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Recommended Citation

Kempski, H., Bonsu, K., Kearney, L., Jalali, G., Hann, I., Khurshid, M., Greaves, M. (2003). Prenatal chromosomal diversification of leukemia in monozygotic twins. *Genes, Chromosomes and Cancer, 37*(4), 406-411.
Available at: https://ecommons.aku.edu/pakistan_fhs_mc_med_haematol_oncol/12

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GENES, CHROMOSOMES & CANCER 37:406–411 (2003)

BRIEF COMMUNICATION

Prenatal Chromosomal Diversification of Leukemia in Monozygotic Twins

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Previous studies on concordant acute lymphoblastic leukemia (ALL) in identical twins have identified the leukemia as monoclonal with *MLL* or *ETV6-RUNX1* gene fusion as early or initiating events in utero. In the latter case, postnatal latency is associated with secondary genetic events such as *ETV6* deletion. We describe here a pair of infant twins with concordant acute monoblastic leukemia (AML). They are a unique pair in that their leukemia blasts display extensive intraclonal chromosomal diversity. Comparison of the leukemic cells between the two twins by karyotype and fluorescence in situ hybridization identifies a common or shared stem line and extensive subclonal diversity for which the twins' leukemic populations are divergent. This case of leukemia illustrates in utero initiation with early imposition of chromosomal instability, the progressively divergent evolution of which can be mapped in the twins into pre- and postnatal periods.
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The concordance rate of acute leukemia in infant identical or monozygotic twins has long been recognized to be extraordinarily high (MacMahon and Levy, 1964; Zuelzer and Cox, 1969; Keith et al., 1973). Several of such twin pairs, as well as older twin children with leukemia, have been shown to share non-constitutive clonotypic gene rearrangements, indicating that they have a common clonal origin (Ford et al., 1993, 1998; Gill Super et al., 1994; Megonigal et al., 1998; Wiemels et al., 1999a,b). The likely explanation for monoclonality in this context is blood cell chimerism: an initiation of leukemia in one twin in utero, followed by spread of clonal progeny to the co-twin by the vascular anastomoses that commonly exist within monochorionic placentas (Clarkson and Boyse, 1971; Ford et al., 1993). The prenatal origin of leukemia and the intraplacental "metastasis" explanation is endorsed, for both twins and singletons with leukemia, by the demonstration of the presence of clonotypic fusion gene sequences in archived neonatal blood spots or Guthrie cards (Gale et al., 1997; Wiemels et al., 1999a). The clonal markers used in twin leukemia studies have been gene fusions generated by chromosome translocations (Ford et al., 1993, 1998; Wiemels et al., 1999a) and *IGH/TCR* rearrangements (Ford et al., 1997).

Before these molecular studies, some earlier reports of leukemic karyotypes also provided support for a common clonal origin of concordant leukemia in twin pairs (Hilton et al., 1970; Chaganti et al., 1979; Hartley and Sainsbury, 1981), although these were equivocal because of the quality of karyotypes and because it was not then appreciated that clonally unrelated leukemias from different individuals can share similar chromosomal abnormalities. Chromosome markers can provide evidence of clonal identity in the twin context only if they are very unusual or complex. Shared complexity might seem unlikely, given that this would require that such a chromosomal status was rapidly acquired during a pre-leukemic prenatal phase, for example, by chromosomal instability. Richkind et al. (1998) described a pair of twins (ages 3 and 4 years at diagnosis) with an apparently identical karyotype: inv(16)(p13q22),+8,+21. We now describe such a twin pair in whom the leukemic cells have extensive diversity of chromosomal abnormalities that nonetheless can be dissected into components that are shared and therefore early and prenatal in ori-

Supported by: Leukemia Research Fund, United Kingdom.
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Received 18 November 2002; Accepted 7 March 2003
DOI 10.1002/gcc.10233

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gin. This twin pair provides an unusual insight into the timing and course of chromosomal instability underpinning pediatric leukemia.

