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TO THE EDITOR:

ERCC6L2 defines a novel entity within inherited acute myeloid leukemia

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ERCC excision repair 6 like 2 (*ERCC6L2*) is a newly identified gene with an impact on hematological disease development. Lack of ERCC6L2 results in defects in the transcription-coupled nucleotide excision repair pathway, leading to genome instability.[1] It also affects mitochondrial function, increasing reactive oxygen species levels and altering cellular homeostasis.[2]

Biallelic germ line mutations in *ERCC6L2* were recently reported to cause bone marrow failure (BMF).[2-6] The first article described two consanguineous families where affected children experienced developmental delay and microcephaly in addition to BMF.[2] However, subsequent studies have excluded these extrahematopoietic manifestations from the disease phenotype.[1,3,4] Järviaho et al[3] reported the *ERCC6L2* c.1457delT, p.Ile486ThrfsTer36 mutation (NM_001010895.2, GRCh37; rs768081343) in 2 Finnish BMF cases.

Most BMF syndromes predispose to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Four cases of MDS and/or AML have been reported among 24 patients with biallelic *ERCC6L2* mutations.[1,4] These patients were diagnosed with MDS or AML in childhood or as young adults (age 2-22 years), with only 1 patient alive at the time of the original reports.[1,4] AML/MDS subtypes were not reported; however, all patients were described as carrying monosomy 7.[1,4] This is a common abnormality in therapy-related, secondary, erythroid, and germ line predisposed leukemias.[7,8]

The definition of AML with erythroid characteristics (AML M6 by French-American-British [FAB] classification) has been under debate.[9,10] In practice, AML M6a and AML M6b are considered as MDS or AML, NOS, nonerythroid subtype and AML, NOS, erythroid leukemia (pure erythroid type), respectively, in the current World Health Organization (WHO) classification of myeloid malignancies.[11] For clarity, we use FAB nomenclature here.

We report causality of a germ line homozygous *ERCC6L2* c.1457delT, p.Ile486ThrfsTer36 mutation (supplemental Figure 1,

