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Acute myeloid leukemia with t(10;17)(p15;q21)/*ZMYND11::MBTD1*: a subtype with minimal differentiation, CD7/CD56 expression, and generally poor outcomes in adults

Qing Wei[1], Naveen Pemmaraju[2], Sa A. Wang[1], Shimin Hu[1], Courtney DiNardo[2], Ghayas C. Issa[2], Carlos E. Bueso-Ramos[1], Jie Xu[1], Shaoying Li[1], L. Jeffrey Medeiros[1], Guilin Tang[1*]

[1]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[2]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Running Title: AML with t(10;17)/*ZMYND11::MBTD1*

*Corresponding Author:

Guilin Tang, M.D., Ph.D.

Department of Hematopathology, The University of Texas MD Anderson Cancer Center

6565 MD Anderson Blvd, Houston, Texas 77030

Phone: (713)-792-5870

Email: gtang@mdanderson.org

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The t(10;17)(p15;q21) resulting in the *ZMYND11::MBTD1* is a rare but recurrent cytogenetic abnormality previously reported in approximately 10 cases of acute myeloid leukemia (AML), predominantly in AML with minimal differentiation (also known as M0)[1-5]. Prior studies have noted frequent expression of CD7 and CD56 in these cases. However, due to the limited number of reported cases, the clinicopathologic characteristics, gene mutation profiles, treatment responses and patient outcomes associated with *ZMYND11::MBTD1* remain poorly understood. In this study, we describe 5 additional cases of AML harboring t(10;17)(p15;q21), with comprehensive clinicopathologic, immunophenotypic, cytogenetic and molecular characterization. We also summarize the findings from 7 previously reported cases in the literature. This study was approved by the Institutional Review Board of MD Anderson Cancer Center and was conducted in accord with the Declaration of Helsinki.

Demographic, clinicopathologic, cytogenetic and molecular findings are summarized in **Table 1**. All 5 patients presented with AML characterized by primitive blasts showing minimal differentiation. Flow cytometric immunophenotypic profiles are summarized in **Table 2**. In all cases, the blasts were uniformly positive for CD7, CD33, CD56 (bright) and CD117, and were negative for myeloperoxidase (MPO), monocytic markers (CD4, CD14, CD64), CD19, and the T-cell markers (CD2, sCD3, cytoCD3, CD5). HLA-DR was completely absent in 4 cases, and minimally expressed in one case. Cytochemical staining for MPO was negative or showed reactivity in less than 3% of blasts in all cases. All cases had a non-complex karyotype and in 4 cases no mutations were identified.

Patient 1 presented with fatigue and fever. Bone marrow (BM) aspiration revealed 58% blasts. The blasts were medium to large, with scant cytoplasm, fine chromatin, distinct nucleoli, and without Auer rods (**Fig. 1A-B**). Flow cytometric immunophenotyping (FCI) results are shown in **Fig. 1C** and summarized in **Table 2**. Conventional karyotyping revealed t(10;17)(p15;q21) as the sole abnormality (**Fig. 1D**). The patient was diagnosed with AML with minimal differentiation (M0) and received induction chemotherapy. He achieved complete remission at 3 months, but the AML relapsed at 23 months. Optical genome mapping (OGM) confirmed t(10;17)(p15.3;q21.33)(244532;51223617) and detected a fusion gene *ZMYND11::MBTD1* (**Fig. 1E–1F**). The patient received multiple lines of salvage therapy but was refractory to all and died at 34 months after diagnosis.

Patient 2 had a history of breast cancer (diagnosed 9 years prior) treated by mastectomy and hormonal therapy. She presented with fatigue and 16-pound weight loss over several months. BM aspiration and biopsy showed sheets of neoplastic cells that appeared “cohesive” on aspirate smears. Immunohistochemistry and FCI showed that the neoplastic cells were strongly positive for CD7, CD33, CD43, CD56 and CD99, weak CD117, and negative for MPO, HLA-DR, all other lineage-specific markers and cytokeratin. OGM detected a t(10;17)(p15.3;q21.33) with the fusion gene *ZMYND11::MBTD1*. The patient was treated with venetoclax, cladribine and low dose cytarabine. However, persistent disease was noted at the 1-month follow up and the patient was lost to follow-up 2 months later.