The twins, identical boys, were born in Pakistan, after an uncomplicated pregnancy, with a single or monochorionic placenta. There was no family history of leukemia. Twin one (T1) was diagnosed with M5 acute monoblastic leukemia (AML) at 6 months and twin two (T2), with the same diagnosis at 13 months. GTG-banded karyotype analysis was carried out on T1 at the Aga Khan University Hospital, Karachi. Twin 2 was diagnosed in London, where diagnostic material from both twins was assessed by GTG banding and fluorescence in situ hybridization (FISH) by use of whole chromosome paints (WCPs) and locus-specific (LSI) probes. Between 51 and 80 metaphase cells from each twin sample were examined by GTG-band analysis and confirmed by appropriate WCPs and LSI probes, where possible.

The leukemic cells had extensive chromosomal abnormalities, and these are summarized in Table 1. Cytogenetic analysis showed a complex karyotype characterized by aneuploidy and characteristic structural changes. In addition to chromosomal gains of 8, 10, and 19, common structural changes involving chromosomes 2, 7, and 9 were discovered in both twins (Fig. 1). A del(7)(p15) was found in both children. The dup(2) and der(9) marker chromosomes were karyotypically indistinguishable in both twins. The der(9) was further defined by FISH, and was found to contain an insertion from chromosome 2, which was microscopically identified as a light-staining region sandwiched between chromosome 9 and terminal chromosome 7 material in the translocation [Fig. 2(i)A and (ii)A]. Through use of a locus-specific probe for *ABL*, we were able to demonstrate the retention of *ABL* on the der(9), confirming that the breakpoint was distal to this gene [Fig. 2(i)B and (ii)B]. A candidate gene distal to *ABL*, and associated with AML, is *CAN* (*CAIN*, *NUP*214). This gene has been described as a fusion partner with *DEK* in the t(6;9)(p23;q34) in a subset of patients with AML (von Lindern et al., 1992). However, because of the very limited amount of material remaining from T2 and no further material from T1, the possible involvement of *CAN* was not pursued.

The abnormalities present in both twins were defined as: dup(2)(q35q31),del(7)(p15),+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+10,+19. The insertion of chromosome 2 material into the t(7;9) was thought to originate from the proximal breakpoint region at 2q?31 from the dup(2). The rationale behind this was based on most of the metaphase chromosomes available for analysis being at <400 band resolution and, because band 2q31 is a larger, more prominent, light-staining region compared to that of band 2q35, the second breakpoint region identified in the duplication, the material was deduced to be of 2q?31 origin. The size of the insertion from chromosome 2 into der(9) was comparable to that of the 2q31 band found in the normal chromosome 2 homolog. The identification of these breakpoint regions was made at the GTG-band level during standard analysis. We were unable to obtain suitable probes that mapped to either of the estimated breakpoint regions on chromosome 2, and were therefore unable to confirm or characterize these rearrangements further. Whole chromosome paints for chromosomes 7 and 9 established that the t(7;9) was not reciprocal. Beyond these common changes, T1 showed a deletion of chromosome 15 between bands q12 and q24 and subsequent gain of an additional del(15q) and one further copy each of chromosomes 19 and 21; T2 showed additional gains of chromosomes del(7p) and 8. T1 showed two main clones, lines 2a and 4a (Table 1), with 23/51 (45.2%) and 9/51 (17.7%) of cells involved, respectively; 4/51 (7.8%) of cells showed dup(2) as a sole change, 4/51 (7.8%) of cells were normal, and of the remainder of the cells analyzed, 11/51 (21.5%) showed diverse subclonal changes. Twin 2 also revealed two main clones, lines 3b and 6b (Table 1), with 22/80 (27.5%) and 33/80 (41.2%) of cells involved, respectively; 2/80 (2.5%) of cells showed dup(2) as a single change, 12/80 (15%) of cells were normal, and of the remainder of the cells analyzed, 11/80 (13.8%) showed varied subclonal changes.