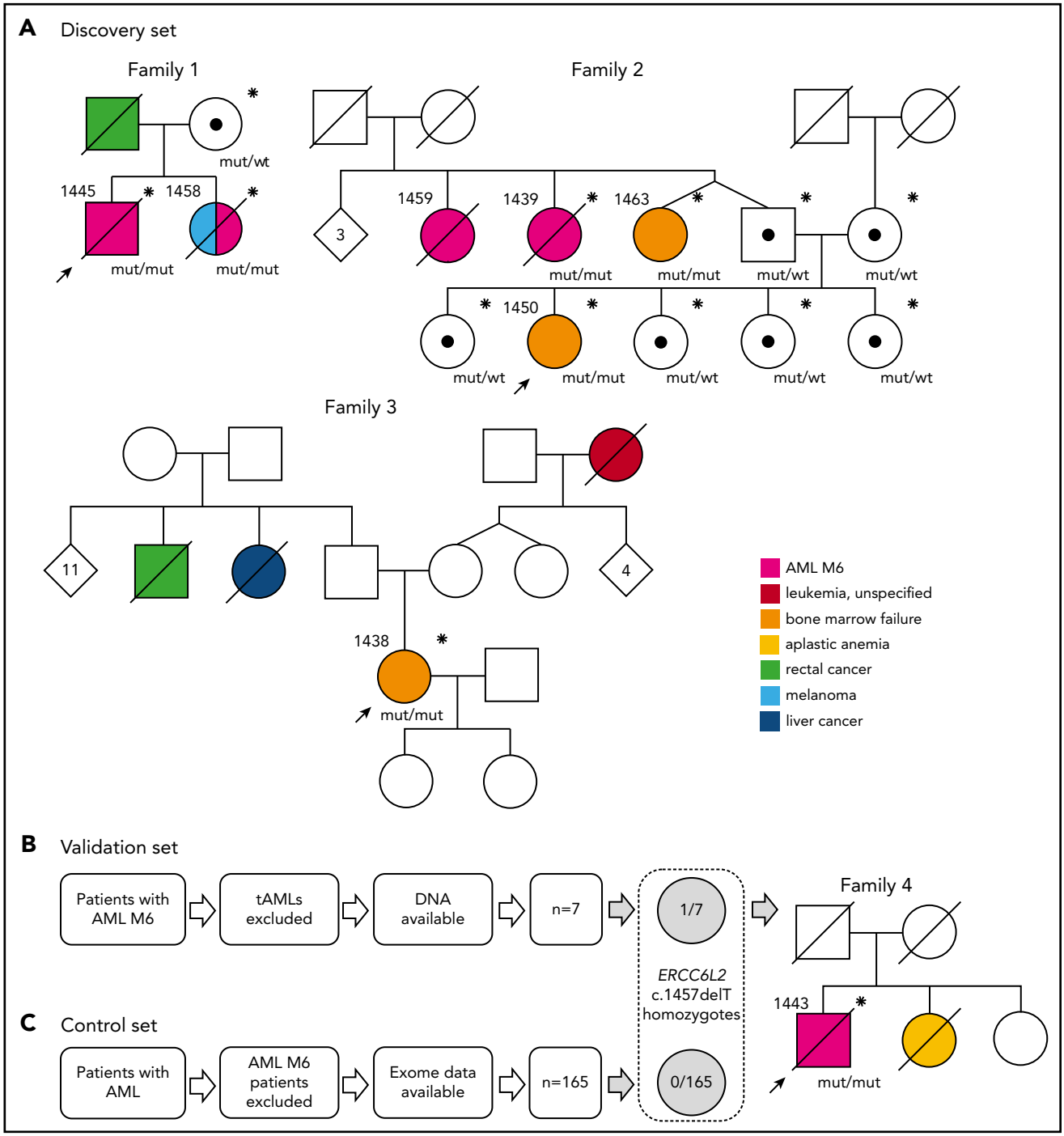

Figure 1. Families in this study and the selection process of patient data. Individuals who have been genotyped for the *ERCC6L2* c.1457delT mutation are marked with an asterisk (*). Black dots (•) represent heterozygous carriers of the mutation. Probands in each family are marked with arrows. (A) Families (1-3) in the discovery set. Family 1: patient 1445 was age 38 years when referred to hematologist because of pancytopenia. His BM was dysplastic with strong erythroid predominance and an excess of myeloid blasts. Aiming at allogeneic hematopoietic stem cell transplantation (HSCT), his 36-year-old sister (patient 1458) was examined as a donor candidate. Tests revealed peripheral blood cytopenias. The following BM examination revealed MDS, which quickly progressed to AML M6. She died as a result of refractory leukemia. Patient 1445 underwent HSCT from a registry donor but relapsed quickly with a therapy-resistant AML M6 and died as a result of the disease. Family 2: the index patient (1450) age 18 years was diagnosed with BMF of unknown origin and referred to the hematology department in 2018. Her 2 paternal aunts (patients 1459 and 1439) had died as a result of AML M6. The twin sister (patient 1463) of the index's father had mild thrombocytopenia and was diagnosed with BMF and 3 acquired *TP53* mutations along with this study. Family 3: patient 1438 had spontaneously recovered from aplastic anemia in her childhood. At age 31 years, while pregnant, she was identified as having persistent thrombocytopenia. A next-generation sequencing myeloid gene panel on her peripheral blood sample detected a somatically mutated *TP53* clone. BM samples showed severe BMF. (B) Analysis of the validation set. One (patient 1443) of 7 AML M6 patients was found homozygous for *ERCC6L2* c.1457delT. Family 4: patient 1443 was age 65 years when diagnosed with AML M6. His sister had died as a result of severe aplastic anemia (or BMF) at a young age. (C) No *ERCC6L2* c.1457delT homozygotes were found in the control set of 165 AML patients with other subtypes. Mut, mutated; tAML, therapy-related AML; wt, wild type.