Patient 3 was diagnosed with AML harboring chromosomal translocation t(10;17) and *TET2* mutation. She received standard 7+3 induction chemotherapy and achieved morphologic

remission at the 1-month BM evaluation. She underwent hematopoietic stem cell transplant (HSCT) at 8-month post diagnosis. Unfortunately, she relapsed 3 months post-HSCT. After relapse, the patient was refractory to salvage therapies and died four months after relapse.

Patient 4 was diagnosed with AML with cytogenetic abnormalities of t(10;17) and del(16q). He received standard 7+3 induction chemotherapy and achieved complete remission at the 1-month follow-up. The patient subsequently underwent first HSCT at 4 months post-diagnosis. However, the AML relapsed at 30 months with recurrence of the same chromosomal abnormalities. The patient was treated with mitoxantrone plus VP-16 and achieved a second remission, followed by a second HSCT at 36 months. Unfortunately, the disease relapsed again at 45 months. Karyotyping revealed clonal evolution with a newly acquired inv(2)(p11.2q21). Following second relapse, the patient was refractory to multiple lines of salvage therapy and died 57 months after diagnosis.

Patient 5 was diagnosed with AML with t(10;17). She received azacitidine for four cycles, but persistent disease was noted. The patient was later managed at her local hospital, where details of her subsequent therapy and disease status were unavailable. She died at 11 months after initial diagnosis.

ZMYND11 (chr 10p15) has 14 exons and *MBTD1* (chr 17q21) has 17 exons. The t(10;17)(p15;q21) produces an in-frame chimeric fusion, joining *ZMYND11* exons 1–12[2,4,5] (less often exon 1–11[3]) with *MBTD1* exons 3–17[2-5]. In this cohort, OGM revealed breakpoints on *ZMYND11* between exons 9-13 and on *MBTD1* between exons 3-4 in two cases. The fusion

protein retained the N-terminal chromatin reader domains of *ZMYND11* (PHD, bromodomain and PWWP) which recognizes H3.3K36me3 at transcriptional active loci.[6] *MBTD1* contributes components of the NuA4/TIP60 histone acetyltransferase complex, a transcriptional coactivator[7]. *ZMYND11::MBTD1* misdirects TIP60 to *ZMYND11*-bound loci, leading to aberrant histone acetylation, transcriptional upregulation and altered RNA splicing,[8,9] including activation of *MYC.* In mouse models, *ZMYND11::MBTD1* enforces a pro-leukemic stem-like gene-expression program, including upregulation of pro-oncogenic transcription factors such as *HOXA*, *MEIS1*, *SOX4*, *MYC* and *MYB*[8,9]. Most cases with *ZMYND11::MBTD1* exhibit a simple or non-complex karyotype even at relapse, and gene mutations are rare. These findings suggest that *ZMYND11::MBTD1* is very potent leukemogenic driver in AML and does not require additional cooperating mutations.

AML with t(10;17)/ *ZMYND11::MBTD1* is a rare but recurrent cytogenetic abnormality, with only 6 confirmed cases reported in the literature to date (cases #6-11 in Table 1 & 2)[1-5,10]. One additional case (#12) with t(10;17) exhibited a distinctive immunophenotype highly suggestive of *ZMYND11::MBTD1* although the fusion was not confirmed[11]. Three other AML cases with t(10;17)(p15;q21) have been described, however these cases lack confirmation of the fusion and detailed immunophenotypic characterization[12-14]. Although t(10;17)(p15;q21) is readily identifiable by conventional chromosomal analysis, confirmation of the *ZMYND11::MBTD1* may be challenging because these genes are not typically included in targeted RNA sequencing panels. Furthermore, FISH probes for this fusion are not routinely available in clinical cytogenetics laboratories. Prior studies have used bacterial artificial chromosome (BAC) FISH probes (RP11-10D13 and RP11-379D19)[1] or RT-PCR to detect this fusion[2-5]. In the current

cohort, the fusion was identified by OGM. Greater awareness of the distinctive cytogenetic and immunophenotypic features associated with this fusion may aid in recognizing this entity when t(10;17)(p15;q21) is observed on chromosomal analysis.

