TECHNICAL PAPER ON Lena Q51®

There are currently more than 200 fusion genes. LENA Q51 actually detects 52 fusion genes. The selection of these 52 fusion genes is to consider an optimal cost performance. If all of these more than 200 fusion genes are detected, the cost is too high. The selection of these 52 fusion genes is based on the fact that the total mutation frequency of these 52 genes exceeds 85%, and the mutation frequency of the remaining more than 100 fusion genes does not exceed 15%.

The 52 fusion genes we selected had a total of more than 200 breakpoints by the time of product development. See below the detection significance of each of the 52 genes selected by our Q51.

No.	Fusion Gene	Karyotype	Feature description
1	BCR-ABL1 p190	t(9;22)(q34;q11)	Has strong tyrosine protein kinase activity, P190 protein can participate in the signaling pathway of integrins, leading to the occurrence of tumors, and it has a strong effect on stimulating lymphocyte proliferation. Mostly seen in ALL, but can also be seen in CML .
2	BCR-ABL1 p210	t(9;22)(q34;q11)	Seen in approx.95% of Philadelphia chromosome positive CML cases, also seen in acute lymphoblastic leukemia ALL. It has abnormally enhanced tyrosine kinase activity, induces cell proliferation and resists apoptosis by activating cell-related signaling pathways, leading to tumorigenesis. e14a2 expressive CML patients with platelet levels higher than e13a2 expressive CML patients with low levels of white blood cells, and studies have found e13a2 expression are more common in males.
3	PML-RARα L	t(15;17)(q24;q22)	The complete remission after initial induction of L-type was significantly higher than that of S-type, and the recurrence rate and mortality rate are lower than those of S-type. The prognosis of patients with L-type APL is better than that of S-type.
4	PML-RARα S	t(15;17)(q24;q23)	Morphologically S-type cells are often poorly differentiated and secondary cytogenetic abnormalities may be seen.
5	PML-RARα V	t(15;17)(q24;q24)	Patients with type V cells have low sensitivity to ATRA.
6	AML1-ETO	(8;21)(q22;q22)	AML1-ETO positive leukemia cells have a certain degree of differentiation ability, can differentiate into more mature neutrophils and eosinophils, and are more sensitive to high-dose cytarabine therapy, with a complete remission rate of up to 90%. 5-year disease-free survival rate can be up to 60%, and the prognosis is better than other AMLPositive.
7	TEL-AML1	t(12;21)(p13;q22)	25% incidence in children ALL, not yet inT-ALL, AML or NHL. Incidence in adult leukemia patients is lower than2%. The general age of onset is younger (2-10age), and WBC count is low (<50000/L). The immunophenotype of such patients is pre-B-ALL, good response to treatment, long time to complete remission, good prognosis, can be used to distinguish low-risk and high-risk ALLpatients, and help determine appropriate treatment options.
8	E2A-PBX1	t(1;19)(q23;p13)	Seen in 5% of ALL, and in front B-ALL, the positive rate is as high as 23%. Positive patients had higher white blood cell counts, developed CNS leukemia, poor prognosis, and average disease-free survival (DFS) is only 6-month. 3-year DFS is 20%, which requires intensive treatment for these patients to obtain a better prognosis. It is a high-risk marker, and is closely related to early treatment failure.

