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An Emerging Face of Fanconi Anemia: Cancer
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1. Introduction
Fanconi anemia (FA) is a chromosomal instability syndrome characterized by various congenital malformations, progressive pancytopenia, chromosome breakage and predisposition to malignancy (Alter, 2003a). Autosomal recessive, FA is also inherited with X-linked inheritance reported in FA complementation group B (Meetei et al., 2004). FA pathway controls genomic stabilisation in mammalian cells and is referred to as FA pathway of antioncogenesis. Children with FA have a very high risk of developing acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). The incidence of AML in children with FA is 15,000 times that of children in the general population (Auerbach & Allen, 1991). Acute leukemia is the terminal event in about 5-20% of these cases (Ebell et al., 1989), MDS in about 5-10%, and solid tumors was held responsible in about 5-10% of the remaining cases. Patients with FA are at a high risk of developing solid tumors of the head, neck, esophagus, liver and female genitalia (Alter, 2003c, Rosenberg, Greene & Alter, 2003). In order to clarify the relationship between FA and cancer, the description of FA was recently updated as "an inherited genomic instability disorder, caused by mutations in genes regulating replication-dependent removal of interstrand DNA crosslinks" (Moldovan & D'Andrea, 2009). The research on the complex roles of FA proteins in repairing DNA improved our understanding of cancer biology. In this chapter, my main objective is twofold: to analyze clinical findings, diagnosis and hematological characteristics of FA, and to evaluate the relationship between FA pathway and cancer from the perspective of a pediatrician.

2. Fanconi anemia
FA is a familial pancytopenia associated with bone marrow hypoplasia and congenital malformations, originally discovered in three brothers by Fanconi in 1927 (Gözda şoğlu et al., 1980). 2000 cases were reported in the literature between the years of 1927 and 2009 (Alter, 2011). FA should be considered a syndrome, not a disease due to its heterogeneity. The physical phenotype ranges from normal appearance to manifest congenital malformations, the hematological spectrum ranges from nominal values to those associated with severe aplastic anemia (Alter, 1993b). Clinical heterogeneity in FA follows from genetic heterogeneity. The heterozygote prevalence for FA is estimated to be 1 in 300 in the United States (Alter, 1993a). Homozygote frequency is estimated at 1-3 per million (Joenje et al., 1995). The male-female ratio of occurrence is 1.2:1 (Alter, 2003a). The age of diagnosis ranges...
Anemia from birth to 48 years with an average of 8 years. About 10-20% of families have consanguineous marriage (Alter, 1992).

2.1 Congenital abnormalities

Several congenital abnormalities may accompany this disorder such as skeletal abnormalities, hyperpigmentation, renal malformation, microcephaly, hypogonadism and mental and growth retardations (Gözdaşoğlu et al., 1980; Akar & Gözdaşoğlu, 1984). Among skeletal system anomalies, radial ray defects such as hypoplasia of the thumb and the radius are observed most (Figures 1, 2, 3). In addition to congenital hip dislocations, scoliosis, vertebral anomalies, cafe-au-lait spots, diffuse hyperpigmentation and hypopigmentation are frequent. A short stature is prominent in more than half of the cases in utero and following birth. The median height is about 50 percentile in the patients, which can be related to growth hormone deficiency or hypothyroidism. Mycophtalmia, microcephaly and deafness may be observed, renal anomalies such as unilateral and renal aplasia, renal hypoplasia, horse-shoe kidney and double ureter may be encountered in about a third of the cases. Boys have genital anomalies as hypogenitalia, undescended testis and hypospadias. Girls have uterus anomalies. There have been reports of gastrointestinal defects such as esophageal, duodenal atresia, imperforated anus, tracheo-esophageal fistula, cardiac defects such as patent ductus arteriosus, ventricle septal defect, pulmonary stenosis, aortic stenosis, aortic coarctation, central nervous system anomalies such as hydrocephalus and absence of septum pellucidum (Alter, 2003b; Kwee & Kuyt, 1989; Smith et al., 1989). The FA phenotype can vary within family members; a report of four FA cases within two related consanguineous families who all had the same FANCA mutation demonstrated a wide variation in birth weight, skin pigmentation and the severity of skeletal, renal and genital abnormalities (Koç et al., 1999). Approximately 25-40% of the FA patients in the International Fanconi Anemia Registry (IFAR) do not exhibit any major malformation (Alter, 2003a).
Fig. 2. The picture of a 10-year-old boy with aplastic anemia showing the absence of radius and thumb on the right hand, hypoplastic thumb on the left hand and hypogenitalismus.