Morphologically, the blasts were poorly differentiated, displaying primitive morphology and lacking cytoplasmic granules. In some cases, including case #2 and a previously reported case[4], the blasts formed clusters, mimicking solid tumor involvement in the bone marrow. Immunophenotypically, the blasts were positive for CD7 (12/12), CD33 (12/12), CD56 (11/11), and CD117 (11/11), negative for HLA-DR (8/10) or positive in small subset (2/10), and negative for MPO (9/9). Of note, CD7 and CD56 expression could raise the differential diagnosis of blastic plasmacytoid dendritic cell neoplasm (BPDCN), however, the absence of CD4 and bright CD123 expression makes BPDCN unlikely.

Clinically, most patients presented with de novo AML with anemia, thrombocytopenia and normal or low white blood cell counts, without reported extramedullary disease. Although some patients achieved initial remission following intensive chemotherapy, most experienced early relapse[2,5,10]. Notably two pediatric patients (#6 and #12) achieved long-term remission. Four patients (#3-4, #7-8) underwent HSCT but all subsequently relapsed. Responses to salvage regimens after relapse were generally poor, emphasizing the urgent need for novel therapeutic approaches.

In conclusion, AML with t(10;17)/*ZMYND11::MBTD1* appears to represent a distinct subtype of AML that may warrant recognition as a separate entity under the category of “other rare

recurrent genetic abnormalities" in future AML classification systems. The blasts typically have primitive morphologic features, with uniform expression of CD7 and CD56, and absence of HLA-DR and MPO. Genetically, patients often harbor t(10;17) as the sole abnormality or have a non-complex karyotype, with a paucity of co-occurring gene mutations. Further studies in larger cohorts are needed to better understand the biology of this entity and to identify effective therapeutic strategies to improve patient outcomes.

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Table 1: Demographic, Clinicopathologic, Cytogenetic and Molecular Findings.

Case	Sex/ age	WBC (10^9/L)	Hb (g/dL)	Plts (10^9/L)	BM Blasts	Karyotype	ZMYND11:: MBTD1	Gene mutation*	Treatments	Response	FU (mon)	Outcome
Cases in this study cohort												
1	M/40	6.9	9.6	77	58%	46,XY,t(10;17)(p15;q21)[20]	OGM	None	CLIA+VEN	Initially responded; relapsed	34	Died
2	F/73	1.3	8.2	77	57%	46,XX,inv(3)(p13q27),t(10;17)(p15;q21)[15]/ 46,XX[2]	OGM	None	cladribine + cytarabine +venetoclax	refractory	2	Lost FU
3	F/60	1	9.5	28	35%	46,XX,t(10;17)(p15;q21)[19]/46,XX[1]	NA	*TET2*	7+3, cytarabine + daunorubicin + decitabine, SCT	Initially responded; relapsed	15	Died
4	M/42	4	9.9	14	80%	46,XY,t(10;17)(p15;q21)[16]/ 46,idem,del(16)(q12)[4]	NA	None	Multiple therapies and SCT (x2)	Initially responded; relapsed	57	Died
5	F/78	2.7	9.2	110	50%	46,XX,t(10;17)(p15;q21)[17]/ 46,XX[3]	NA	None	azacitidine	refractory	11	Died
Cases Reported in the Literature												
6	M/13	2.2	6.1	101	82%	46,XY,t(10;17)(p15;q21)[5]/ 47,idem,+13[9]/46,XY[9]	FISH	NA	ELAM 2002 protocol	Remission	71	ACR
7	F/40	7.4	6.3	61	59%	46,XX,t(10;17)(p15;q21)[3]/ 46,idem,add(11)(q11),add(13)(q32)[6]/ 46,XX[16]	FISH	NA	7+3, SCT (x2)	Responded, then relapsed	37	Died
8	M/13	6.5	na	na	na	46,XY,t(10;17)(p15;q21)[9]/ 46,XY[1]	RT-PCR (E12::E3)	NA	DCOG ANLL97/MRC AML 12 protocol, SCT	Initially responded; relapsed at 11 mon	30	Died
9	M/67	3.8	12.3	199	21%	47,XY,+Y,t(10;17)(p15;q21)[8]/ 47,sl,del(12)(p?)[8]/46,XY[4]	RT-PCR (E11::E3)	NA	idarubicin + cytarabine	Remission	14	ACR
10	M/19	4.1	11.5	81	90%	t(10;17)(p15;q21)	RT-PCR (E12::E3)	NA	7+3 induction	Remission	NA	ACR
11	F/67	3.6	5.1	2.1	76%	46, XX,t(10;17)(p15;q21.3) [17]/ 46,XX [3]	RT-PCR (E12::E3)	NA	idarubicin + cytarabine	Initially responded; relapsed at 6 mon	10	Died
12	M/11	5	8.1	249	98%	46,XY,t(10;17)(p15;q21)[5] /46,sl,i(7)(q10)[10]	NA	NA	ADE followed by MACE, FLAG	Remission after the second course of ADE	42	ACR

