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Letter to the Editor

Isochromosome 17q; A Novel Finding in Myeloid Sarcoma

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TO THE EDITOR

Chromosome 17 abnormalities in haematologic malignancies are important because the *TP53* tumour suppressor gene is found on 17p 13.1.[1] Chromosome 17 abnormalities were reported in 49 (4.3%) of cases in a study of patients with myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML). In this cohort, 14 patients had monosomy 17 and 35 patients had unbalanced translocations between chromosome 17p and another chromosome. Most of them also had other cytogenetic abnormalities and 10 were therapy related, 69% also had a *TP53* mutation. The pseudo Pelger-Huët like anomaly and vacuolated neutrophils were described in 70% of these patients.[2] Chromosome 17 abnormalities have also been associated with therapy related myeloid neoplasms, unbalanced translocations involving chromosome 17, monosomy 17 and isochromosome 17q or 17p deletion having been reported.[3]

Isochromosome(17q) occurs when chromosome 17 has two identical arms, i.e. no "p" arm but two "q" arms. This results in a cell having only one copy of 17p and three copies of 17q. It is thought to occur due to breakage of the proximal part of 17p followed by rejoining of the centromere containing chromatids and inactivation of one centromere.[4] Isochromosome(17q) has been reported in a variety of haematologic and solid malignancies, it is usually associated with a complex karyotype but has less commonly been reported in isolation.[5-9] Myeloid neoplasms with isolated i(17q) have been reported to have features of an MDS/myeloproliferative neoplasm (MPN) overlap syndrome. Myeloid dysplasia, monocytosis and a high propensity for leukaemic transformation with a short overall survival are features of this condition.[10]

Myeloid sarcoma (MS) is characterized by extramedullary tumour masses composed of myeloblasts or myelomonocytic cells.[11] MS may present *de novo* or occur concomitantly with MDS, MPN or AML. Alternatively MS may represent transformation of a MPN or MDS to AML or occur at relapse.[12] Fluorescence *in situ* hybridization analysis of 49 MS specimens showed clonal abnormalities in 25, specifically, monosomy 7 (10%), trisomy 8 (10%) and *MLL* gene rearrangement (8.5%). Concordance between fluorescence *in situ* hybridization on the MS specimen and bone marrow karyotyping was shown in 10 of 14 cases in which both analyses were performed.[11] Interestingly, t(8;21) has been found in paediatric cases of MS and in orbital tumours.[13] Comparative genomic hybridization (CGH) of seven MS cases showed chromosome 8 abnormalities in 3, with other abnormalities including loss of 4q, 6q, 12p and gain of 11q, 13q, 19 and 21.[14] Li and co-workers performed next generation sequencing of 21 AML/MDS related genes in 6 cases of MS. They detected mutations in tyrosine kinases (*FLT-3* and *KIT*), the *WT1* tumour suppressor gene, the epigenetic regulators *EZH2, ASXL1* and *TET1* as well as *SF3B1*, an RNA splicosome protein.[15] This study showed a genetic overlap between MS and AML, it is likely however that there are differences between these entities which account for the extramedullary localization of MS. A patient with AML and concomitant testicular MS was found to have i(17)q as part of a near tetraploid karyotype on cytogenetic analysis of the

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bone marrow.[16] Genomic analysis of the MS tissue was not however performed in this case. It is noteworthy that i(17)q has not been reported previously in a tissue biopsy of MS.

A 79 year-old male presented with a one month history of lethargy and ankle oedema. He had no bleeding symptoms and denied weight loss, night sweats, fever or rash. Physical examination revealed bilateral cervical lymphadenopathy and moderate splenomegaly. Initial investigations revealed; haemoglobin 11.0 g/dL, white blood cells 17.8 x 10^9/L, neutrophils 7.3 x10^9/L, monocytes 3.2 x 10^9/L, eosinophils 1.42 x 10^9/L, and basophils 1.96 x 10^9/L. A peripheral blood film showed dysplastic neutrophils and monocytes with platelet anisocytosis. A left shift was seen with blasts comprising 8% of white blood cells (Fig. 1a). His bone marrow aspirate and trephine were hypercellular with dysplastic granulopoiesis and megakaryopoiesis. Myeloblasts comprised 19% of nucleated cells with eosinophilia (12%) and basophilia (4%) (Fig. 1b & 1c). Multiparameter flow cytometry showed dyscoordinated granulocytic maturation with CD34 positive myeloblasts comprising 13% of events.