9	SIL-TAL1	del(1) (p32)	Seen in 26% of children T-ALL and 16% of adults. The fusion gene can be used to assist T-ALL diagnosis, efficacy monitoring and MRD. It is a sign of good prognosis.
10	CBFβ-MYH11	inv(16)(p13;q22)/t(16;16)(p13;q22)	Seen in 5~10% ofAML, Mostly M4Eo type; in M2 and M5, it has also been reported. It is a good prognostic factor. The fusion gene has multiple variants, among which A-type accounts 80%.
11	AML1-MDS1/EV11	t(3;21)(q26;q22)	The positive rate is about 1% AML, all ages can be affected. EVI1Positive patients have shorter remission time and higher early mortality than negative patients, which are factors of poor prognosis.
12	FIP1L1-PDGFRA	del(4)(q12)	Seen in about 23% of CEL. The fusion gene suggests a better response to Gleevec.
13	SET-CAN	del(9)(q34)	Seen in 6% of T-ALL, and also in AUL(Acute Undifferentiated Leukemia). It is resistant to corticosteroids and chemotherapy, but has a normal prognosis.
14	E2A-HLF	t(17;19)(q22;p13)	Occurs in a few ALL. The fusion gene suggests a poor prognosis, no response to intensive chemotherapy, and short survival.
15	DEK-CAN	t(6;9)(p23;q34)	Seen in 1% of AML, and also in MDS. It is characterized by early onset and poor prognosis.
16	TLS-ERG	t(16;21)(p11;q22)	More common in intial ANLL and more common in young adults, and also present in non-leukemias (Ewing's sarcoma). Patients with acute leukemia who are positive for this fusion gene are often severely ill. It is a factor suggesting a poor prognosis.
17	TEL-PDGFRB	t(5;12)(q33;p13)	More common in CML andMDS patients. Patients who are positive for this fusion gene often respond to Gleevec therapy.

18	NPM-RARα	t(5;17)(q35;q21)	There are two transcripts of NPM-RARA, which are NPM S-RARA and NPM L-RARA. It occurs mostly in APL. Patients with this fusion gene are often ineffective on retinoic acid treatment, while traditional acute myeloid leukemia chemotherapy may be effective.
19	NPM-MLF1	t(3;5)(q25;q34)	It occurs in AML (M2, M4 and M6), MDS and MPS. Patients with this fusion gene tend to have a poor prognosis. Although they have a high treatment remission rate, they are prone to early relapse, and the median survival time is often less than 1 year. These patients are better treated with bone marrow transplantation than chemotherapy.
20	PLZF-RARα	t(11;17)(q23;q21)	Seen in <1% ofAPL, not sensitive to ATRA.
21	TEL-ABL1	t(9;12) (q34;p13)	Can be seen in acute or chronic leukemia, myeloid or lymphocytic leukemia. Most cases are accompanied by eosinophilia and have a poor prognosis.
22	AML1-MTG16	t(16;21)(q24;q22)	Very rare, mainly in treatment-related AML or MDS. Patients carrying the fusion gene are sensitive to chemotherapy and have good response to treatment, but have strong toxicity to chemotherapy, so a more moderate chemotherapy regimen is required.
23	AML1-EAP	t(3;21)(q26; q22)	Mainly occurs in CML, MDS and treatment-related leukemia. Rare invAML. It can be used as the marker of transformation process of MDS towards AML.
24	NUP98-PMX1	t(1;11)(q23;p15)	More common in M2-type ANLL.
25	NUP98-HOXD13	t(2;11)(q31;p15)	Currently only reported in initial AML.
26	NUP98-HOXA9	t(7;11)(p15; p15)	Mostly in Japan, manifested as AML, also seen isd CML-like manifestations without t(9;22) or CML in t(9;22) primitive cell crisis
27	NUP98-HOXA13	t(7;11)(p15; p15)	Currently only reported in initial AML.

28	NUP98-HOXC11	t(11;12)(p15;q13)	Currently only reported in initial AML.
29	NUP98-HOXA11	t(7;11)(p15; p15)	Incidence is extremely low, with case reports seen in Philadelphia chromosome-negative CML, and juvenile myelomonocytic leukemia (JMML).
30	STAT5b-RARα	der(17)/t (17;17)(q21;q21)	Seen in APL, the incidence is very low; not sensitive to ATRAInsensitive and prognosis unknown.
31	NUMA-RARα	t(11;17)(q13;q21)	Atypical APL: The incidence rate is extremely low, and clinical reports have made patients with complete remission using all-trans retinoic acid therapy and autologous stem cell transplantation.
32	FIPIL1-RARα	t(4;17)(q12;q21)	Prognosis unknown, there are cases with good effects by using ATRA.
33	PRKAR1A-RARα	der(17)	seen in APL.
34	CALM-AF10	t(10;11)(p13;q21)	The age of onset is low and the prognosis is poor.
35	TEL-JAK2	t(9;12)(p24; p13)	It is rare, and seen in acute leukemia. 36% in MDS, 63% in high-risk MDS, and 25% in low-risk MDS. The gene helps understand the severity of the condition.
36	ETV6-PDGFRA	t(4;12)(q12;p13)	Exist in AML; tyrosine kinase inhibitor therapy for AML caused by ETV6-PDGFRA may have some effect.
37	MLL-AF4	t(4;11)(q21;q23)	It is with the highest incidence among all MLL fusion genes, achieving 43.1%~68.1% (with all positive MLL fusion gene as base). The incidence in baby ALL is5 0-70%, the incidence in children is 2%, the incidence in adults is 3-6%. Patients with MLL-AF4 usually have younger ages of onset (usually younger than 2-year-old), the condition is dangerous and the prognosis is poor. Patients may not respond to standard treatment regimens and require intensive treatment. High doses of Ara-c treatment can improve patient outcomes.