Table 1. Patients with a homozygous *ERCC6L2* mutation

Family	Patient	Disease course	Age at hematological diagnosis, y	Previous conditions	Family history of malignancies	BM karyotype	Somatic mutations in BM			Somatic mutation analysis
							FLT3/*NPM1*	*TP53*, VAF	Other	
1	1445	MDS → AML M6 → relapse soon after allogeneic HSCT; died	MDS at 38; AML M6 at 39	No	Father died as a result of CRC in his 50s; paternal cousin died of pancreatic cancer in 40s; 1458	Hypodiploid 41-43, −5, −7 −17, −18, −19, −20	−/−	c.532C>G p.(His178Asp) 35%	None	Whole-exome sequencing
1	1458	MDS → AML M6 → relapsed on chemotherapy; died	MDS at 36; AML M6 at 37	Melanoma in situ × 2 (surgery)	Father died as a result of CRC in his 50s; paternal cousin died of pancreatic cancer in 40s; 1445	Hypodiploid 43, −7, −12, 5q−	−/−	c.517G>A p.(Val173Met)	N/A	Capillary sequencing of TP53
2	1450	BMF; alive	14	No	2 paternal aunts (1439, 1459) died as a result of AML M6	CN	−/−	None	None	NGS panel
2	1439	AML M6 → relapsed 13 mo after allogeneic HSCT; died	59	No	Sister (1459) died as a result of AML M6; other sister (1463) has BMF	t(3;12;?),t(12;?), −7, −5, t(5;?)	−/−	c.577C>T p.(His193Tyr), c.818G>A p.(Arg273His)	N/A	Capillary sequencing of TP53
2	1459*	AML M6 → refractory disease; died	38	No	Sister (1439) died as a result of AML M6; other sister (1463) has BMF	Complex (specific data N/A)	N/A	N/A	N/A	N/A
2	1463	Mild neutropenia and thrombocytopenia → BMF; alive	Cytopenias at 47; BMF at 59	No	2 sisters (1459 and 1439) died as a result of AML M6	CN	−/−	c.743G>A p.(Arg248Gln) 5%, c.830G>T p.(Cys277Phe) 23%, c.843C>A p.(Asp281Glu) 11%	None	NGS panel
3	1438	AA, spontaneous recovery → marginal neutropenia and thrombocytopenia and severe BMF 20 y later	AA at 11; mild cytopenias at 20; BMF at 31	Cerebral vein thrombosis, Rathke's cyst	2 cousins (mother's side) with some hematological symptoms; grandmother died as a result of leukemia NOS; 6/7 of grandmother's siblings died of solid tumors; 2/13 of father's siblings died of cancer (CRC and liver)	CN	−/−	c.659A>G p.(Tyr220Cys) 31%	None	NGS panel
4	1443	AML M6 → relapsed soon after allogeneic HSCT; died	AML M6 at 65	Tubular adenoma with dysplasia in rectum at 59	Sister died as a result of AA at 34	42-46, del(5)(q31), dup(5)(q31)/t(5;5), −7, 11q23/MLL amplification or translocation, −4	−/−	c.818G>A p.(Arg273His), c.856G>A p.(Glu286Lys)	N/A	Capillary sequencing of TP53

All *TP53* mutations reported in NM_000546.5. Variant allele frequency (VAF) not available for capillary sequencing data. Only hotspot exons 5-9 were checked with capillary sequencing (supplemental methods).

AA, aplastic anemia; CN, normal chromosomes; CRC, colorectal cancer; NGS, next-generation sequencing; NOS, not otherwise specified; N/A, not available.

*Not tested.

available on the *Blood* Web site) resulting in early somatic *TP53* mutations and AML with erythroid characteristics resembling AML M6.

Initially, we discovered 3 families with a homozygous germ line *ERCC6L2* c.1457delT mutation and validated the result in a series of AML M6 patients (n = 7; excluding AML M6 arising after chemotherapy or radiation treatment for another malignancy) identified in the Finnish Hematology Registry (Figure 1B). A series of AMLs of other subtypes with whole-exome sequencing data available (n = 165) were used as a control set (Figure 1C). In the discovery families, we identified 6 individuals with the homozygous mutation (Figure 1A), all of whom had AML M6 (n = 3) or BMF (n = 3; Table 1). Only patients with BMF were alive. Additionally, 1 individual (1459, family 2) whose BM morphology data but not tissue or DNA samples were available had died as a result of AML M6.

In the series of 7 other AML M6 patients, we found 1 with the same homozygous *ERCC6L2* mutation. Clinical characteristics of all *ERCC6L2*-mutated patients are listed in Table 1 and in the supplemental Data. *ERCC6L2* c.1457delT was identified as heterozygous in 3 patients (consistent with gnomAD MAF of .005) in the control set of 165 AMLs of other subtypes. No other *ERCC6L2* mutations were present in the AML germ line exomes, nor did we detect any biallelic *ERCC6L2* mutations. In summary, 4 of the 10 tested AML M6 cases carried the homozygous *ERCC6L2* mutation in comparison with 0 of 165 in the control group of other subtypes of AML ($P = 9.734 \times 10^{-5}$; only statistically independent cases [n = 3] were included). We also investigated germ line *ERCC6L2* variants in 10 389 cancer patients (including 142 AML cases) available in The Cancer Genome Atlas PanCanAtlas data set.[12] No homozygous protein-truncating rare (<5% minor allele frequency [MAF]) variants were found.

Somatic tumor protein p53 (*TP53*) mutations are prevalent in AML M6, at 36% compared with 11% in other AML subtypes.[9,13] Two of 3 BMF cases and all AML patients with biallelic *ERCC6L2* mutation already had acquired somatic *TP53* mutations in their BM before AML diagnosis (Table 1). No other somatic mutations in myeloid genes with recurrent mutations in AML or MDS were found.