Fig. 3. Bifid left thumb and proximally placed right thumb.

2.2 Hematologic abnormalities

In homozygote FA, the most prominent finding is hematologic disorders. The blood count at birth is mostly normal and macrocytosis is generally the first sign of FA. This is followed by thrombocytopenia and anemia. Pancytopenia develops typically at 5-10 years of age, median at seven years (birth to 31 years) (Butturini et al., 1994). IFAR defined hematologic abnormality as hemoglobin level below 10 g/dL, absolute neutrophil count below 1x10^9/L or platelet count below 100 x 10^9/L (Alter et al., 2003a). On retrospective analysis of 145 FA patients, some congenital anomalies were seen to carry a potential risk of the development of bone marrow failure. The risk of bone marrow failure in those with radius anomaly is 5.5 times more than those without. The presence of abnormal head, deafness, developmental delay, cardiopulmonary abnormality and abnormal kidney, also known as 5-item congenital abnormality, increase the risk of bone marrow failure (Rosenberg et al., 2004).
Hematologic disorders are the first sign of FA in young adults not exhibiting any congenital anomalies. Stress erythropoesis exists in FA with characteristics of macrocytosis, increased HbF and the antigen \( i \) (Table 1). These characteristics may also be found in the anemia free siblings of FA patients (Alter, 2003a). Aspiration from bone marrow reveals marked depression or absence of hematopoietic cells and replacement by fatty tissue containing reticulum cells, lymphocytes, plasma cells and usually tissue mast cells. Nucleated red cells are also decreased in number and they may display megaloblastic features (Fig. 4). Bone marrow biopsy is essential for diagnosis (Lanzkowksy, 1999). In a study based on data from 388 cases with FA, actuarial risk of developing hematopoietic abnormalities was 98% by the age of 40 (Butturini et al., 1994).

Trombocytopenia, anemia

**Pancytopenia median age: 7 years (5-10 years)**

Bone marrow failure in radius aplasia; 5.5

**Table 1. Hematological findings in FA.**

The most striking feature of FA cells is an increased spontaneous chromosomal instability. Diepoxybutane (DEB) test remains a classical test for diagnosis, involving the detection of chromosomal breaks, gaps, rearrangements, radials, exchange and endoreduplications in peripheral lymphocytes following culturing with clastogenic agents (such as DEB or mitomycin-C) (Fig. 5a, b) (Auerbach et al., 1981). FA homozygotes have a mean of 8.96 breaks per cell in the DEB test according to the IFAR (Alter, 2003a).
Fig. 5. a) Chromosomal structure abnormalities in the patient with FA. Arrow indicates typical quadriradial chromosome. b) Cytogenetic abnormalities in the metaphase plaque. Arrow indicates chromatid breaks and fragmentation.

Interpretation of the results of DEB test may be complicated by mosaicism. Approximately 25% of patients with FA have evidence of spontaneously occurring mosaicism as manifest by the presence of two subpopulations of lymphocytes, one of which is hypersensitive to cross-linking agents while the other behaves normally in response to these agents. Mosaicism might be associated with a relatively mild hematological course (Lo Ten Foe et al., 1997). DEB test gives a false negative for these patients. DEB testing to establish the diagnosis could be performed on an alternative cell type, such as skin fibroblasts (Alter & Kupfer, 2011). Although DEB test is of crucial importance in the diagnosis of FA, it should be also noted that molecular genetic diagnostic methods have also started to be used in the identification of this disorder.
Patients with FA generally develop some degree of bone marrow dysfunction ranging from mild asymptomatic cytopenias in any lineage to severe aplastic anemia, MDS or AML. The absence of marrow failure does not rule out FA (Shimamura, 2003). A number of cytokines are critical in the control and regulation of cellular homoeostasis in bone marrow. Several cellular disorders associated with FA were reported in a large number of studies. FA cells have important phenotypic abnormalities related to hematopoiesis as shown in Table 2.