* by 81-gene panel next generation sequencing except case #5

ACR: alive in complete remission; F: female; FU: follow-up; Hb: hemoglobin; M: male; mon: months; NA: not available; OGM: optical genome mapping; Plt: platelets; SCT: stem cell transplant; WBC: white cell counts.

ADE: cytarabine, doxorubicin and etoposide; CLIA: cladribine, idarubicin, and cytarabine; MACE: amsacrine, cytarabine and etoposide; FLAG: fludarabine, cytosine arabinoside and G-CSF; VEN: venetoclax

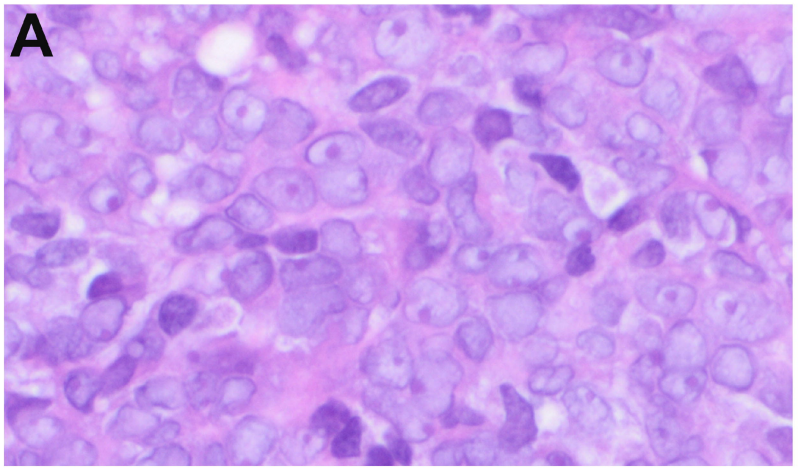
Table 2: Immunophenotypic findings.

	CD7	CD13	CD33	CD34	CD38	CD45	**CD56**	CD117	CD123	HLA-DR	**MPO**
Cases in current cohort											
1	Pos/uniform	Pos/partial	Pos	Pos	Pos/decreased	Pos	Pos/bright	Pos	Pos/partial dim	Neg	Neg
2	Pos/uniform	Pos	Pos	Neg	Pos/decreased	Pos	Pos/bright	Pos	Pos/partial dim	Neg	Neg
3	Pos/uniform	Neg	Pos	Neg	Pos/decreased	Pos	Pos/bright	Pos	Pos/partial dim	small subset	Neg
4	Pos/uniform	Pos/partial	Pos	Pos	Neg	Pos	Pos/bright	Pos	Pos/partial dim	Neg	Neg
5	Pos/uniform	Pos/partial	Pos	Small subset	Pos/decreased	Pos/dim	Pos/bright	Pos	Neg	Neg	Neg
Cases Reported in the Literature											
6	Pos	Pos	Pos	NA	NA	NA	Pos	Pos	NA	NA	NA
7	Pos	Pos	Pos	Pos	NA	NA	Pos	Pos	NA	NA	NA
8	Pos	NA	Pos	Pos	NA	Pos	Pos	Pos	NA	Neg	Neg
9	Pos	Pos/partial	Pos	Pos	NA	Pos	Pos/bright	NA	NA	subset	Neg
10	Pos	Pos/partial	Pos	Pos	Pos/dim	Pos/dim	Pos/bright	Pos	Pos	Neg	NA
11	Pos	Pos	Pos	Pos	Pos/decreased	NA	Pos	Pos/dim	NA	Neg	Neg
12	Pos	Pos	Pos	Pos	NA	Pos	NA	NA	NA	Neg	Neg

NA: not available; Neg: negative; Pos: positive.