He underwent a cervical lymph node biopsy, which showed effacement of the lymph node architecture and infiltration with myeloblasts staining positive for CD34 and CD117 by immunohistochemistry, consistent with MS of the myeloblastic type (Fig. 1d & 1e). Flow cytometry of the lymph node confirmed the presence of $CD117^{dim}HLA\text{-}DR^{+}$ myeloblasts and $HLA\text{-}DR^{bright}CD117^{dim}$ monoblasts (Fig. 1f). Bone marrow karyotyping revealed a karyotype of 46, XY i(17)(q10)[12]/46,XY[8] (Fig. 2). Reverse transcriptase polymerase chain reaction for the *FIP1L1-PDGFRA* and *BCR-ABL* transcripts were negative, as was polymerase chain reaction for the *JAK-2 V617F* mutation. We performed array CGH (Oncoscan™) on the lymph node MS specimen which showed a gain of 17q and loss of 17p, consistent with i(17q), and no other significant copy number abnormalities (CNA) (Fig. 3). In summary, this patient had chronic myelomonocytic leukaemia 2 associated with i(17q), transforming to AML with a concomitant MS. In view of his age he was managed conservatively and eventually succumbed to the disease.

To the best of our knowledge, this is the first report of i(17q) being demonstrated in MS. The presence of i(17q) as the sole copy number abnormality in the MS specimen by CGH strongly suggests that i(17q) is contributing to the pathogenesis of MS. The molecular basis of i(17q)-mediated leukaemogenesis has not been well described. Sequencing of the *TP53* gene in 17 patients with haematologic malignancies associated with i(17q) showed no *TP53* mutations, suggesting the presence of an alternative tumour suppressor gene on chromosome 17.[17] Transfection of a *TP53* deficient cell line with an intact chromosome 17 from a *TP53* mutant cell line lead to a reduced tumour growth. This provides functional evidence for the presence of an alternative tumour suppressor gene on chromosome 17p.[18] The heterozygous deletion of chromosome 11B3 has recently been shown in mice to be a potential driver of leukaemia and lymphoma in this context.[19] Further studies are required for definitive identification of the gene(s) involved in humans.

An alternative explanation for i(17q) mediated neoplasia is the presence of oncogenes on 17q. Genes coding for signaling proteins of the *N-Myc* and *c-Myc* oncogene pathways (*nm23-H1* and *nm23-H2*) are found on chromosome 17q. Neuroblastomas with an unfavourable prognosis commonly have *Myc* overexpression together with a gain of 17q which is hypothesized to play a role in the pathogenesis of these tumours.[20]

The *ERBB2* (*HER2*) oncogene is located on 17q, and the over expression of *HER 2* has been implicated in solid malignancies as well as B-acute lymphoblastic leukaemia.[21,22] The role of *HER2* in myeloid malignancy is not certain but it is reasonable to speculate whether it could play a role in i(17q) related neoplasms. *HER2* expression in i(17q) associated malignancies would be of clinical relevance given the availability of trastuzumab as a therapeutic option.[23]

Tissue inhibitor of metalloproteinase 2 (*TIMP-2*) plays an important role in tissue homeostasis. *TIMP-2* is overexpressed in the highly tissue invasive SH1 AML cell lines as well as bone marrow from AML patients.[24,25] It was postulated that the overexpression of *TIMP-2* could contribute to the tissue invasive properties of myeloblasts.[25] The *TIMP-2* gene is located on 17q and it maybe overexpressed in i(17q) related myeloid neoplasms. The tissue invasive properties conferred by *TIMP-2* overexpression could provide a link between i(17q) and MS. The mechanism of i(17q) mediated neoplasia was not further investigated in our patient due to inadequate material. Further studies to explore these potential oncogenic pathways in MS are called for.

Myeloid malignancies associated with i(17q) have a dismal prognosis.[10] In young patients, intensive chemotherapy followed by allogeneic stem cell transplant would be appropriate. Unfortunately, many of these patients are elderly and ineligible for intensive therapy. There is an urgent need for effective targeted therapy and future studies should focus on identifying actionable targets in this disease.

