The Growing Complexity of the Monosomy 1p36 Syndrome

Even before the first draft of the human reference genome and the genome-wide screening methods based on this reference became available, several recognizable ‘deletion syndromes’ were known to the medical genetics community. For instance, a syndrome characterized by distinct dysmorphic features, such as large anterior fontanelles, microcephaly, brachycephaly, deep-set eyes, flat nose and nasal bridge, and a pointed chin was found in ~1 out of 5,000 live births [Shapira et al., 1997; Slavotinek et al., 1999; Gajecka et al., 2007]. By classical karyotyping and FISH, a deletion in the 1p36 region of one of the chromosomes of the patient was detected. Thus, ‘deletion 1p36’ or ‘monosomy 1p36’ became the most common terminal deletion syndrome in humans. Patients with monosomy 1p36 often show hypotonia, brachycamptodactyly, short feet, intellectual disability, and speech problems. Less frequently, congenital heart defects, vision problems, including visual inattention, seizures, sensorineural deafness, gastrointestinal anomalies, hypothyroidism, and anomalies of the kidneys and the external genitalia are also observed [Battaglia, 1993]. Genome-wide aneuploidy screening with BAC-, oligonucleotide and SNP arrays revealed a remarkable variability in size and position of the terminal and interstitial deletions in these patients. These findings have been used to map and identify candidate genes for some of the clinical features of monosomy 1p36 patients [Jordan et al., 2015]. More detailed molecular cytogenetic studies with higher resolution arrays revealed an unexpected complexity of 1p36 rearrangements and gave rise to speculations as to its putative mechanism(s) of origin [Ballif et al., 2003; Zanardo et al., 2014; Gamba et al., 2015].

Although the 1p36 region contains several blocks of segmental duplications, the deletions in patients with monosomy 1p36 vary widely in size and share no common breakpoints [Ballif et al., 2003]. This means that these deletions in 1p36 are not recurrent and not likely the result of nonallelic homologous recombination [Sharp et al., 2005]. Using arrays consisting of tiling BAC-clones and PCR, Ballif et al. [2003] mapped deletion breakpoints and subsequently analyzed the sequences of the breakpoint junctions. In 1 case, a pure terminal 1p36 deletion was stabilized by telomeric repeat sequences, while 2 other cases had terminal deletions associated with cryptic interrupted inverted duplications. These inverted duplication/deletion breakpoints prompted the authors to propose a model based on premeiotic breakage-fusion-bridge (BFB) cycles in the germline [Ballif et al., 2003]. This would then produce gametes with terminal deletions associated with proximal inverted duplications.

Recently, 2 cases with monosomy 1p36 have been described in which multiple deletions, interspersed with diploid segments and flanked by a proximal duplication, were characterized by FISH and array-CGH [Zanardo et al., 2014; Gamba et al., 2015]. Notwithstanding the remarkable similarity of these rearrangements, the authors suggested 2 distinct mechanisms of origin: chromoanagenesis and chromothripsis. Chromoanagenesis is a mechanism by which a cell responds to a collapsed DNA replication fork by generating a double-strand break followed by DNA synthesis, during which templates are switched repeatedly [Holland and Cleveland, 2012]. The latter is also known as fork stalling and template switching (FoSTes) and may string segments of a single or multiple chromosomes to-

gether such that complex patterns of duplications, triplications, deletions, and diploid segments result [Poot and Haaf, 2015]. At the joining points of these segments, small regions of microhomology are generated, which serve as a 'molecular signature' of FoSTes. Alternatively, chromoanagenesis may involve microhomology-mediated break-induced repair, which will also produce small regions of microhomology at the joining points, similar to those resulting from FoSTes. A special form of chromoanagenesis is chromoanasythesis, which produces no deletions but only duplications [Plaisancié et al., 2014].

To explain 5 deletions interspersed with diploid segments and flanked by a proximal duplication, Gamba et al. [2015] proposed chromothripsis as a possible cause. This mechanism is based on shattering of one or several chromosomes in many segments, which are subsequently fused together by nonhomologous end joining [Korbel and Campbell, 2013]. During this process, a few chromosomal segments may be lost, so that the final product will contain deletions. This fusion process does not involve the use of a DNA template. Consequently, no regions of microhomology are found at the joining points, and the segments are fused in random order [Kloosterman et al., 2011, 2012; Korbel and Campbell, 2013].

