To the Editor: Ataxia telangiectasia (A-T) is an autosomal recessive disease, characterised by progressive neurodegeneration with cerebellar ataxia, oculo-cutaneous telangiectasia, immunodeficiency, and cancer predisposition. It is caused by biallelic mutations in ATM (ataxia telangiectasia mutated, chromosome 11q22.3) encoding a serine/threonine kinase essential in cell cycle control, DNA double-strand break repair and haematopoietic stem cell maintenance.1,2 Individuals with A-T classically develop lymphoid malignancies, a broad spectrum of other malignancies3 and rarely, acute myeloid leukaemia (AML).4-7 Previous AT-AML reports have described the karyotype and dismal clinical course (Table S1). We performed sequential sample genomic profiling of an AML that developed in a 17-year-old female with A-T to identify secondary genetic events toward myeloid malignancy and explore the changes in mutational burden over time (full clinical case history in Supporting Information).

Whole exome sequencing was performed on DNA extracted from blood taken at A-T diagnosis (age 8 years, "germline") and repeat samples during the AML disease course (age 17 years): bone marrow (BM) and blood samples collected at AML diagnosis (T1) and then at 1 month (T2) and 11 months later (T5) (Figure 1; Table S2 and Supporting Information Materials and Methods for sample collection, preparation and data analysis). All selected variants were validated by Sanger sequencing (Table S3; Figures S2 and S4-S8).

Germline analysis confirmed the pathogenic homozygous ATM splice acceptor site variant c.5763-1G>C (IVS8-1G>C; hg.19 chr.11:108180886G>C). No other pathogenic variants were identified in genes known to be associated with AML predisposition8 (Figure S1; Tables S4 and S5).

Cytogenetic analysis at AML diagnosis identified an abnormal complex karyotype (Table S1). We examined gross copy number changes over time with subsequent WES samples, and a single nucleotide polymorphism (SNP) array was performed on a DNA sample (T6) collected 1 year after AML diagnosis, with consistent results (Figure 1). The data showed large chromosomal deletions at 2q, 5q and 17q, and smaller ones at 1p and 7q, all present from the earliest AML time point. The 12p deletion was a late event present only in 20% of T6 cells, and the 12q copy number neutral LOH was not detectable by the exome analysis method. The copy number gain events within 1q, 4p and 6q were also present from the earliest time points and only those at Xq and 5p were late events in T5 and T6, respectively.

To determine smaller scale somatic events, we compared sequence data obtained at each disease time point to the germline sample. This identified 22 somatic variants from which several candidates may be contributing to leukaemogenesis but none in TP53 (Figure S3; Tables S6 and S7). One candidate was the heterozygous missense substitution in KRAS NM_004985.4:c.468C>G (p.Phe156Leu), where the affected conserved residue within the catalytic domain functionally activates KRAS by facilitating faster cycling of GTP/GDP substrate.9 Activated KRAS and downstream signalling has been shown to preferentially drive myeloproliferative neoplasms over T-cell acute lymphoblastic leukaemia (ALL).10

A loss-of-function mutation was identified in the DNA/RNA helicase G3BP1, known to interact with Ras signalling.11 The stop-gain substitution c.1275T>A (p.Leu377*), causing premature truncation within the RNA recognition and binding domain, falls within the common AML 5q deletion (Figure 1B) and shows increasing variant allele frequency (VAF) in the tumour samples (50%, 83%, 91% and 85% in BM, T1, T2 and T5, respectively). In myeloid neoplasms with 5q deletions, G3BP1 demonstrates haploinsufficiency and is associated with poor survival.12

Other variants that may functionally cooperate in MAPK/ERK signalling, downstream of activated KRAS, were identified in ZNF436 and TBL1XR1.

Furthermore, we detected an oncogenic variant in exon 6 of IL7R, interleukin-7 receptor, appearing as two variants, although a composite aberration of a single nucleotide deletion and four nucleotide insertion, c.752delinsGCCA (p.Phe251CysHis). This variant type is associated with T-cell acute lymphoblastic leukaemia and has been mechanistically described.13,14 The introduced unpaired cysteine in the extracellular juxtamembrane-transmembrane region creates intermolecular disulphide bonds leading to constitutive receptor activation and malignant transformation. Located within the late copy number gain chromosome 5p region in our patient (Figure 1B), this variant was detectable from the time of bone marrow collection at AML diagnosis and showed increased VAF in T5 (11%, 5%, 16% and 49% in BM, T1, T2 and T5, respectively).

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In summary, we undertook genomic profiling of an AML arising in an individual with biallelic germline pathogenic variants in ATM. We found a complex karyotype AML with greater than three unbalanced copy number aberrations, including losses at 5q and 7q however without the commonly accompanying TP53 gene disruption.15,16 We observed 22 somatic variants present from the time of AML diagnosis with no increment in mutational burden over time.17 The key candidates for AML leukaemogenesis identified were a well-known activating KRAS mutation, a truncating variant in RasGAP/p53-associated G3BP1 and the chromosomal loss at 5q. Their co-occurrence from the earliest AML sample implies a proliferative advantage for myeloid malignant cells, whether they act synergistically or independently. We also report the concomitant expansion of an archetypal T-cell acute lymphoblastic leukaemia oncogenic exon 6 mutation in IL7R.13,14 Thorough genomic investigation of this case has shown that in an inherently deficient DNA repair environment, multiple genomic alterations may permit different oncogenic pathways to evolve together.

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REFERENCES


SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.