Median age at diagnosis of AML M6 in our *ERCC6L2*-mutated patients was 49 years (39 years if including patient 1459). In the other AML M6 patients, median age was 67 years, consistent with the previously reported median of 68 years.[13] Despite the lower age at leukemia onset in *ERCC6L2*-mutated patients, none survived, which reflects the dismal prognosis of AML M6.[7] None of the AML M6 patients were known to have BMF preceding leukemia, and no blood count data were available from the time before AML diagnosis; however, relatives of patients 1439 and 1459 reported that both individuals had anemia in their youth. This may be explained by the (symptomless) mild cytopenias sometimes observed in BMF.

Although a notably high penetrance was observed here, a larger sample series is needed for a more refined assessment of penetrance. The identified *ERCC6L2* mutation seems to be a founder mutation in Finland (gnomAD Finns MAF = .005 vs global MAF = .0005) and may be enriched in certain areas, explaining the inheritance pattern in family 2 with ancestors from the same region (Figure 1).[14]

We also identified individuals in earlier phases of the disease continuum from BMF to leukemia. Interestingly, 2 of the 3 BMF patients had somatic *TP53* mutations representing clonal evolution. This was also reflected in the *ERCC6L2*-mutated AML M6 cases, because they were all carriers of 1 or 2 somatic *TP53* mutations at the time of leukemia diagnosis, suggesting a strong positive selection. *TP53* alterations in AML M6 are not rare, but we suggest that, at least in the setting of ERCC6L2-driven leukemogenesis, they represent the early steps toward malignancy and lead to poor leukemia therapy results. This may be similar to Shwachman-Diamond syndrome, which is another well-known BMF syndrome with strong leukemia predisposition.[15,16] The order of molecular changes is in contrast to that of 5q− MDS, for example, where *TP53* alterations are thought to occur after chromosomal rearrangements.[8] How ERCC6L2 deficiency predisposes individuals to *TP53* mutations warrants further study. Notably, recent reports have demonstrated the high impact of somatically mutated *TP53* clones in the dynamics of leukemogenesis.[17,18]

We report a direct association of a homozygous truncating germ line mutation in *ERCC6L2* with a specific high-risk leukemia subtype characterized by *TP53* mutation(s) and erythroid predominance resembling AML M6 by FAB classification. Certain genes have been previously associated with AML M6 predisposition, but the study families have also presented with other types of leukemias and/or hematological malignancies, indicating a less lineage-restricted predisposition.[19,20] To our knowledge, this is the first time a germ line alteration has been suggested to cause a strictly specific subset of acute leukemia. In the era of precision medicine, our findings suggest that AML with somatic *TP53* mutations and erythroid predominance stemming from biallelic *ERCC6L2* mutations forms a new entity of AML within myeloid neoplasms with germ line predisposition.

Our families have acknowledged for years that AML with a dismal prognosis runs among them. This study has finally discovered the culprit and has also supplied some family members with a relieving verdict. On the basis of our findings and previous reports on *ERCC6L2*-driven BMF, we suggest hematologists consider careful follow-up and prompt planning of HSCT, which is so far the only potentially lifesaving possibility for *ERCC6L2*-deficient patients with BMF at risk of leukemia.

The study was approved by the ethics committee of Helsinki University Hospital (#206/13/03/03/2016 and #303/13/03/01/2011). All living participants provided informed written consent to take part in the study.

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Authorship

Contribution: S.P.M.D. analyzed the whole-exome sequencing data; P.S. and S.P.M.D. performed the capillary sequencing and analyzed the results; P.E.K. reexamined the bone marrow aspirate slides and biopsy specimens; U.W.-K. collected the patient samples and clinical data, together with M.P., S. Kakko, E.-R.S., U.S., and K.O.; S. Kytölä analyzed and interpreted the next-generation sequencing panel data; E.P. performed the statistical analysis and analyzed the online data sets for truncating *ERCC6L2* mutations; K.P. provided the control exome data; S.P.M.D. drafted the manuscript; O.K. and U.W.-K. designed the study, supervised the experiments, and finalized the manuscript; and all authors revised and approved the final version of the manuscript.

Conflict-of-interest disclosure: M.P. has had travel, accommodations, and expenses provided by Amgen and Pfizer; U.S. has provided consulting for Mylan; K.O. has had travel, accommodations, and expenses provided by Novartis, Novartis Oncology, and AstraZeneca; and U.W.-K. has provided consulting for Pfizer and Sanofi-Genzyme. The remaining authors declare no competing financial interests.

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Footnotes

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