Thus far, 2 mechanisms for chromothripsis have been described: isolation and under-replication of one or sev-

eral chromosomes in a micronucleus or a telomere crisis followed by BFB cycles, rupture of the nuclear envelope and kataegis [Maciejowski et al., 2015; Zhang et al., 2015]. The micronucleus-based mechanism involves microhomology-mediated break-induced repair and produces deletions alternating with diploid segments [Zhang et al., 2015]. Chromothripsis after telomere crisis and BFB cycles affects at least 2 chromosomes and produces strings of deletions, duplications and diploid segments [Maciejowski et al., 2015]. Premeiotic BFB cycles were earlier proposed as a possible cause of monosomy 1p36 [Ballif et al., 2003]. To decide whether chromoanagenesis, chromothripsis or any other mechanism of chromosomal rearrangements may underlay monosomy 1p36, the relative orientation and the sequences of the joining points of all involved chromosome segments have to be determined using high-resolution methods such as paired-end or mate-pair sequencing [Kloosterman et al., 2011, 2012; Korbel and Campbell, 2013]. Given the relatively high prevalence of the recognizable monosomy 1p36 syndrome in the population, this endeavor may serve as a paradigm for such studies. Their outcome may also guide analyses of, for instance, the deletion/duplication 9p syndrome or other cases of deletions with associated duplications [Di Bartolo et al., 2012; Krgovic et al., 2014].

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References

- Ballif BC, Yu W, Shaw CA, Kashork CD, Shaffer LG: Monosomy 1p36 breakpoint junctions suggest pre-meiotic breakage-fusion-bridge cycles are involved in generating terminal deletions. *Hum Mol Genet* 12:2153–2165 (2003).
- Battaglia A: 1p36 deletion syndrome, in: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, et al (eds): *GeneReviews*® [Internet]. (University of Washington, Seattle 1993).
- Di Bartolo DL, El Naggar M, Owen R, Sahoo T, Gilbert F, et al: Characterization of a complex rearrangement involving duplication and deletion of 9p in an infant with craniofacial dysmorphism and cardiac anomalies. *Mol Cytogenet* 5:31 (2012).
- Gajicka M, Mackay KL, Shaffer LG: Monosomy 1p36 deletion syndrome. *Am J Med Genet C Semin Med Genet* 145C:346–356 (2007).
- Gamba BF, Richieri-Costa A, Costa S, Rosenberg C, Ribeiro-Bicudo LA: Chromothripsis with at least 12 breaks at 1p36.33-p35.3 in a boy with multiple congenital anomalies. *Mol Genet Genomics* 290:2213–2216 (2015).
- Holland AJ, Cleveland DW: Chromoanagenesis and cancer: mechanisms and consequences of localized, complex chromosomal rearrangements. *Nat Med* 18:1630–1638 (2012).
- Jordan VK, Zaveri HP, Scott DA: 1p36 deletion syndrome: an update. *Appl Clin Genet* 8:189–200 (2015).
- Kloosterman WP, Guryev V, van Roosmalen M, Duran KJ, de Bruijn E, et al: Chromothripsis as a mechanism driving complex de novo structural rearrangements in the germline. *Hum Mol Genet* 20:1916–1924 (2011).
- Kloosterman WP, Tavakoli-Yaraki M, van Roosmalen MJ, van Binsbergen E, Renkens I, et al: Constitutional chromothripsis rearrangements involve clustered double-stranded DNA breaks and nonhomologous repair mechanisms. *Cell Rep* 1:648–655 (2012).
- Korbel JO, Campbell PJ: Criteria for inference of chromothripsis in cancer genomes. *Cell* 152:1226–1236 (2013).
- Krgovic D, Blatnik A, Burmas A, Zagorac A, Kokalj Vokac N: A coalescence of two syndromes in a girl with terminal deletion and inverted duplication of chromosome 5. *BMC Med Genet* 15:21 (2014).
- Maciejowski J, Li Y, Bosco N, Campbell PJ, de Lange T: Chromothripsis and kataegis induced by telomere crisis. *Cell* 163:1641–1654 (2015).
- Plaisancié J, Kleinfinger P, Cances C, Bazin A, Julia S, et al: Constitutional chromoanasythesis: description of a rare chromosomal event in a patient. *Eur J Med Genet* 57:567–570 (2014).
- Poot M, Haaf T: Mechanisms of origin, phenotypic effects and diagnostic implications of complex chromosome rearrangements. *Mol Syndromol* 6:110–134 (2015).
- Shapira SK, McCaskill C, Northrup H, Spikes AS, Elder FF, et al: Chromosome 1p36 deletions: the clinical phenotype and molecular characterization of a common newly delineated syndrome. *Am J Hum Genet* 61:642–650 (1997).
- Sharp AJ, Locke DP, McGrath SD, Cheng Z, Bailey JA, et al: Segmental duplications and copy-number variation in the human genome. *Am J Hum Genet* 77:78–88 (2005).
- Slavotinek A, Shaffer LG, Shapira SK: Monosomy 1p36. *J Med Genet* 36:657–663 (1999).
- Zanardo ÉA, Piazzon FB, Dutra RL, Dias AT, Montenegro MM, et al: Complex structural rearrangement features suggesting chromoanagenesis mechanism in a case of 1p36 deletion syndrome. *Mol Genet Genomics* 289:1037–1043 (2014).
- Zhang CZ, Spektor A, Cornils H, Francis JM, Jackson EK, et al: Chromothripsis from DNA damage in micronuclei. *Nature* 522:179–184 (2015).