In conclusion, we present the first report of i(17q) demonstrated in a tissue biopsy of MS. Further studies using next generation sequencing are required to delineate the genetic architecture of MS with a view to development of novel therapeutic options.

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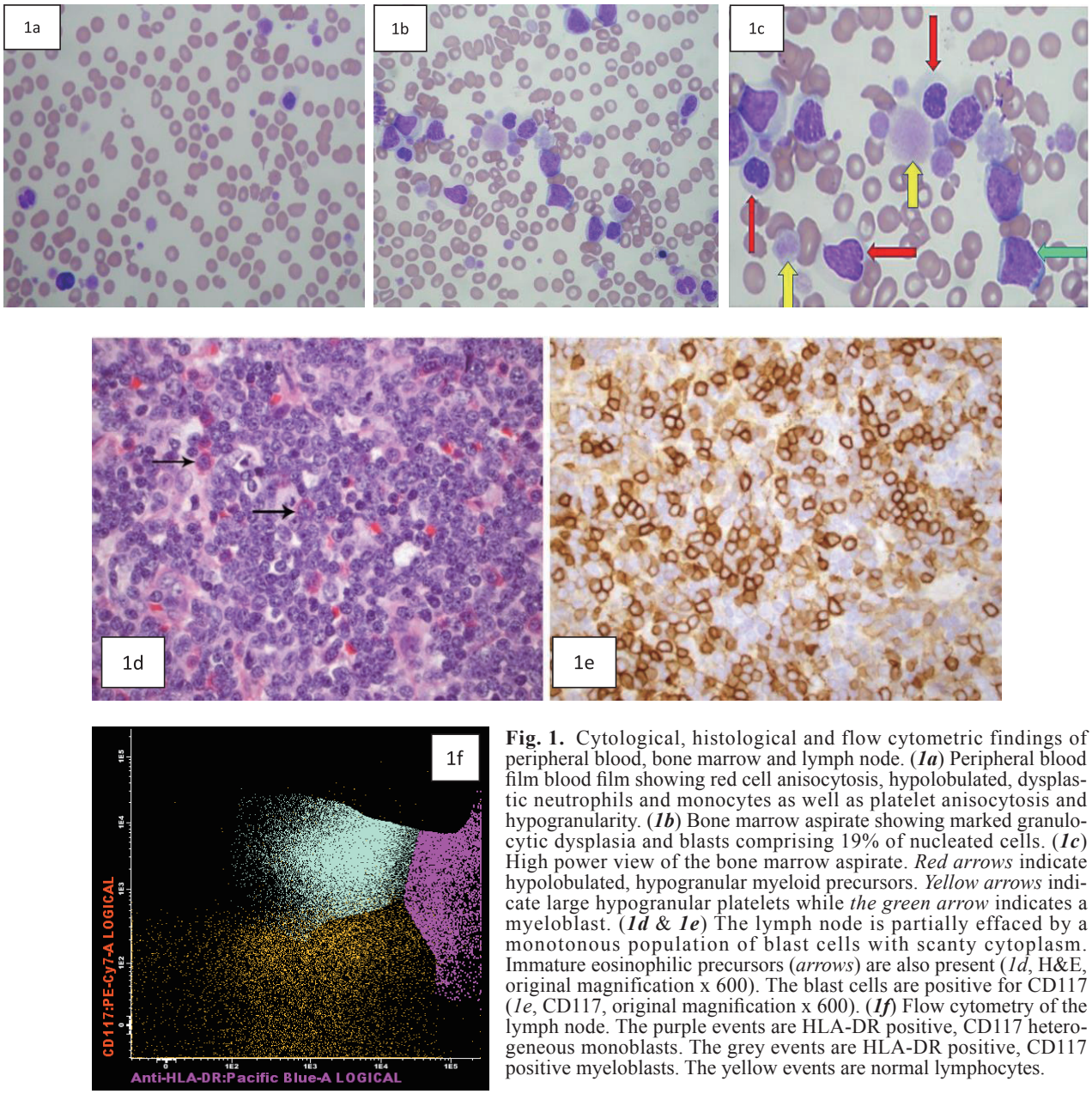

