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Introductory Chapter: Germline Mutations Associated with Leukaemia - Different Genetic Landscape and Therapeutic Strategies

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1. Introduction

Dr. Barbara McClintock, the 1983 Nobel Prize winner in physiology or medicine, described that “the most remarkable kinds of mutations are not (usually) produced by such extrinsic factors as radiation and chemicals, but by factors that are intrinsic to the cells themselves”.

Evidences obtained from studies proved that genomic mutations are the direct root causes of increased susceptibility to almost all disorders/diseases in the manner of either somatic or germline mutations. Diseases associated with somatic mutations have been well studied; in contrast, studies on diseases associated with germline mutations have been just started, particularly in malignancies.

The estimation by 2015 showed that there were about 17.5 million cancer cases and 8.7 million deaths worldwide per annum [1]. Cancer is a genetic disease caused by mutations from environmental and genetic factors and their interactions. Genetic factors include somatic (acquired) and germline: the difference between germline and somatic mutations is that the germline mutation occurring in reproductive cells (sperm, egg) inherits to the offspring, whereas somatic mutation occurring in body cells is not inherent to the offspring.

In the recent years, more and more attention has been paid to the studies on cancers associated with germline mutations, and more and more discoveries have been achieved by increasing the recognition of such disease. TP53 was the typical and most commonly germline-mutated gene associated with Li-Fraumeni syndrome (colorectal cancer). Studies from Zhang group showed that the rate of germline mutation in cancer-predisposition genes was 8.5%. They estimated that in the hereditary breast/ovarian cancer (HBOC) from BRCA1 and BRCA2 mutations, women with BRCA1 mutations have a 47–66% chance of developing breast cancer and a 35–46% chance of developing ovarian cancer by the age of 70 years [2].

Leukaemia is a type of haematological malignancy (liquid cancer) occurring in haematopoietic tissue caused by environmental and genetic factors, such as other types of cancers, typically presented with fever, bleeding, infection, bone pain and anaemia. The presentation can vary, however, depending on the many different factors of individuals. Among all leukaemia types of the myeloid malignancies, acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS) and chronic myeloid leukaemia (CML) are the common types.

In a similar scenario with germline mutations associated with solid cancers, about 5–10% of some particular germline mutations will develop to haematological malignancies including MDS, MDS/myeloproliferative neoplasms (MPN) and AML. Germline predisposition of myeloid malignancies is estimated at about 5–10% in the genetic manner, either from functional haplo-insufficiency due to loss of an allele or gain of oncogenic function, but the loss of an allele is more common than gain of oncogenic function in such a type of leukaemia [3].

Studies showed that myeloid neoplasms associated with predisposing of germline mutations are found to be more common than was thought. But it is still under-investigated, under-diagnosed and under-reported due to the low case numbers and nature of disease complexity.

2. Understanding of the WHO's germline mutations associated with neoplasms from gene mutations and syndromes

To increase the recognition for germline predisposition, the major changes were made in the 2016 version of the book *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* for the myeloid neoplasms, with the addition of germline predisposition of the myeloid neoplasms under the following categories [4, 5]:

The first category is myeloid neoplasms with germline predisposition without a pre-existing disorder or organ dysfunction with CEBPA and DDX41 mutations.

CCAAT enhancer-binding protein alpha (CEBPA) is involved in the function of myeloid differentiation by encoding a granulocyte differentiation factor located on chromosome 19q13.1. This germline mutation associated with AML is due to the inheritance of a single copy of mutated CEBPA, and studies suggested such mutation has a favourable prognosis than somatic mutation AML [6, 7].

DEAD-Box Helicase (DDX41) is located on chromosome 5q35.3, and studies found that in about 1.5% of myeloid neoplasms, half of these patients had germline mutations, typically in MDS and AML combined with additional del(5q) presented with erythroid dysplasia, leading to erythroid leukaemia with poor prognosis. CML, CMML and lymphomas have been also reported [8, 9].

The second category is myeloid neoplasms with germline predisposition and pre-existing platelet disorders with RUNX1, ANKRD26 and ETV6 mutations.

Runt-related transcription factor 1 (RUNX1, located on chromosome 21q12) is playing a physiological role in haematopoiesis. RUNX1 mutations cause familial platelet disorder and develop to MDS/AML in 11–100% risk, median 44% [10, 11].

Ankyrin repeat domain-containing protein 26 (ANKRD26, located on chromosome 10p12.1) mutation is characterised by thrombocytopenia from the abnormal megakaryopoiesis and increases risk to MDS and AML in about 30 fold [12, 13].

ETS variant gene 6 (ETV6, located on chromosome 12p13.2) is functional as a haematopoietic regulator in normal physiological condition. ETV6 mutations were found to be associated with several types of haematological malignancies including MDS, AML, B-cell leukaemia and multiple myeloma (MM) as have been identified [14–17].

The third category is the myeloid neoplasms with germline predisposition and other organ dysfunctions with GATA2 mutations and several types of genetic-based syndromes including myeloid neoplasms associated with telomere biology disorders, juvenile myelomonocytic leukaemia associated with neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders and myeloid neoplasms associated with Down syndrome.