### Table 2. Cellular disorders in FA (From Lanzkowsky, P. Manual of Pediatric Hematology and Oncology 1999).

- Sensitivity to cross-linking agents
- Prolongation of G2 phase of cell cycles
- Sensitivity to oxygen
- Sensitivity to ionized radiation
- Overproduction of tumor necrosis factor-α
- Direct defects in DNA repair:
  - Accumulation of DNA adducts
  - Defect in repair DNA cross links
- Genomic instability:
  - Spontaneous chromosome breakage
  - Hypermutability
- Increased apoptosis
- Defective p53 induction
- Intrinsic stem cell defect
- Decreased colony growth

Defective hematopoiesis in FA was shown by the investigation of in vitro bone marrow cell cultures. Interleukin (IL)-6 and granulocyte macrophage-colony stimulating factor expression reduced in many patients with FA (Stark et al., 1993). In another research, the overproduction of tumor necrosis factor-α in FA was also reported (Schultz & Shahidi, 1993). On the other hand, these patients have increased loss of telomere signals compared with controls (Hanson et al., 2001). Abnormal telomere metabolism might play a role in the evolution of bone marrow failure and malignant transformation in FA (Li et al., 2003). The cytokine changes, increased apoptosis and telomere shortening play a significant role in the microenvironment of bone marrow and the regulation of cellular homeostasis (Fig. 6). Bone marrow failure occurs at a median age of 7 years. Hematopoietic tissue is particularly sensitive to DNA damage caused by radiation or cytotoxic drugs. Genome instability and telomere shortening alter the signals and form mutant clones resistant to apoptosis and consequently AML develops (Lensch et al., 1999; Tischkowitz & Dokal, 2004).
The role of p53 in preventing DNA damage in FA cells was shown in a theoretical model (Kennedy & D’Andrea 2005). As revealed in Fig. 7, when severe DNA damage occurs in FA cells, p53 activates apoptosis and tumor progression is inhibited. If this process occurs in embryonic stem cells, it may cause anomalies. Stem cell loss in bone marrow leads to progressive anemia associated with FA.

Loss of p53 or other genes related to apoptosis due to DNA breakage by viral infection or cross-link agents, might inhibit the cell apoptosis. Cells with severe DNA damage continue dividing and this, in turn, may result in malignant transformation. Also a tumor may develop with human papilloma virus (HPV) infections. Since HPV E6 protein decreases the...
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p53 protein level, the apoptotic pathway activation is inhibited. Loss of p53 function may lead to cancer by allowing premalignant cells to survive (Kennedy & D'Andrea, 2005).

### 2.4 Complementation groups, genes and DNA repair

| Complementation group | Gene | Frequency |
|-----------------------|------|-----------|
| FA – A | FANCA | 60% |
| FA – B | FANCB | <1% |
| FA – C | FANCC | 15% |
| FA – D1 | BRCA2 | <5% |
| FA – D2 | FANCD2 | <5% |
| FA – E | FANCE | <1% |
| FA – F | FANCF | <1% |
| FA – G | FANCG | 10% |
| FA – I | FANCI | <1% |
| FA – J | BRIP1 | <1% |
| FA – L | FANCL | <1% |
| FA – M | FANC M | <1% |
| FA – N | PALB2 | <1% |
| FA – O | RAD51C | <1% |
| FA – P | SLX4 | <1% |

Table 3. FA complementation groups and genes (Adapted from Alter & Kupfer, 2011; Kennedy & D'Andrea, 2005).

FA-A mutations are the most frequent ones observed in about 60% of the cases; FA-C and FA-G mutations are recognized in 15% and 10% of the cases, respectively. While the frequencies of FA-D1 (BRCA2) and FA-D2 are 5% each, the prevalence of other complementation groups is rare (Kennedy & D'Andrea, 2005). The first gene cloned is the FA-C complementation group gene composed of 1674 nucleotides and 14 exons (Fig. 8). Six mutations are recognized in the gene. More than 90% of FA-C mutations are in exon 1 and in exon 4. There is a mild form of FA in mutation related with "dG 322" deletion in exon 1.