Fig. 1. Cytological, histological and flow cytometric findings of peripheral blood, bone marrow and lymph node. (***1a***) Peripheral blood film blood film showing red cell anisocytosis, hypolobulated, dysplastic neutrophils and monocytes as well as platelet anisocytosis and hypogranularity. (***1b***) Bone marrow aspirate showing marked granulocytic dysplasia and blasts comprising 19% of nucleated cells. (***1c***) High power view of the bone marrow aspirate. *Red arrows* indicate hypolobulated, hypogranular myeloid precursors. *Yellow arrows* indicate large hypogranular platelets while *the green arrow* indicates a myeloblast. (***1d*** & ***1e***) The lymph node is partially effaced by a monotonous population of blast cells with scanty cytoplasm. Immature eosinophilic precursors (*arrows*) are also present (*1d*, H&E, original magnification x 600). The blast cells are positive for CD117 (*1e*, CD117, original magnification x 600). (***1f***) Flow cytometry of the lymph node. The purple events are HLA-DR positive, CD117 heterogeneous monoblasts. The grey events are HLA-DR positive, CD117 positive myeloblasts. The yellow events are normal lymphocytes.

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The authors declare that they have no conflict of interest.

REFERENCES

1 Seifert H, Mohr B, Thiede C, Oelschlägel U, Schäkel U, *et al.*: The prognostic impact of 17p (p53) deletion in 2272 adults with acute myeloid leukemia. Leukemia 23:656-663, 2009

2 Lai JL, Preudhomme C, Zandecki M, Flactif M, Vanrumbeke M, *et al.*: Myelodysplastic syndromes and acute myeloid leukemia with 17p deletion. An entity characterized by specific dysgranulopoiesis and a high incidence of P53 mutations. Leukemia 9:370-381, 1995

3 Merlat A, Lai JL, Sterkers Y, Demory JL, Bauters F, *et al.*: Therapy-related myelodysplastic syndrome and acute myeloid leukemia with 17p deletion. A report on 25 cases. Leukemia 13:250-257, 1999