38	MLL-AF9	t(9;11)(p22;q23)	Mainly occurs in AML, the proportion is 18.6% (with all MLLpositive as base). Higher incidence in M5a than in M5b. Mainly occured in AML, the fusion gene often suggests a poor prognosis.
39	MLL-ENL	t(11;19)(q23;p13.3)	Seen in ALL, AML-M4, M5, M1, and M2. Patients are mostly infants less than 1-year-old. The majority of infants are neonatal congenital leukemia. The prognosis of this fusion gene has not been clearly stated, and it is related to age and immunophenotype. There are clinical cases reporting poor prognosis and bone marrow transplantation is recommended.
40	MLL-ELL	t(11;19)(q23;p13.1)	AML specificity abnormal, mostly in adults. Organomegaly in half of the cases, some accumulate in the central nervous system, and the prognosis is very poor (median 6 months). The two-year disease-free survival rate is 50%. Bone marrow transplantation is recommended.
41	MLL-AF10	t(10;11)(p12;q23)	Specific marker of AML-M5, more common in children. 80% of patients are less than 3-year-old. The fusion gene often suggests a poor prognosis.
42	MLL-AF6	t(6;11)(q27;q23)	Mainly occurs in AML. The fusion gene has a very poor prognosis, with little remission and short survival.
43	MLL-AF17	t(11;17)(q23; q12-21)	Mostly seen in AML. The prognostic significance is unclear.
44	MLL-AF1q	t(1;11)(q21;q23)	Mostly seen in AML. The prognostic significance is unclear.
45	MLL-SEPT6	t(X;11)(q24;q23)	Currently only found inAML, can beM1, M2, M4, M5. Prognosis is generally poor (chemotherapy1died within the year), and bone marrow transplantation was slightly better.
46	MLL-AF1P	t(1;11)(p32;q23)	Seen in ALL, AML and MDS. Prognosis is related to gender and type.

47	MLL-AFX1	t(x;11)(q13;q23)	Seen in infant AML, ALL and CLL. The prognosis is poor, and can enhance the self-renewal of hematopoietic stem cells and prevent them from maturing. Caused by t(X;11) (q13;q23.3), it will lead to B cellular chronic lymphocytic leukemia (B-CLL) pathogenesis, characterized by low survival rates. The breakpoint of 11q23 affects ARHGAP20 gene, which encodes a protein predicted to be involved in the regulation of Rho family GTPases. The breakpoint of Xq13 occurs in BRWD3, which encodes a putative novel transcription factor. The rearrangement of ARHGAP20 and BRWD3 does not result in a fusion transcript, but it disrupts both genes. Thus, through altered gene expression or through gene disruption (but not point mutation), the dissonance of ARHGAP20T is the general molecular mechanisms of B-CLL leukemia.
48	NPM1-ALK	t(2;5)(p23;q35)	Occurs in more than half of anaplastic large cell lymphomas (ALCL, aka ALK+ALCL) and 10% of non-Hodgkin lymphoma (NHL). Although occurring in high-grade aggressive tumors, 80% of patients survive longer than 5 years.
49	dupMLL(MLL IDT)	11q23	Occurs in 3~5% of AML, and associated with poor prognosis, with shorter progression-free survival and overall survival in positive patients. In adult AML, dupMLL is often accompanied by 11-trisomy or FLT3-ITD. It is reported that in children AML, the incidence is 2.5% (7/276), with 1case has 11-trisomy, the rest are normal karyotypes, and 4 cases have FLT3-ITD. DupMLL emerges after exons3~9 inserting into exon9(e9e3), Exon10(e10e3) and exons11(e11e3). Steudel et al (2003) found 5.4% of dupMLL positive in 956 random AML cases, most of which (7.5%) are of the normal karyotype, less than one third (3.1%) with chromosomal abnormalities (1). In 11-thisomy cases, 47% have dupMLL, which has higher incidence rate in adult than in children. (7.2% vs. 0.8%).