IVS4 + 4A > T mutations are distinguished for the majority of FA in Ashkenazi Jewish patients having severe phenotype of multiple congenital malformations and early onset of hematological disease (Joenje et al., 1995a, 1995b).

Fig. 8. Mutations in FA-C gene (From Joenje, H. et al., Fanconi Anemia Research: Current Status and Prospects, European Journal of Cancer 1995; 31:268-272).
Several types of, sometimes overlapping, DNA repair processes are identified based on the targeted types of damage. Three types of excision repair processes have been described: base excision repair (BER), nucleotide excision repair (NER) and mismatch repair (MMR). Two additional types of DNA repair, homologous recombination (HR) and nonhomologous end-joining (NHEJ) are employed in response to a double strand break, the most serious type of DNA damage. HR is considered to be an error-free pathway since it uses a copy of the damaged segment. NHEJ is accepted as an error-prone pathway since free ends are joined in the absence of a template which might cause an associated loss of nucleotides or translocation (Risinger & Groden, 2004). FA pathway has an important role in three classic DNA repair processes, namely homologous recombination, nucleotide excision repair and translesion synthesis which is DNA polymerization on damaged templates (Moldovan & D'Andrea, 2009).

FA proteins have a significant role in regulating DNA repair by homologous recombination. FA proteins cooperate in a common pathway known as the FA/BRCA pathway. Eight of the FA proteins (A, B, C, E, F, G, L, M and possibly I subunits) form a nuclear core complex required for the monoubiquitination of FANCD2 protein. In response to DNA damage, the FA complex (complex 1) is activated and initiates the monoubiquitination of FANCD2. Then FANCD2 – Ub interacts with BRCA2 in complex 2, leading to repair of the cross-link possibly through homologous recombination and translesion synthesis. The FANCD1 gene is identical to the breast and ovarian cancer susceptibility gene, BRCA2. FANCD2 is deubiquitinated by USP1, thereby inactivating the pathway (Fig. 9). The FA proteins are also important in the arrangement of an intra-S-phase checkpoint (D'Andrea, 2003; Kennedy & D'Andrea, 2005; Wang & D'Andrea, 2004). In the absence of BRCA2, DNA repair cannot be performed by homologous recombination. DNA damage is repaired by nonhomologous end-joining (Fig. 10).
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Fig. 10. Repair of double-strand break in normal and FA cells (Adapted from Venkitaraman, 2004). HR: Homologous recombination; NHEJ: Nonhomologous end-joining.

In the cytoplasm, only FANCA, FANCC, FANCF and FANCG proteins are present. Cytoplasmic functions and interactions of FANCC and FANCG are decoded. The FANCC protein binds to NADPH cytochrome P-450 reductase and regulates the major detoxification pathway. FANCC also interacts with glutathione-S-transferase PI-I, and protects the cell from oxidative stress. FANCC interacts with HSP70 to prevent the apoptosis in hematopoietic cells exposed to IFN-γ and TNF-α. FANCC is required for optimal activation of STAT1 in the JAK/STAT pathway. FANCG protein directly interacts with CYP2E1 and prevents oxidative DNA damage (Thompson et al., 2005).