4 Pasquali F: Mechanism of origin of the isochromosome i(17q). Cancer Genet Cytogenet 80:170, 1995

5 Kanagal-Shamanna R, Bueso-Ramos CE, Barkoh B, Lu G, Wang S, *et al.*: Myeloid neoplasms with isolated isochromosome

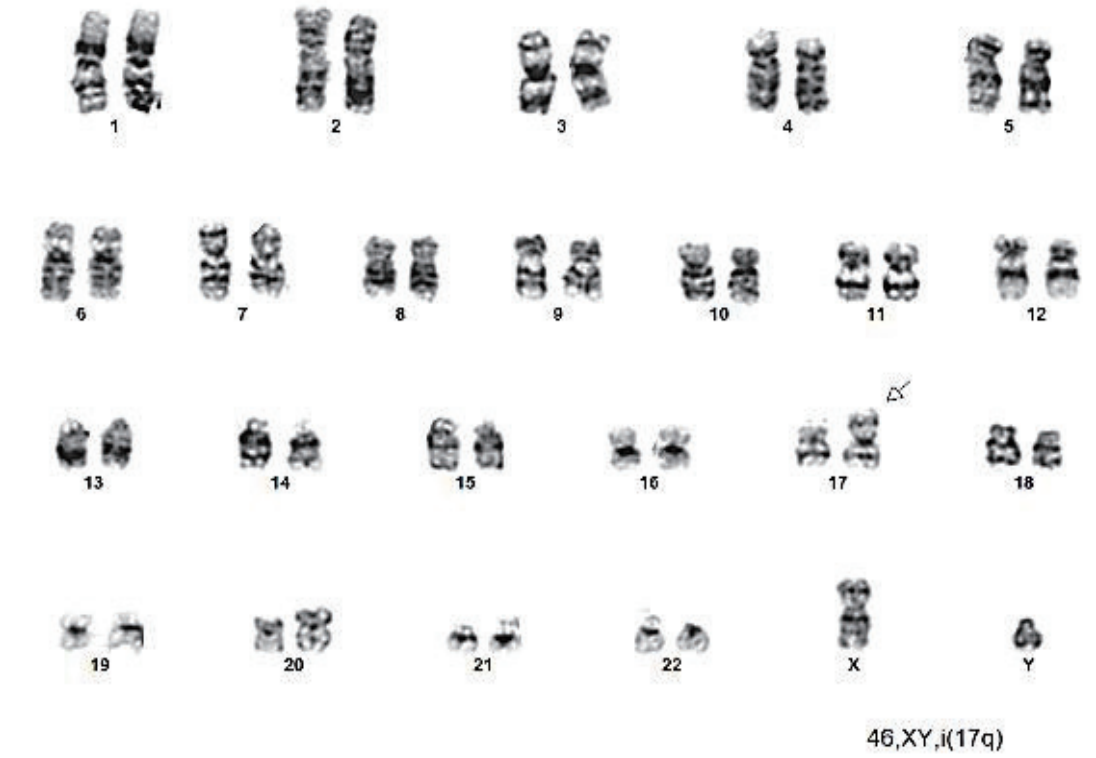

Fig. 2. Bone marrow karyotyping revealed a karyotype of 46,XY,i(17)(q10)[12]/46,XY[8].

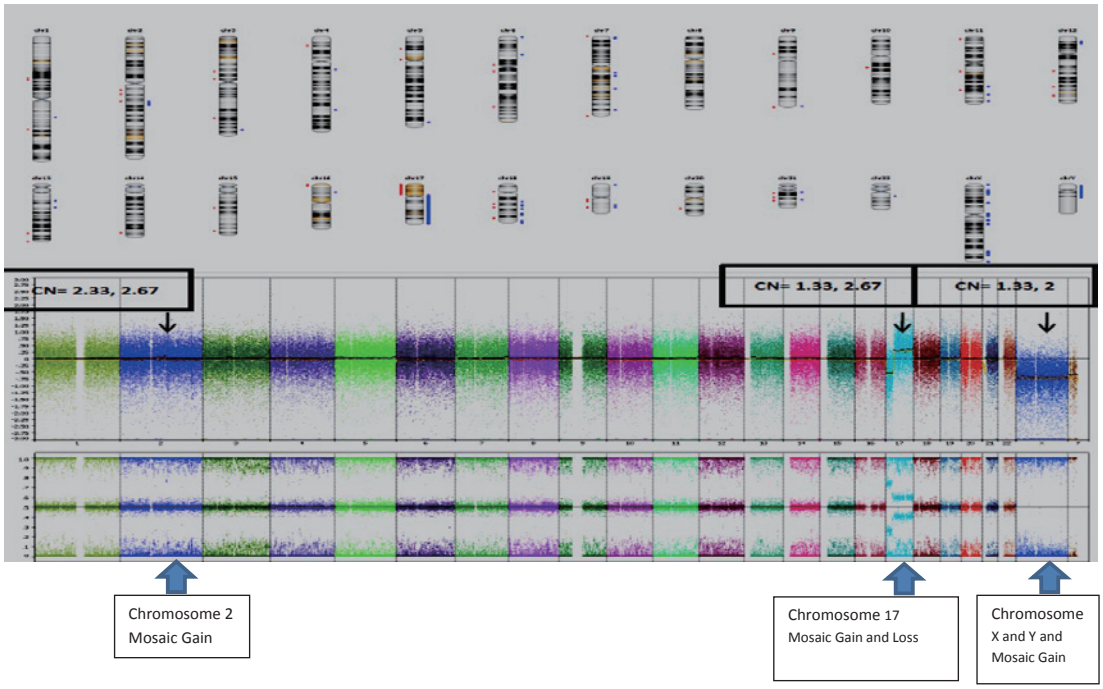

Fig. 3. Array comparative genomic hybridisation. A mosaic gain of 17q and loss of 17p is demonstrated. This pattern is consistent with i(17q).

