNPs[70]、基因突变等的关系, 及其发生和存在的机理定会被逐渐认识。

由于人类存在某些特定的致病易感基因, CNVs是否与之存在某些联系, 或者说CNVs是如何导致疾病, 如何引起基因的改变而诱发疾病的机理也需更进一步的研究加以验证和证实。另外, 据Kapranov等[71]的最近一项研究证实, 人体中的RNA并不完全来自于DNA的转录, 其自身也可以直接完成自我的复制, CNVs作为一种基因拷贝的存在形式, 也可能与RNA的形成及调控之间存在一定的联系, 这也将会给研究RNA如何发挥作用提供新的方向。

最后, 所有的研究都将归结到人类健康及疾病的诊治上去, CNVs在疾病筛查与诊治, 尤其是在某些家族或遗传性疾病的筛查和一些特殊疾病的基因治疗等方面的巨大作用也应的到相应的重视。相信, 随着CNVs检测技术的逐步提高和各种研究的逐渐深入, 对CNVs与人类疾病的关系的认识和其在疾病诊治中的巨大作用均将得到更大的推进。

参考文献(References)

1 Iafrate AJ, Feuk L, Rivera MN, Listewnik ML, Donahoe PK, Qi Y, *et al*. Detection of large-scale variation in the human genome. Nat Genet 2004; 36(9): 949-51.

2 Sebat J, Lakshmi B, Troge J, Alexander J, Young J, Lundin P, *et al*. Large-scale copy number polymorphism in the human genome. Science 2004; 305(5683): 525-8.

3 Beckmann JS, Estivill X, Antonarakis SE. Copy number variants and genetic traits: Closer to the resolution of phenotypic to genotypic variability. Nat Rev Genet 2007; 8(8): 639-46.

4 Check E. Human genome: Patchwork people. Nature 2005; 437(7062): 1084-6.

5 Lejeune J, Turpin R, Gautier M. Mongolism; a chromosomal disease (trisomy). Bull Acad Natl Med 1959; 143(11-12): 256-65.

6 Buckland PR. Polymorphically duplicated genes: their relevance to phenotypic variation in humans. Annals of Medicine 2003; 35(5): 308-15.

7 Stranger BE, Forrest MS, Dunning M, Ingle CE, Beazley C, Thorne N, *et al*. Relative impact of nucleotide and copy number variation on gene expression phenotypes. Science 2007; 315(5813): 848-53.

8 Freeman JL, Perry GH, Feuk L, Redon R, McCarroll SA, Altshuler DM, *et al*. Copy number variation: New insights in genome diversity. Genome Res 2006; 16(8): 949-61.