Comparison of the abnormalities in the paired twin samples therefore revealed that some major changes were common or shared, whereas several more minor, subclonal alterations were unique to each twin. A key clonal marker is der(9). In addition, the leukemias had in common trisomy of chromosomes 8, 10, and 19 and dup(2). The sharing of markers indicates that in this twin pair, as in others previously analyzed with molecular markers (Ford et al., 1993, 1998; Megonigal et al., 1998; Wiemels et al., 1999b), there was a clonal origin in one twin in utero. By comparing the intraclonal frequency of markers and their concordance or discordance in the twin pair, we can align a putative sequence of chromosomal events in this twin pair (Fig. 3). We assume that all shared markers must have been generated prenatally in one twin, whereas the extensive subclonal changes unique to each twin reflect independent, postnatal chromo-

TABLE 1. Karyotypes of Lines Identified for Twins 1 and 2

Case	Line	Karyotype	Percentage metaphase cells
Twin 1	1a	46,XY,dup(2)(q35q31)[4/51]	07.8
	2a	49,XY,dup(2)(q35q31),del(7)(p15),+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+10,del(15)(q12q24),+19[23/51]	45.2
	3a	50,XY,dup(2)(q35q31),del(7)(p15),+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+10,del(15)(q12q24),+19,+21[2/51]	03.9
	4a	51,XY,dup(2)(q35q31),del(7)(p15),+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+10,del(15)(q12q24),+del(15),+19,+19[9/51]	17.7
	5a	52,XY,dup(2)(q35q31),del(7)(p15),+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+10,del(15)(q12q24),+del(15),+19,+19,+21[4/51]	07.8
	6a	52,XY,dup(2)(q35q31),del(7)(p15),+del(7)(p15),+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+der(9)t(7;9)ins(9;2;7),+10,del(15)(q12q24),+del(15),+19[3/51]	05.9
	7a	54,XY,dup(2)(q35q31),+3,del(7)(p15),+8,+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+10,del(15)(q12q24),+del(15),+19,+19,+21[2/51]	03.9
	N	46,XY[4/51]	07.8
Twin 2	1b	46,XY,dup(2)(q35q31)[2/80	02.5
	2b	48,XY,dup(2)(q35q31),der(?)t(?;2)(q?;q35),del(7)(p15),+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+10[2/80]	02.5
	3b	49,XY,dup(2)(q35q31),del(7)(p15),+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+10,+19[22/80]	27.5
	4b	50,XY,dup(2)(q35q31),del(7)(p15),+8,+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+10,+19[6/80]	07.5
	5b	50,XY,dup(2)(q35q31),del(7)(p15),+del(7)(p15),+8,+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+10[2/80]	02.5
	6b	51,XY,dup(2)(q35q31),del(7)(p15),+del(7)(p15),+8,+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+10,+19[33/80]	41.2
	7b	51,XY,dup(2)(q35q31),der(7)t(7;?)(q22;?),del(7)(p15),+del(7)(p15),+8,+8,der(9)t(7;9)ins(9;2;7)(9pter→9q34::2q?31→2q?31::7p15→7pter),+10,+19[1/80]	01.3
	N	46,XY[12/80]	15.0