2.5 Fanconi anemia and cancer

Mutations in FA genes cause a disorder characterized by bone marrow failure, developmental defects and cancer proneness (Moldovan & D'Andrea, 2009). The FANCD2 knockout mice exhibit micropthalmia, perinatal lethality, and severe hypogonadism. Fancd2 knockout mice also has increased incidences of epithelial cancers such as breast, ovarian and liver cancers (D'Andrea, 2003). FA is a rare cancer susceptibility syndrome that increases the predisposition of the patient to leukemia, squamous cell carcinomas of the head and neck or female genitalia as well as liver tumors. Predisposition to cancer in heterozygotes was also reported by Swift (Alter, 2003a). One thousand three hundred cases of FA were evaluated during the years between 1927 and 2001. Nine percent of these cases had leukemia, 7% had myelodysplastic syndrome, 5% had solid tumors and 3% liver tumors. In approximately 25% of patients with cancer, the malignancy preceded the diagnosis of FA. It is unclear which patients are prone to develop such tumors (Alter, 2003c). In another study, the cumulative incidence of malignancies among 145 patients with FA was 9 leukemias and 18 solid tumors in 14 patients. The ratio of observed to expected neoplasm (O/E) was 50 for all cancers, 48 for all solid tumors and 785 for leukemia. These increased risks were calculated to be statistically significant. The highest solid tumor O/E ratios were 4317 for vulvar cancer, 2362 for esophageal cancer, and 706 for head and neck cancer. The median age of onset of leukemia was 11.3 years, which is significantly lower compared to the median 28.9 years of onset for solid tumors (Rosenberg et al., 2003). Actuarial risk of developing MDS or AML by 40 years of age was 52% (Butturini et al., 1994).
The types of leukemia occurring in FA are primarily non-lymphocytic leukemia although a few lymphoblastic types have also been reported (Alter, 1993a; Yetgin et al., 1994). The incidence of AML in FA patients is 15,000 times more compared to children in the population (Auerbach & Allen, 1991). In these patients, all FAB sub-types occur; the myelomonocytic (M₄) and acute monocytic (M₅) types (Fig. 11, Fig. 12) are the most common (Alter, 2003c, Tischkowitz & Dokal, 2004).

Certain cytogenetic abnormalities are commonly seen in these patients with MDS/AML. In one study of the cytogenetic findings of 23 MDS and AML cases in FA homozygotes in high incidence of monosomy 7, 7q-, rearrangement of 1p36, 1q24-34 and 11q22-25, abnormalities was reported (Butturini et al., 1994). The most frequently observed chromosomal abnormalities in FA-associated leukemia are monosomy 7, duplication of 1q and chromosome 3q abnormalities. Gain of 3q is associated with poor prognosis (Taniguchi & D'Andrea, 2006). As suggested, all FA patients may be considered as preleukemic state and this disorder represents a model for study of the etiology of AML (Auerbach & Allen, 1991).

Leukemia may be the first hematologic manifestation of FA (Auerbach et al., 1982). Five out of the 52 patients with FA developing 3 AML, 1 squamous cell carcinoma of the gingiva, 1 hepatocellular carcinoma were mentioned in another clinical research (Altay et al., 1997). In our series, four out of 39 cases developed AML and one had two malignancies. There were no other cancers among family members in these four patients whereas the sister of a boy with FA developed acute leukemia in another hospital. (Gözdaşoğlu et al., 1980, Gözdashoğlu et al., 2009). The majority of solid tumors occurs after the first or second decade of life (Alter, 2011).
FA-D1 complementation group is different from other complementation groups in its severity. In this group, leukemia and solid tumors develop as early as before 5 years of age. A cell line (termed FA-AML1) was obtained from blast cells after a second relapse following the bone marrow transplantation in a 2 years old boy with FA and AML. FA-AML1 is the first AML cell line obtained from a FA patient. FA-AML1 cells have failed to reveal FA phenotype such as hypersensitivity to growth inhibition and chromosomal breakage by the cross-linking agent mitomycin C. Genomic DNA showed biallelic mutations in FANCD1/BRCA2. Genetic reversion has been observed resulting in the loss of the FA cellular phenotype (Ikeda et al., 2003). In another report, a cross-linker-sensitive AML cell line also was derived from a 2 years old boy who had biallelic FANCD1/BRCA2 (Meyer et al., 2005). FA-D1 subgroup, however, can be associated with a high incidence of leukemia and specific solid tumors such as Wilms tumor and medulloblastoma in very early childhood (Hirsch et al., 2004). BRCA2 mutations predisposes to cancers like the familial breast, ovary, prostate and pancreas (Shivji & Venkitaraman, 2004). From several studies on the issue, it is possible to conclude that the diagnosis of leukemia and solid tumors at early age and worse prognosis are the most important features of FA-D1 complementation group. FA is found as the most common form of inherited bone marrow failure syndrome associated with worst prognosis. A high percentage of patients developed severe bone marrow failure and cancer in a study based on 127 patients whose 66 cases (52%) are with FA. One of the striking findings of this study is the high rate of consanguinity, 68% of patients with FA. Leukemia in 7 patients (11%), MDS in 11 patients (16%) and solid tumors in 6 patients (9%) out of these 66 cases were diagnosed (Tamary et al., 2010). In another study of 181 patients, however, bone marrow failure in 66 patients, acute myeloid leukemia in 14 patients and solid tumors in 10 patients were determined. The ratio of O/E was 44 for all cancers, 26 for all solid tumors and 868 for acute myeloid leukemia. These increased risks were statistically significant. In this study, absent or abnormal radii and a five-item congenital abnormality score were significant risk factors for bone marrow failure. In three of the 48 patients who received a transplant, the three malignancies, namely tongue, liver and esophagus, occurred after 2, 16 and 17 years following the transplants. The age-specific risk of solid tumors was 3.8-fold higher in cases with transplants compared to the cases without (Rosenberg, Alter & Ebell, 2008). Hematopoietic stem cell transplant (HSCT) is presently the only therapy that can restore normal hematopoiesis in patients with FA. The risk of squamous cell cancers increased for FA patients irrespective of receiving and not receiving the transplants. HSCT conditioning regimes may also increase the occurrence of squamous cell cancers in cases with transplants. Rosenberg et al., compared two groups of patients; 117 receiving transplants and 145 not receiving. It was found that the age-specific risk of squamous cell cancer was 4.4 fold higher in patients who received transplants than who did not. Squamous cell cancers developed at significantly younger ages in the transplanted group. Acute and chronic graft-versus-host diseases were significant squamous cell cancer risk factors, and this cancer was also an adverse risk factor for death in both groups. Survival rate following squamous cell cancer was not significantly different between the two groups (Rosenberg et al., 2005). Liver tumors associated with androgens were reported in the patients with FA (Velazquez & Alter, 2004) and the cumulative probability of liver tumors has been estimated to be 46% by age 50 (Alter, 2003c). The patients with FA should be followed in the form of hematologic monitoring and cancer surveillance. Complete blood counts should be taken every 4 months. Annual bone marrow aspirates and biopsies should be performed on all patients. Dental and oropharyngeal...
including naso-laryngoscopy) exams should start at age 10 or within the first year after transplant. Gynecologic examination and Pap smear beginning at age 16, and if necessary, annual esophageal endoscopy should be done as part of cancer surveillance. The patients are advised to avoid toxic agents, smoking and alcohol. Radiographic studies should be minimally utilised. Vaccination of female patients with the human papillomavirus vaccine should be considered starting at nine years of age (Alter, 2011).