9 Lee JA, Carvalho CM, Lupski JR. A DNA replication mechanism for generating nonrecurrent rearrangements associated with genomic disorders. Cell 2007; 131(7): 1235-47.
10 Sharp AJ, Cheng Z, Eichler EE. Structural variation of the human genome. Annu Rev Genomics Hum Genet 2006; 7: 407-42.
11 Dhami P, Coffey AJ, Abbs S, Vermeesch JR, Dumanski JP, Woodward KJ, *et al*. Exon array CGH: Detection of copy-number changes at the resolution of individual exons in the human genome. American Journal of Human Genetics 2005; 76(5): 750-62.
12 Carter NP. Methods and strategies for analyzing copy number variation using DNA microarrays. Nature Genetics 2007; 39: S16-21.
13 Redon R, Ishikawa S, Fitch KR, Feuk L, Perry GH, Andrews TD, *et al*. Global variation in copy number in the human genome. Nature 2006; 444(7118): 444-54.
14 McCarroll SA, Kuruvilla FG, Korn JM, Cawley S, Nemesh J, Wysoker A, *et al*. Integrated detection and population-genetic analysis of SNPs and copy number variation. Nat Genet 2008; 40(10): 1166-74.
15 Butler H, Ragoussis J. BeadArray-based genotyping. Methods Mol Biol 2008; 439: 53-74.
16 Halling KC, King W, Sokolova IA, Meyer RG, Burkhardt HM, Halling AC, *et al*. A comparison of cytology and fluorescence *in situ* hybridization for the detection of urothelial carcinoma. J Urol 2000; 164(5): 1768-75.
17 Huang XL, Isabel de Michelena M, Leon E, Maher TA, McClure R, Milunsky A. Pallister-Killian syndrome: tetrasomy of 12pter->12p11.22 in a boy with an analphoid, inverted duplicated marker chromosome. Clin Genet 2007; 72(5): 434-40.
18 Kirchhoff M, Pedersen S, Kjeldsen E, Rose H, Duno M, Kolvraa S, *et al*. Prospective study comparing HR-CGH and subtelomeric FISH for investigation of individuals with mental retardation and dysmorphic features and an update of a study using only HR-CGH. Am J Med Genet A 2004; 127A(2): 111-7.
19 Ishkanian AS, Malloff CA, Watson SK, DeLeeuw RJ, Chi B, Coe BP, *et al*. A tiling resolution DNA microarray with complete coverage of the human genome. Nat Genet 2004; 36(3): 299-303.
20 Jonsson G, Staaf J, Olsson E, Heidenblad M, Vallon-Christersson J, Osoegawa K, *et al*. High-resolution genomic profiles of breast cancer cell lines assessed by tiling BAC array comparative genomic hybridization. Genes Chromosomes Cancer 2007; 46(6): 543-58.
21 Pollack JR, Perou CM, Alizadeh AA, Eisen MB, Pergamenschikov A, Williams CF, *et al*. Genome-wide analysis of DNA copy-number changes using cDNA microarrays. Nat Genet 1999; 23(1): 41-6.
22 Borze I, Juvonen E, Ninomiya S, Jee KJ, Elonen E, Knuutila S. High-resolution oligonucleotide array comparative genomic hybridization study and methylation status of the RPS14 gene in de novo myelodysplastic syndromes. Cancer Genet Cytogenet 2010; 197(2): 166-73.
23 Ijssel P, Ylstra B. Oligonucleotide array comparative genomic hybridization. Methods Mol Biol 2007; 396: 207-21.
24 Armour JA, Sismani C, Patsalis PC, Cross G. Measurement of locus copy number by hybridisation with amplifiable probes. Nucleic Acids Res 2000; 28(2): 605-9.
25 Zhou X, Ren L, Meng Q, Li Y, Yu Y, Yu J. The next-generation sequencing technology and application. Protein Cell 2010; 1(6): 520-36.
26 Lucito R, Healy J, Alexander J, Reiner A, Esposito D, Chi M, *et al*. Representational oligonucleotide microarray analysis: A high-resolution method to detect genome copy number variation. Genome Res 2003; 13(10): 2291-305.
27 Hollox EJ, Atia T, Cross G, Parkin T, Armour JA. High throughput screening of human subtelomeric DNA for copy number changes using multiplex amplifiable probe hybridisation (MAPH). J Med Genet 2002; 39(11): 790-5.
28 Schouten JP, McElgunn CJ, Waaijer R, Zwijnenburg D, Diepvens F, Pals G. Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. Nucleic Acids Res 2002; 30(12): e57.
29 Gibbons B, Datta P, Wu Y, Chan A, Al Armour J. Microarray MAPH: Accurate array-based detection of relative copy number in genomic DNA. BMC Genomics 2006; 7: 163.
30 Shaw-Smith C, Redon R, Rickman L, Rio M, Willatt L, Fiegler H, *et al*. Microarray based comparative genomic hybridisation (array-CGH) detects submicroscopic chromosomal deletions and duplications in patients with learning disability/mental retardation and dysmorphic features. J Med Genet 2004; 41(4): 241-8.
31 Kurahashi H, Emanuel BS. Long AT-rich palindromes and the constitutional t(11;22) breakpoint. Hum Mol Genet 2001; 10(23): 2605-17.
32 Bacolla A, Jaworski A, Larson JE, Jakupciak JP, Chuzhanova N, Abeysinghe SS, *et al*. Breakpoints of gross deletions coincide with non-B DNA conformations. Proc Natl Acad Sci USA 2004; 101(39): 14162-7.
33 Inoue K, Lupski JR. Molecular mechanisms for genomic disorders. Annu Rev Genomics Hum Genet 2002; 3: 199-242.
34 Lupski JR, Stankiewicz P. Genomic disorders: Molecular mechanisms for rearrangements and conveyed phenotypes. PLoS Genet 2005; 1(6): e49.
35 McCarroll SA, Hadnott TN, Perry GH, Sabeti PC, Zody MC, Barrett JC, *et al*. Common deletion polymorphisms in the human genome. Nat Genet 2006; 38(1): 86-92.
36 Nguyen DQ, Webber C, Ponting CP. Bias of selection on human copy-number variants. PLoS Genet 2006; 2(2): e20.
37 Repping S, van Daalen SKM, Brown LG, Korver CM, Lange J, Marszalek JD, *et al*. High mutation rates have driven extensive structural polymorphism among human Y chromosomes. Nature Genetics 2006; 38(4): 463-7.
38 Feuk L, Marshall CR, Wintle RF, Scherer SW. Structural variants: Changing the landscape of chromosomes and design of

disease studies. Hum Mol Genet 2006; 15(S1): R57-66.