GATA-binding protein 2 (GATA2, located on chromosome 3q21.3) mutations were found to be associated with some syndromes, including MonoMac syndrome, dendritic cell, monocyte, B and NK cell deficiency, familial MDS and Emberger

syndrome and some types of disorders such as congenital neutropenia and aplastic anaemia. The risk of developing MDS/AML from GATA2 germline mutations is increased by 70% [18, 19, 20, 21].

3. Germline mutations associated with haematological malignancies in myeloid and lymphoid leukaemias

Most of the findings of germline mutations associated with leukaemia were from myeloid neoplasms. Recent studies found that lymphoid malignancies in acute lymphoblastic leukaemia (ALL) and chronic lymphocytic leukaemia (CLL) are associated with germline mutations. Speedy et al. demonstrated the existence of germline mutations associated with familial CLL by using whole-exome sequencing of 66 CLL families and identified 4 families where loss-of-function mutations in protection of telomeres 1 (POT1) co-segregated with CLL [22]. Qian group studied the loss-of-function germline TP53 variants, and their results suggested that such mutations lead to predispose children to ALL and with adverse treatment outcomes with ALL therapy and increase the risk of second malignant neoplasms [23]. Chang et al. have identified germline mutations from congenital ALL by using the exome sequencing technology [24].

Studies showed that some more genetic-based cancer-prone syndromes with specific germline predisposition syndromes and multiple-cancer hereditary predisposition syndromes are all at an increased risk for haematologic malignancies, commonly in AML, including chromosomal instability syndromes (CIS) such as Nijmegen breakage syndrome, Ataxia telangiectasia, Ataxia telangiectasia-like disorder and Bloom syndrome and including inherited bone marrow failure syndromes (IBMFS) such as dyskeratosis congenita, Shwachman-Diamond syndrome, Diamond-Blackfan anaemia, congenital amegakaryocytic thrombocytopenia, severe congenital neutropenia and thrombocytopenia-absent radii [25].

The most representative example is the Fanconi anaemia (FA) with germline mutations and predisposition to leukaemia. It overlaps in both CIS and IBMFS in its phenotypes. Historically, it was first recognised as a cause of juvenile leukaemia in 1967 [26]. FA is a hereditary disorder with defects in DNA repair and is characterised with multiple gene mutations, multiple types of genetic abnormalities, multiple organ involvements and multiple types of cancer risks [27, 28]. So far, 22 genes responsible for FA have been identified, 4 of them are genes found in breast cancer and some genes were found to be associated with other types of cancers as well.

Patients with FA have very high susceptibility to both haematologic and non-haematologic malignancies. The risk of developing AML and MDS is increased to 785 fold, and the median age of patients developing to AML is 14 years. AML occurs at about 9% and MDS is about 7% of all patients with FA, respectively [29]. Cells from FA patient associated with leukaemia showed high sensitive reaction to chemotherapies than non-FA patient with leukaemia.

FA was the first successful remarkable milestone in cord blood stem cell transplantation in 1988. The studies on FA offered insights into the pathogenesis of many types of human diseases, particularly in non-genetic bone marrow failure, ageing and cancer. So the study on FA is named as a paradigm for the understanding of cancer and ageing.

In the last couple of years, studies, by using the modern genetic technologies particularly by the next-generation sequencing (NGS) approach to study known and new germline mutations in familial acute myeloid leukaemia and myelodysplastic syndromes, found more leukaemia predisposition genes associated with germline in variants in cancer-predisposition genes, mainly as ASXL1, BCOR, NRAS,

TP53, CEBPA, FLT3, EZH2, IDH1, IDH2, NPM1, DNMT3A, TET2, CBL, KRAS, SF3B1, SRSF2, U2AF1, ZRSR2, TERT, TERC and SRP72 [30–32]. Studies from Seiter group provided the direct evidence from ASXL1 germline mutation associated with leukaemia studied on father and son [33]. Buijs et al. defined CBFA2 single-nucleotide mutation in a familial leukaemia [34].

Recommendations and guides are available by the applications of the next-generation sequencing approaches (NGS) [35, 36]. Churpek et al. proposed recommendations on the screening, identification, genetic counselling and managements on inherited susceptibility to MDS and acute leukaemia [37].

4. Conclusion

To increase the awareness and recognition for germline mutations associated with leukaemia is extremely important and imperative in the clinical practice by performing the specific tests. The significances are (1) to diagnose such type of patients earlier even if before the occurrence of such type of leukaemia, (2) to prevent the occurrence of secondary cancers, (3) to care other members of the family, (4) to design a specific therapeutical strategy, personalised medicine and long-term follow-up and (5) to guide the selection of donors for patient bone marrow stem cell transplantation.

To study germline mutations and syndromes associated with leukaemia has provided exciting and significant opportunities with such new discoveries. The studies on germline mutations associated with leukaemia will not only be useful in its clinical diagnosis, classification, stratification and specific treatment strategies, but it will also provide an insight to understand human diseases, such as tumorigenesis, particularly in somatic mutations associated with leukemogenesis. It is certainly that more and more such disorders will be identified in the future.

The huge challenges are to identify germline mutation associated with leukaemia due to the lack of awareness and knowledge about these disorders, lack of at least easy and practical available testing methods and sufficient familial history of individuals and lack of specimen source to represent genome for these individuals. The complex and mysterious genetic variation is another challenging issue just as the English novelist, George Orwell, described that “all cancer is genetic, but some cancers are more genetic than others which it hinted the mechanism and genetic variations of cancers”.

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