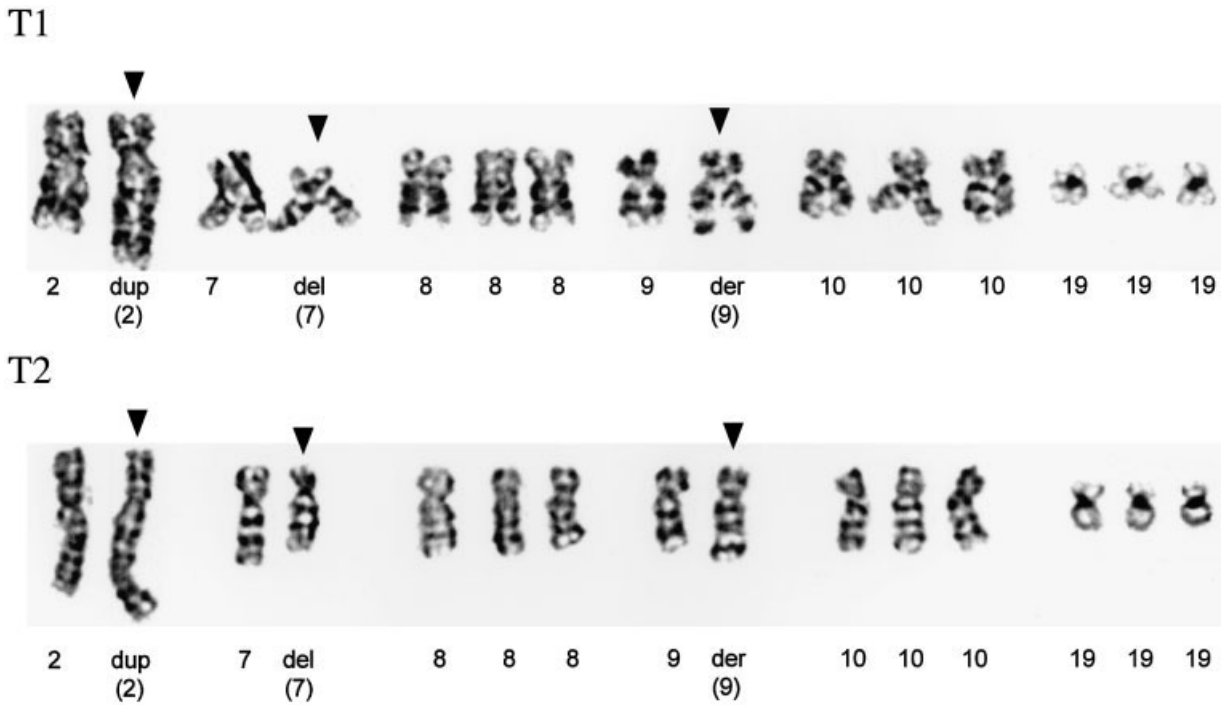

Figure 1. G-banded partial karyotype of the shared chromosome abnormalities in the twins' leukemic cells. Both the dup(2) and der(9) were distinctive and could be easily distinguished by G-banding. FISH characterization of these structural abnormalities was carried out on leukemic metaphases from Twin 2. Nomenclature based on banded karyotype and FISH data (see text).

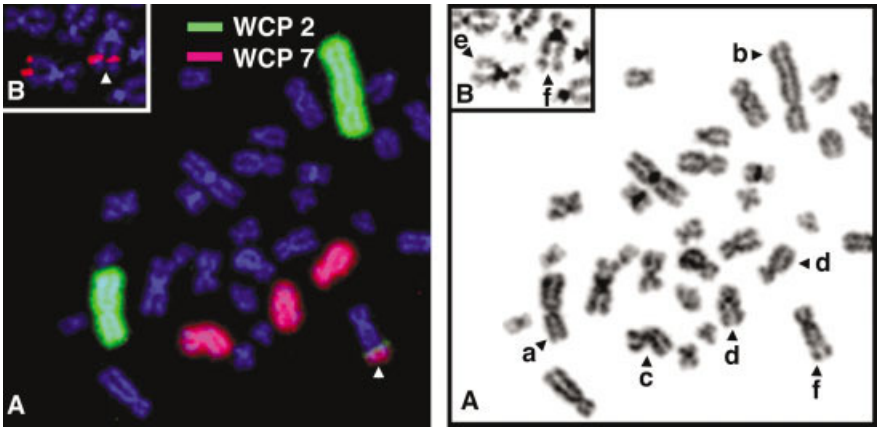

Figure 2. (i) **A:** Partial metaphase cell from clonal line 6b of Twin 2 (T2), hybridized with WCPs for chromosome 2 (green signal) and chromosome 7 (red signal), showing structural clonal changes detected. The derivative 9 is arrowed. **B:** Partial metaphase cell, hybridized with a probe spanning *ABL*, demonstrating that *ABL* is retained in both the normal chromosome 9 and the derivative chromosome 9 (arrowed). (ii) **A, B:** DAPI-banded images of (i) showing (a) normal chromosome 2, (b) dup(2)(q31q35), (c) normal chromosome 7, (d) del(7)(p15), (e) normal chromosome 9, and (f) der(9)t(7;9)ins(9;2;7).