39 Feuk L, Carson AR, Scherer SW. Structural variation in the human genome. Nat Rev Genet 2006; 7(2): 85-97.

40 Carlson C, Sirotkin H, Pandita R, Goldberg R, McKie J, Wadey R, *et al*. Molecular definition of 22q11 deletions in 151 velo-cardio-facial syndrome patients. Am J Hum Genet 1997; 61(3): 620-9.

41 Prasad SE, Howley S, Murphy KC. Candidate genes and the behavioral phenotype in 22q11.2 deletion syndrome. Dev Disabil Res Rev 2008; 14(1): 26-34.

42 Osborne LR, Li M, Pober B, Chitayat D, Bodurtha J, Mandel A, *et al*. A 1.5 million-base pair inversion polymorphism in families with Williams-Beuren syndrome. Nat Genet 2001; 29(3): 321-5.

43 Scherer SW, Cheung J, MacDonald JR, Osborne LR, Nakabayashi K, Herbrick JA, *et al*. Human chromosome 7: DNA sequence and biology. Science 2003; 300(5620): 767-72.

44 Meyer-Lindenberg A, Mervis CB, Berman KF. Neural mechanisms in Williams syndrome: A unique window to genetic influences on cognition and behaviour. Nat Rev Neurosci 2006; 7(5): 380-93.

45 Bittel DC, Butler MG. Prader-Willi syndrome: Clinical genetics, cytogenetics and molecular biology. Expert Rev Mol Med 2005; 7(14): 1-20.

46 Gonzalez E, Kulkarni H, Bolivar H, Mangano A, Sanchez R, Catano G, *et al*. The influence of CCL3L1 gene-containing segmental duplications on HIV-1/AIDS susceptibility. Science 2005; 307(5714): 1434-40.

47 Aitman TJ, Dong R, Vyse TJ, Norsworthy PJ, Johnson MD, Smith J, *et al*. Copy number polymorphism in Fcgr3 predisposes to glomerulonephritis in rats and humans. Nature 2006; 439(7078): 851-5.

48 Vissers LE, Veltman JA, van Kessel AG, Brunner HG. Identification of disease genes by whole genome CGH arrays. Hum Mol Genet 2005; 14(S2): R215-23.

49 Rovelet-Lecrux A, Hannequin D, Raux G, Le Meur N, Laquerriere A, Vital A, *et al*. APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. Nat Genet 2006; 38(1): 24-6.

50 Heinzen EL, Need AC, Hayden KM, Chiba-Falek O, Roses AD, Strittmatter WJ, *et al*. Genome-wide scan of copy number variation in late-onset Alzheimer's disease. J Alzheimers Dis 2010; 19(1): 69-77.

51 Heinzen EL, Need AC, Hayden KM, Chiba-Falek O, Roses AD, Strittmatter WJ, *et al*. Genome-wide scan of copy number variation in late-onset Alzheimer's Disease. J Alzheimers Dis 2010; 19(1): 69-77.

52 Nuytemans K, Meeus B, Crosiers D, Brouwers N, Goossens D, Engelborghs S, *et al*. Relative contribution of simple mutations vs. copy number variations in five Parkinson disease genes in the Belgian population. Hum Mutat 2009; 30(7): 1054-61.

53 Marder KS, Tang MX, Mejia-Santana H, Rosado L, Louis ED, Comella CL, *et al*. Predictors of parkin mutations in early-onset Parkinson disease: The consortium on risk for early-onset Parkinson disease study. Arch Neurol 2010; 67(6): 731-8.

54 Cybulski C, Wokolorczyk D, Huzarski T, Byrski T, Gronwald J, Gorski B, *et al*. A deletion in CHEK2 of 5 395 bp predisposes to breast cancer in Poland. Breast Cancer Res Treat 2007; 102(1): 119-22.

55 Horvath A, Bossis I, Giatzakis C, Levine E, Weinberg F, Meoli E, *et al*. Large deletions of the PRKAR1A gene in Carney complex. Clin Cancer Res 2008; 14(2): 388-95.

56 van Hattem WA, Brosens LA, de Leng WW, Morsink FH, Lens S, Carvalho R, *et al*. Large genomic deletions of SMAD4, BMPR1A and PTEN in juvenile polyposis. Gut 2008; 57(5): 623-7.