50	EVI-1	3q26.2	Ecotropic virus integration site-1gene. This gene is located in 3q26.2. EVI-1 gene has low expression in normal peripheral blood and bone marrow cells, and high expression in embryonic and hematopoietic stem cells. EVI-1's abnormal expression is usually caused by transversion or insertion of chromosome three (inv(3)(q21;q26) inversions/ t(3;3)(q21;q26)) and causes leukemia. Its abnormal expression occurs in 8~10% of adult AML, 27% of children leukemia that has MLL rearranged, 10% of MDS (severe anemia and myelodysplasia), and CML. Still 10% of MDS/AML by EVI-1's abnormal expressio does not have rearrangement of Chromosomal 3. (There are studies report that the overexpression not caused by rearrangement of Chromosomal 3 has no prognostic significance). Simultaneously, a small number of patients with Chromosomal 3 rearrangment do not have EVI-1Gene overexpression. Therefore, the synergy of EVI-1's overexpression and Chromosomal 3 cannot explain the whole situation. EVI-1 Gene overexpression is an independent poor prognostic factor in hematological malignancies due to its close association with hematopoietic diseases (affecting leukemia cell differentiation, proliferation and apoptosis). HADC (Histone deacetylase) inhibitors may be one of the drugs for the treatment of leukemia associated with it.
51	HOX11 (TLX1)	10q24	HOX11 gene is located in10q24on. Translocation of t(7;10)(q35;q24) and t(10;14)(q24;q11) or the target gene (as MLL gene) will causes its activation, resulting in abnormal expression of the target gene in leukemia (4-7% of T-ALL), thereby affecting the sensitivity of tumor cells to chemotherapeutic drugs, which in turn affects ALL (mainlyT-ALL) prognosis. Children T-ALL with HOX11 high expression has better prognosis than the negative. Studies have shown that in the control group, there is no expression of this gene in hematopoietic stem cells (without CD43), normal peripheral blood T cells and thymocytes. Research shows that HOXll Gene plays a role in hematopoietic regulation. Most HOX Genes can promote the proliferation of hematopoietic progenitor cells and inhibit their differentiation. Some studies even believe that high expression of this gene can lead to the occurrence of central nervous system leukemia (ANSI), and need to give lumbar puncture or intrathecal methotrexate for prevention. Some studies have also found that abnormal methylation of some related target gene promoters of HOX11 can affect intracellular signal transduction pathways and some important cellular physiological functions, thereby affecting the effect of chemotherapy in patients. Notes: Among positive HOX11 cases, a small part is high expression, and most of them are low expression (the difference is about550 times).

52	HOX11L2(RNX,TLX3)	t(5;14)(q35;q32)	HOX11L2 Gene's overexpression often occurs in childrenT-ALL, causing ALL. It is a poor prognostic factor. Researches show that patients with lymph node hyperplasia or B-ALL do not have overexpression of this gene. HOX11L2 expression and(or) t(5;14)(q35;q32) incidence in children T-ALL is up to 24%, and for adults 13%. It has become one of the most common specific gene alterations in children T-ALL . Notes: HOX11L2 positive is generally high expression. HOX11L2 and HOX11 are mutually exclusive, i.e.while HOX11L2 expressing, HOX11 generally has low expression or no expression, and when HOX11L2 negative, HOX11is of high expression.