some diversification. In a previous twin pair with a common, clonotypic *ETV6-RUNX1* fusion, it was found that associated chromosomal deletions (including *ETV6*) were distinct and therefore, as in the present case, probably independently acquired as postnatal, secondary events (Maia et al., 2001).

Multiple trisomies such as those described here are a relatively uncommon finding in AML, and are more usually found in association with recognized structural rearrangements such as t(8;21)(q22;q22), t(9;22)(q34;q11), or 11q23 rearrangements (Mitelman et al., 2002). More than 50% of newly diagnosed cases of AML do display karyotypic abnormalities, but these are predominantly single cytogenetic abnormalities (Mrozek et al., 2001). However, highly complex chromosomal changes have been described in infant AML (Chessells et al., 2002). The latter study describes complex karyotypic changes that were found in 12/57 (21%) infants with AML, of whom 5/12 (42%) were diagnosed with FAB type M5, a diagnosis similar to that of the twins described here. The infant leu-

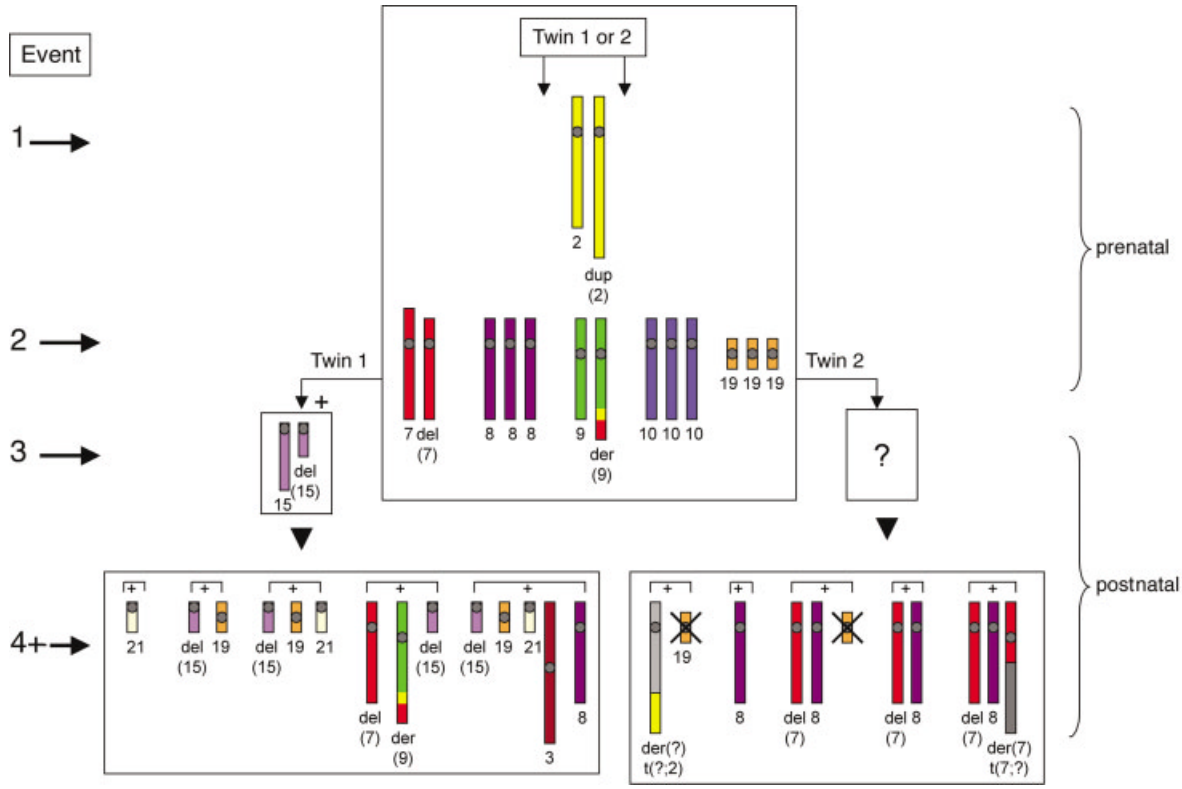

Figure 3. Schematic representation of a proposed prenatal and postnatal sequence of cytogenetic events: Prenatal events 1 and 2 involve the acquisition of complex structural and numerical chromosomal changes, in either Twin 1 (T1) or Twin 2 (T2). Post-natal divergence in T1 is identified by the deletion of one copy of chromosome 15 (event 3), followed by diverse subclonal changes (event 4+). T2 shows variant subclonal changes without a perceptible (and distinct) antecedent cytogenetic change.

kemias with gain of chromosomes, in addition to structural changes, were predominantly found in the group without 11q23 *MLL* gene abnormalities. Neither twin in the current study had abnormalities of 11q23. A sizeable fraction of infant AML, without *MLL* gene fusion, have the translocation t(7;12)(q36;p13), strongly associated with trisomy 19 (Tosi et al., 2000). However, despite the presence of trisomy 19, our twin pair did not have the t(7;12)(q36;p13). This was confirmed by FISH investigation by use of WCPs for chromosomes 7 and 12 and also by use of a locus-specific probe for the *ETV6* gene, which is invariably rearranged in the recurrent t(7;12) translocation (Tosi et al., 2000; Simmons et al., 2002). No translocation was disclosed by the WCPs; and *ETV6* remained intact in both chromosome 12 homologs.