57 Calva-Cerqueira D, Chinnathambi S, Pechman B, Bair J, Larsen-Haidle J, Howe JR. The rate of germline mutations and large deletions of SMAD4 and BMPR1A in juvenile polyposis. Clin Genet 2009; 75(1): 79-85.

58 Preudhomme C, Renneville A, Bourdon V, Philippe N, Roche-Lestienne C, Boissel N, *et al*. High frequency of RUNX1 biallelic alteration in acute myeloid leukemia secondary to familial platelet disorder. Blood 2009; 113(22): 5583-7.

59 Jongmans MC, Kuiper RP, Carmichael CL, Wilkins EJ, Dors N, Carmagnac A, *et al*. Novel RUNX1 mutations in familial platelet disorder with enhanced risk for acute myeloid leukemia: Clues for improved identification of the FPD/AML syndrome. Leukemia 2010; 24(1): 242-6.

60 Oliveira C, Senz J, Kaurah P, Pinheiro H, Sanges R, Haegert A, *et al*. Germline CDH1 deletions in hereditary diffuse gastric cancer families. Hum Mol Genet 2009; 18(9): 1545-55.

61 Nakajima T, Kaur G, Mehra N, Kimura A. HIV-1/AIDS susceptibility and copy number variation in CCL3L1, a gene encoding a natural ligand for HIV-1 co-receptor CCR5. Cytogenet Genome Res 2008; 123(1-4): 156-60.

62 Ibanez P, Bonnet AM, Debarges B, Lohmann E, Tison F, Pollak P, *et al*. Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. Lancet 2004; 364(9440): 1169-71.

63 Passage E, Norreel JC, Noack-Fraissignes P, Sanguedolce V, Pizant J, Thirion X, *et al*. Ascorbic acid treatment corrects the phenotype of a mouse model of Charcot-Marie-Tooth disease. Nat Med 2004; 10(4): 396-401.

64 Sussan TE, Yang A, Li F, Ostrowski MC, Reeves RH. Trisomy represses Apc(Min)-mediated tumours in mouse models of Down's syndrome. Nature 2008; 451(7174): 73-5.

65 Kirov G. The role of copy number variation in schizophrenia. Expert Rev Neurother 2010; 10(1): 25-32.

66 Stone JL, O'Donovan MC, Gurling H, Kirov GK, Blackwood DH, Corvin A, *et al*. Rare chromosomal deletions and duplications increase risk of schizophrenia. Nature 2008; 455(7210): 237-41.

67 Yang TL, Chen XD, Guo Y, Lei SF, Wang JT, Zhou Q, *et al*. Genome-wide copy-number-variation study identified a suscepti-

bility gene, UGT2B17, for osteoporosis. Am J Hum Genet 2008; 83(6): 663-74.

68 Bae JS, Cheong HS, Kim JO, Lee SO, Kim EM, Lee HW, *et al*. Identification of SNP markers for common CNV regions and association analysis of risk of subarachnoid aneurysmal hemorrhage in Japanese population. Biochem Biophys Res Commun 2008; 373(4): 593-6.

69 Ouahchi K, Lindeman N, Lee C. Copy number variants and pharmacogenomics. Pharmacogenomics 2006; 7(1): 25-9.

70 Yavas G, Koyuturk M, Ozsoyoglu M, Gould MP, Laframboise T. Cokgen: A software for the identification of rare copy number variation from SNP microarrays. Pac Symp Biocomput 2010: 371-82.

71 Kapranov P, Ozsolak F, Kim SW, Foissac S, Lipson D, Hart C, *et al*. New class of gene-termini-associated human RNAs suggests a novel RNA copying mechanism. Nature 2010; 466(7306): 642-6.

The Progress on Gene Copy Number Variations

Cheng Yuqiang, Guo Weixing, Cheng Shuqun*

(*Second Military Medical University, Shanghai 200438, China*)

Abstract Copy number variations (CNVs) are structurally mutation regions of DNA which comprises deletion, insertion, recombination, and complex variation of DNA copy number. CNVs are detected not only in patients, but also in normal individuals. The existence of CNVs has tremendous enriched the difference in genome among random individuals and turned the concept of genetic disparity. Although there are lots of researches on CNVs, many of which are in primary stage. CNVs may play an important role in pathogenesis, but the mechanism that how CNVs cause diseases or evoke the alteration of genes is still unclear and to be proved. Here, we review the recent advancements of CNVs.

Key words CNVs; tumor; SNPs; array-CGH

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*Corresponding author. Tel: 86-21-81875251, Fax: 86-21-65562400, E-mail: chengshuqun@yahoo.com.cn