3. Conclusion

FA is a rare autosomal recessive or X-linked inherited chromosomal instability syndrome. Affected individuals have a highly increased risk of developing bone marrow failure, hematologic malignancies and solid tumors. FA-pathway has an important role in repairing DNA damage namely homologous recombination, nucleotide excision repair and translesion synthesis. Fifteen complementation groups and genes that cause FA have been identified. FA-D1 subgroup can be associated with high incidence of leukemia and solid tumors such as Wilms tumor, medulloblastoma, neuroblastoma at early ages. BRCA2 mutations predispose to cancers such as familial breast, ovary, prostate and pancreas. Leukemia in FA is generally very difficult to treat and survival is rare. The deficiency in DNA repair leads to increased sensitivity to the side effects of chemotherapy and the patients are either vulnerable to treatment toxicity or may receive inadequate treatment. The effective treatment modalities have to be further developed. Patients with FA should be followed with regard to AML and solid tumors which should be considered as first manifestations of FA. It is also important to note that the family members of the patients with FA must be scanned for cancer as well. Genetic counseling and psychosocial support should be employed as soon as possible.

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This book provides an up-to-date summary of many advances in our understanding of anemia, including its causes and pathogenesis, methods of diagnosis, and the morbidity and mortality associated with it. Special attention is paid to the anemia of chronic disease. Nutritional causes of anemia, especially in developing countries, are discussed. Also presented are anemias related to pregnancy, the fetus and the newborn infant. Two common infections that cause anemia in developing countries, malaria and trypanosomiasis are discussed. The genetic diseases sickle cell disease and thalassemia are reviewed as are Paroxysmal Nocturnal Hemoglobinuria, Fanconi anemia and some anemias caused by toxins. Thus this book provides a wide coverage of anemia which should be useful to those involved in many fields of anemia from basic researchers to epidemiologists to clinical practitioners.

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