FIGURE LEGENDS:

Figure 1. Morphologic, flow cytometric immunophenotyping, karyotyping and optical genome mapping findings in case #1. **A**: bone marrow core biopsy specimen (400x) exhibits sheets of immature-looking cells with distinct/prominent nucleoli. **B**: bone marrow aspirate smear (1000x) shows that the blasts are intermediate-size with scant cytoplasm, immature chromatin and distinct nucleoli. **C.** CD45 dim positive (~70% of total events) cells were CD7+/CD13+dim/CD14-/CD33+/CD34+/CD38decreased/CD56+bright/CD64-/CD117+/ CD123+dim/HLA-DR-/MPO-. **D**. G-banded chromosomal analysis shows t(10;17)(p15;q21). Arrows indicate abnormal chr10 and chr17 with t(10;17)**. E.** Circos plot of optical genome mapping shows t(10;17) as the sole abnormality. **F**. Genome browser of optical genome mapping demonstrates a fusion gene *ZMYND11::MBTD1* that arose via t(10;17). The middle blue bar represents the chimeric DNA fragment generated from t(10;17).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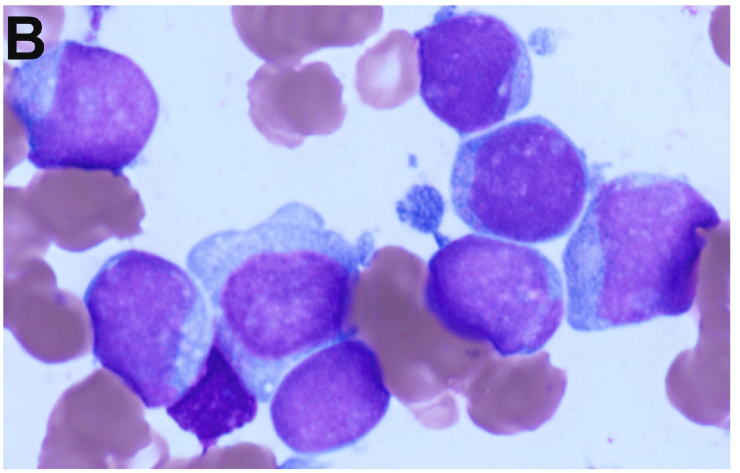
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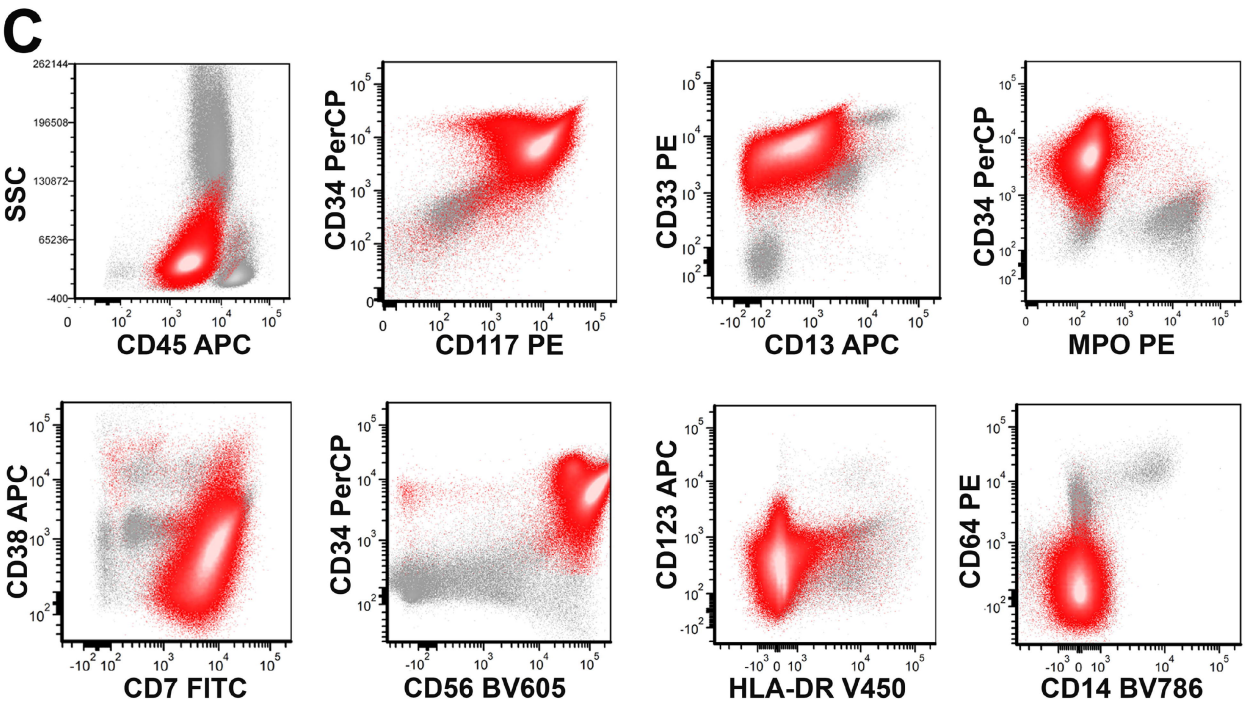
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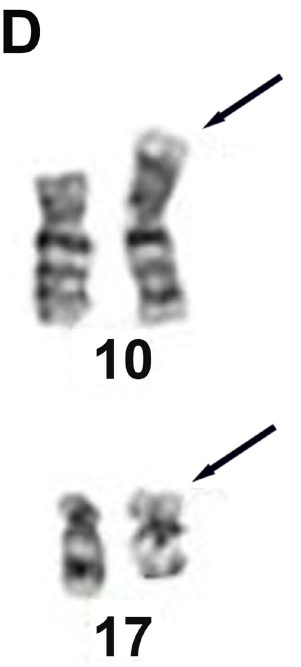
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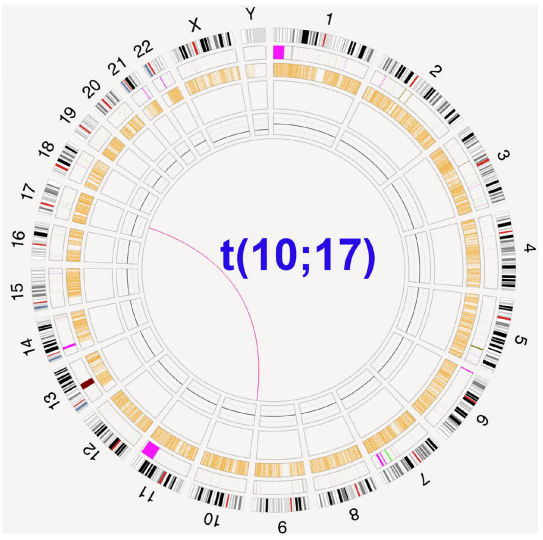
17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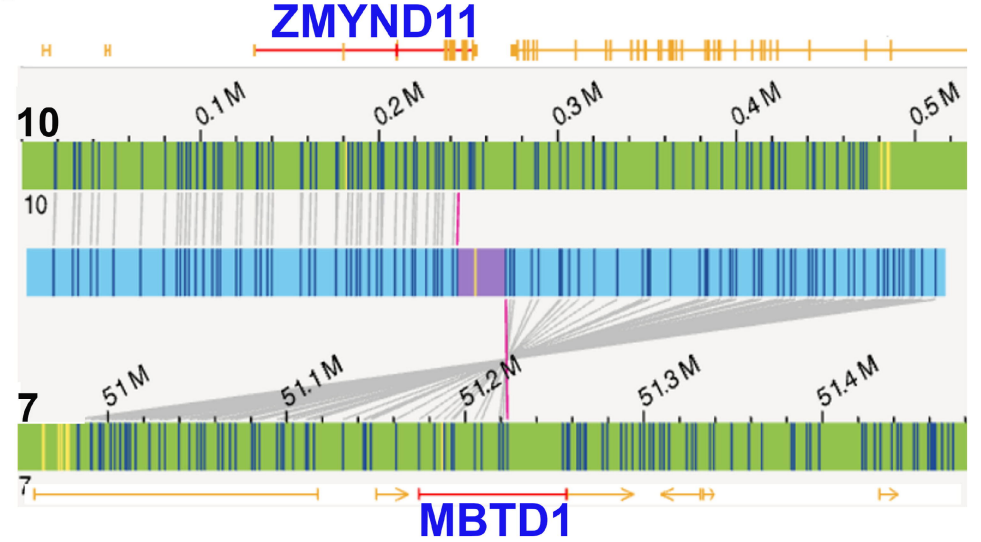
t(10;17)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ZMYND11
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0.1 M
0.2 M
0.3 M
0.4 M
0.5 M
7
51 M
51.1 M
51.2 M
51.3 M
51.4 M
MBTD1