The features of the twin pair reported here and other infants with AML are clearly indicative of chromosome instability (CIN). The distinction between these infant leukemias (in both twins and singletons) with *MLL* gene fusions and those with chromosome instability is likely to have etiological implications. Balanced chromosome translocations, particularly those involving 11q23/*MLL*, have been associated in secondary leukemias with prior exposure to topoisomerase II (topo II)–inhibiting epidophyllotoxins or anthracyclins (Felix, 1998). It has been proposed that infant de novo leukemias with *MLL* gene fusions may involve a unique causal pathway in utero involving transplacental exposure to substances that similarly interfere with topo II (Ross et al., 1996; Greaves, 1997). Some experimental (Strick et al., 2000), epidemiological (Ross et al., 1996; Alexander et al., 2001), and genetic (Wiemels et al., 1999c) data support this contention. Breivik and Gaudernack (1999) proposed that chromosome instability, in cancer in general, might reflect the selective pressure exerted by particular genotoxic chemicals. They predicted that bulky adduct-forming agents might represent such a class, and experimental evidence in favor of this has recently been produced by use of 2-amino-1-methyl-6-phenylimidazol[4,5-*b*]pyridine exposure of cell lines (Bardelli et al., 2001). In secondary AML, complex karyotypes have been found to be associated with prior exposure to alkylating agents (Pedersen-Bjergaard, 2002). The molecular mech-

anisms involved in generating CIN are unclear but could involve direct induction of chromosome changes by bulky adducts themselves or incisions generated by nucleotide excision repair (Breivik and Gaudernack, 1999). Alternatively, abnormalities involving telomerase dysfunction (Gisselsson et al., 2001), centrosome abnormalities (Ghadimi et al., 2000), or mitotic spindle checkpoints (Cahill et al., 1998) could be important. We have no evidence implicating possible in utero chemical exposure of the twins reported here, although such exposure could have been inadvertent. This twin pair adds to the evidence for in utero initiation of pediatric leukemia, showing that not only balanced translocations but CIN may be very early or initiating events.

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