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BENIGN AND PATHOLOGICAL GAIN OR LOSS OF GENETIC MATERIAL — ABOUT MICROSCOPIC AND SUBMICROSCOPIC COPY NUMBER VARIATIONS (CNVs) IN HUMAN GENETICS

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Submicroscopic gains or losses of chromosomal material are known as copy number variations (CNVs). Such CNVs are either connected with a disease or can also be (much more frequently) just a manifestation of human's genetic range of variation. Besides cytogenetic visible copy number variations (CG-CNVs) first discovered as chromosomal heteromorphisms, and later e. g. as euchromatic variants (EVs), there are also submicroscopic CNVs (MG-CNVs). Especially the latter may be a headache for diagnostics as the same MG-CNV may be found in clinically healthy and diseased persons. A so-called two-hit model has been introduced to solve this puzzle. As this considers the number of CNVs present overall in a genome the question arises if CG-CNVs are considered enough in routine cytogenetic as well as MG-CNVs in array-comparative genomic hybridization analysis.

K e y w o r d s: copy number variations (CNVs), heteromorphisms, banding cytogenetics, copy number variations, molecular cytogenetics, array comparative genomic hybridization.

A b b r e v i a t i o n s: aCGH — array-based of comparative genomic hybridization, CG-CNVs — cytogenetic visible copy number variations, CNVs — copy number variations, EVs — euchromatic variants, MG-CNVs — submicroscopic copy number variations.

The question of there is gain or loss of genetic material in the tissue of a studied person is one of the main questions of human genetics when doing prenatal, postnatal or tumor-related diagnostics. One may think that in the majority of the cases, if such an alteration is detected this is equated with having identified the genetic reason for a clinical problem. However, one has to consider that this is not always true, as there are benign and pathological copy number variations (CNVs) (Liehr, 2014). These CNVs can be of different size and thus be detected by different kinds of approaches. There are 1) cytogenetically visible copy number variations (CG-CNVs), and 2) submicroscopic CNVs detectable by molecular (cyto)genetics, especially array-based of comparative genomic hybridization (aCGH) (Shinawi, Cheung, 2008) (MG-CNVs).

CG-CNVs are detected in GTG-banding approach (G-bands by Trypsin using Giemsa), being still the gold-standard for all cytogenetic techniques (Claussen et al., 2002), MG-CNVs are mainly found by aCGH. However, both kinds of CNVs also may be seen when molecular cytogenetics i. e. fluorescence *in situ* hybridization (FISH) is done (Liehr, Claussen, 2002).

A recent review of the CNV-related literature (Liehr, 2014) highlighted that it seems to be difficult, if not impossible to define, what the «normal» size of MG-CNVs as well as MG-CNVs is. While size differences of heterochromatic regions in human chromosomes are known since decades (for review see Liehr, 2014) it lasted until 2004 that it was realized that even no two clinically healthy individuals of the same gender are alike (Iafrate et al., 2004; Sebat et al., 2004) (this is also true for monozygote twins (Mkrtchyan et al., 2010) and that each human differs in the amount of euchromatic DNA on average by 0.5 megabasepair (Mb) in MG-CNVs (Girirajan et al., 2010).

Concerning CG-CNVs, the majority of them are heterochromatic CG-CNVs located in 1q12, 9q12, 13pter-q11, 14pter-q11.1, 15pter-q11.1, 16q11.2, 19p12-q12, 21pter-q11.1, 22pter-q11.1 and in male in Yq12. Besides euchromatic CG-CNVs were described as so-called euchromatic variants (EV; i. e. large scale cytogenetically visible copy number variants) and unbalanced chromosome abnormalities without phenotypic consequences (UBCA). All of them can be pure gain or loss but also appear in connection with translocations or other rearrangements (Liehr, 2014).

While heterochromatic CG-CNVs interestingly are not annotated in human genome browsers, MG-CNVs are exactly mapped within the human genome and can be identified and located in mapped human sequences. It has to be considered that heterochromatic CG-CNVs cannot be detected by means of aCGH, and euchromatic MG-CNVs normally are not visible after banding cytogenetics. I. e. each of both approaches is technically based blind for major parts of the human genome.

Especially MG-CNVs are considered as benign if inherited from a parent (Lee et al., 2007) and when *de novo*, as most likely pathological (Tyson et al., 2005). The major determi-

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nant for the clinical impact of a those CNVs maybe if dosage sensitive genes are present in the corresponding DNA-stretch (Canales, Walz, 2011; Weise et al., 2012). Still, «it was recently observed that more than one (submicroscopic) CNV (larger than 500 kb) can contribute to severe developmental delay and often is responsible for phenotypic variability associated with genomic disorders»; this is the so-called «two-hit»-model (Girirajan et al., 2010).

In conclusion one can state again what we recently published as «overall there is no biological reason to distinguish MG-CNVs and CG-CNVs. i. e. besides size there is no real difference between them. Nothing could underline this fact better than identical copy number variant regions reported „independently" by cytogenetic approaches on the one side and by molecular techniques on the other side; examples are CNVs in 8q21.2 or 15q11.2. Also, it might be necessary to list all detected MG-CNVs in aCGH-reports and all CG-CNVs, especially heterochromatin variants, in cytogenetic reports» (Liehr, 2013).

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ДОБРОКАЧЕСТВЕННЫЕ И ПАТОЛОГИЧЕСКИЕ ПРИОБРЕТЕНИЯ И ПОТЕРИ ГЕНЕТИЧЕСКОГО МАТЕРИАЛА — МИКРОСКОПИЧЕСКИЕ И СУБМИКРОСКОПИЧЕСКИЕ ВАРИАЦИИ ЧИСЛА КОПИЙ В ГЕНЕТИКЕ ЧЕЛОВЕКА

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Субмикроскопические приобретения и потери генетического материала известны как вариации числа копий (copy number variations — CNVs). По своему проявлению CNVs могут быть либо связаны с болезнью, либо представлять собой часть нейтральной популяционной изменчивости. Помимо цитологически детектируемых вариантов числа копий (CG-CNVs), впервые описанных как гетероморфизм хромосом, а позже в том числе и в виде эухроматиновых вариантов (EVs), существуют и субмикроскопические CNVs (MG-CNVs). Вторые могут быть особенно проблемными для диагностики, поскольку одинаковые MG-CNV встречаются как у клинически здоровых, так и больных индивидуумов. Так называемая теория двойного удара была использована для решения этой проблемы. Однако, поскольку она учитывает число CNVs, присутствующих во всем геноме, появляется вопрос о том, достаточно ли хорошо учитываются в рутинной цитогенетике CG-CNVs, в анализе геномной гибридизации на микрочипах — MG-CNVs.

Ключевые слова: вариации числа копий (CNVs), гетероморфизмы, цитогенетика, бэндинг, молекулярная цитогенетика, сравнительная геномная гибридизация на микрочипах.