17q represent a clinicopathologic entity associated with myelodysplastic/myeloproliferative features, a high risk of leukemic transformation, and wild-type TP53. Cancer 118:2879-2888, 2012

6 Lazarević V, Djordjević V, Magić Z, Marisavljevic D, Colović M: Refractory anemia with ring sideroblasts associated with i(17q) and mutation of the TP53 gene. Cancer Genet Cytogenet 136:86-89, 2002

7 Pinheiro RF, Chauffaille Mde L, Silva MR: Isochromosome 17q in MDS: a marker of a distinct entity. Cancer Genet Cytogenet 166:189-190, 2006

8 Testa JR, Cohen BC: Dicentric chromosome 17 in patients with leukemia. Cancer Genet Cytogenet 23:47-52, 1986

9 Mertens F, Johansson B, Mitelman F: Isochromosomes in neoplasia. Genes Chromosomes Cancer 10:221-230, 1994

10 McClure RF, Dewald GW, Hoyer JD, Hanson CA: Isolated isochromosome 17q: a distinct type of mixed myeloproliferative disorder/myelodysplastic syndrome with an aggressive clinical course. Br J Haematol 106:445-454, 1999

11 Pileri SA, Ascani S, Cox MC, Campidelli C, Bacci F, *et al.*: Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. Leukemia 21:340-350, 2007

12 Campidelli C, Agostinelli C, Stitson R, Pileri SA: Myeloid sarcoma: extramedullary manifestation of myeloid disorders. Am J Clin Pathol 132:426-437, 2009

13 Schwyzer R, Sherman GG, Cohn RJ, Poole JE, Willem P: Granulocytic sarcoma in children with acute myeloblastic leukemia and t(8;21). Med Pediatr Oncol 31:144-149, 1998

14 Deeb G, Baer MR, Gaile DP, Sait SN, Barcos M, *et al.*: Genomic profiling of myeloid sarcoma by array comparative genomic hybridization. Genes Chromosomes Cancer 44:373-383, 2005

15 Li Z, Stölzel F, Onel K, Sukhanova M, Mirza MK, *et al.*: Next-generation sequencing reveals clinically actionable molecular markers in myeloid sarcoma. Leukemia 29:2113-2116, 2015

16 Bettio D, Venci A, Sarina B: Near-tetraploid karyotype with an isochromosome 17q as the sole structural chromosomal rearrangement in a case of testicular granulocytic sarcoma. Cancer Genet Cytogenet 181:69-71, 2008

17 Fioretos T, Strömbeck B, Sandberg T, Johansson B, Billström R, *et al.*: Isochromosome 17q in blast crisis of chronic myeloid leukemia and in other hematologic malignancies is the result of clustered breakpoints in 17p11 and is not associated with coding TP53 mutations. Blood 94:225-232, 1999

18 Chen P, Ellmore N, Weissman BE: Functional evidence for a second tumor suppressor gene on human chromosome 17. Mol Cell Biol 14:534-542, 1994

19 Liu Y, Chen C, Xu Z, Scuoppo C, Rillahan CD, *et al.*: Deletions linked to TP53 loss drive cancer through p53-independent mechanisms. Nature 531:471-475, 2016

20 Godfried MB, Veenstra M, v Sluis P, Boon K, v Asperen R, *et al.*: The N-myc and c-myc downstream pathways include the chromosome 17q genes nm23-H1 and nm23-H2. Oncogene 21:2097-2101, 2002

21 Gutierrez C, Schiff R: HER2: biology, detection, and clinical implications. Arch Pathol Lab Med 135:55-62, 2011

22 Chevallier P, Robillard N, Wuilleme-Toumi S, Méchinaud F, Harousseau JL, *et al.*: Overexpression of Her2/neu is observed in one third of adult acute lymphoblastic leukemia patients and is associated with chemoresistance in these patients. Haematologica 89:1399-1401, 2004

23 Chevallier P, Robillard N, Charbonnier A, Raffoux E, Maury S, *et al.*: Trastuzumab for treatment of refractory/relapsed HER2-positive adult B-ALL: results of a phase 2 GRAALL study. Blood 119:2474-2477, 2012

24 Lin LI, Lin DT, Chang CJ, Lee CY, Tang JL, *et al.*: Marrow matrix metalloproteinases (MMPs) and tissue inhibitors of MMP in acute leukaemia: potential role of MMP-9 as a surrogate marker to monitor leukaemic status in patients with acute myelogenous leukaemia. Br J Haematol 117:835-841, 2002

25 Wang C, Chen Z, Li Z, Cen J: The essential roles of matrix metalloproteinase-2, membrane type 1 metalloproteinase and tissue inhibitor of metalloproteinase-2 in the invasive capacity of acute monocytic leukemia SHI-1 cells. Leuk Res 34:1083-1090, 2010