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Fanconi Anemia Markers

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Abstract

Fanconi anemia is a serious genetic disorder that can damage the bone marrow and increase the risk of developing cancer, particularly conditions such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Diagnosing this disease is difficult; it cannot be done based solely on external symptoms upon the patient's admission. The most reliable diagnostic method is cytogenetic analysis—that is, the examination of chromosomes. It makes it possible to detect chromosomal breaks caused by exposure to DNA-damaging agents.Patients with Fanconi anemia often exhibit specific chromosomal abnormalities—such as alterations in chromosomes 1q, 3q, and 7. These abnormalities are associated with progressive bone marrow failure and preleukemic conditions.

Keywords: myelodysplastic syndrome

Introduction

Fanconi anemia (FA) was first described in 1927 by the Swiss pediatrician Dr. Guido Fanconi after he observed a family with three brothers who had congenital physical abnormalities and died from a condition resembling pernicious anemia—specifically, macrocytic red blood cells and pancytopenia—along with several physical anomalies.[1,2,3]Patients with FA exhibit distinct and complex congenital anomalies, such as VACTERL-H (an acronym for vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula, esophageal atresia, renal and radial ray anomalies, limb abnormalities, and hydrocephalus) and PHENOS (an acronym for skin pigmentation, café-au-lait spots, microcephaly, microphthalmia, neurological abnormalities, otologic issues, and short stature). Although not all patients present with malformations or pancytopenia—indeed, a third of FA patients may reach adulthood with a normal physical appearance and normal hematopoiesis—these individuals are diagnosed either following the development of malignancies or through family screening [4].

Fanconi anemia (FA) is a rare disease with an incidence of 1 case per 300,000 live births and a prevalence of 1–9 cases per million people. However, this frequency may vary depending on the population, where a founder effect may be present [5]. FA is caused by the inactivation of at least one of the 23 genes that play a crucial role in the repair of DNA damage, particularly interstrand crosslinks (ICLs).

Mutations have been described in 21 FA genes, all of which have been shown to follow an autosomal recessive inheritance pattern[6,7].Exceptions include mutations in the *FANCB* gene, which is known to be X-linked, and mutations in the *FANCR*/*RAD51* gene, which are autosomal dominant[8,9.10].Fanconi anemia (FA) is a complex disorder characterized by phenotypic heterogeneity and variable expressivity; it cannot be diagnosed based solely on the clinical presentation. Furthermore, its clinical manifestations resemble those of other conditions—such as Diamond-Blackfan anemia (DBA), dyskeratosis congenita (DC), and Shwachman-Diamond syndrome (SDS)—complicating differential clinical diagnosis. Consequently, not all patients exhibit a clear clinical picture[5].The complex clinical presentation of FA can lead to a delay in definitive diagnosis, which directly impacts patient outcomes. Accurate and early diagnosis—utilizing the diagnostic gold standard (chromosomal breakage analysis)—enables parents to receive genetic counseling and make informed, more reliable family planning decisions, taking into account the likelihood of having another child with the condition. Furthermore, early diagnosis provides information regarding the need for therapy to address developmental abnormalities[11].

- **Analysis of chromosomal breaks**

FA was recognized as a disorder characterized by chromosomal instability thanks to pioneering observations made by Schroeder in 1964, when he noted that lymphocytes from patients exhibited a significantly higher number of chromosomal breaks in culture than those from healthy individuals. Consequently, Schroeder proposed the potential utility of this spontaneous phenomenon as a biomarker for FA[12,13].Later, Schuler et al. (1969) achieved significant success by demonstrating the feasibility of adding DNA-crosslinking agents—such as tetramethanesulfonyl-D-mannitol (mannitol)—in vitro to detect an increased frequency of breaks in FA samples[14].

In the 1980s, Auerbach reported that hypersensitivity to the clastogenic effect of diepoxybutane (DEB) is a valuable diagnostic marker for Fanconi anemia (FA), proposing a basic diagnostic protocol based on the addition of DEB to patients' peripheral blood[15].This specific agent was used in our laboratory to diagnose 550 patients with FA (data not yet available). However, DEB is a carcinogenic substance and a hygroscopic molecule that slowly loses activity upon contact with water. DEB has a half-life of approximately four days due to hydrolysis into 1,2,3,4-tetrahydroxybutane, a compound lacking cross-linking activity. Similarly, MMC also has limitations, requiring metabolic activation to become an active cross-linking agent[11].

One of the biggest challenges in chromosome breakage analysis (CBA) is mosaicism[16].Somatic mosaicism in FA (hereinafter referred to as mosaicism) arises from reversion or other compensatory mutations in hematopoietic stem/progenitor cells (HSPCs), giving rise to a population of bone marrow and blood cells capable of DNA repair. Patients with a reversion of the pathogenic FA mutation often harbor two distinct blood cell populations: one that is sensitive to DNA-damaging agents—consistent with the FA diagnosis—and another that is resistant to these DNA-damaging (or clastogenic) agents[13,17,18,19].

- **Molecular cytogenetic approaches in the diagnosis of Fanconi anemia**

A key step in the development of FA cytogenetics was the application of molecular methods such as FISH. This method allows for the analysis of a larger number of cells—since metaphase cells are not required—and enables the detection of clonal chromosomal abnormalities in both metaphase and interphase nuclei. However, despite this advantage, FISH can only be used to detect known abnormalities[20],given the need for well-defined FISH probes. Thurston et al. (1999) performed FISH analysis on a retrospective case of FA-associated AML with monosomy 7 and observed the presence of this anomaly 18 months prior to its detection by conventional cytogenetics. If monosomy 7 is indicative of bone marrow transformation, early detection of the monosomy 7 clone via FISH would enable early interventions—such as bone marrow transplantation—to help prevent or delay the onset of leukemia in these patients[21].Significant progress has been made in the study of FA thanks to the development of comparative genomic hybridization (CGH), a method that allows for the detection of chromosomal copy number alterations (CNAs). Like FISH, the CGH method does not require cell culture—an advantage in the case of FA, given the reduced mitotic index[22].

Tönnies et al. (2003) conducted a retrospective series analysis of 53 patients with FA, combining G-banding (Giemsa banding, the most commonly used chromosomal banding method) and CGH, and demonstrated that 18 patients (72% of those with chromosomal abnormalities) had partial trisomy or tetrasomy of the long arm of chromosome 3 (also confirmed by FISH)—a figure significantly higher than previously reported in the literature[23].The low number of cases with 3q alterations may be due to the fact that the gain of this genetic material could result from subtle chromosomal translocations and/or small supernumerary marker chromosomes that cannot be detected by G-banding analysis and were, therefore, missed during karyotyping[24].

- **Microkernels**

Micronucleus analysis is one of the most frequently used methods for detecting genomic instability and is currently primarily employed to assess genotoxicity. Fenech (2007) defined the micronucleus assay as the cytokinesis-block micronucleus (CBMN) assay. This assay quantifies micronuclei (MN), nuclear buds, and nucleoplasmic bridges, which are indicators of genomic instability[26].MN is also an important biomarker for the most common neoplasms found in patients with FA, such as MDS and AML. MN is considered a sign of CIN with prognostic significance in these hematological malignancies. Wang et al. (2013) found that MN formation levels in the blood lymphocytes of AML patients have prognostic value regarding disease progression[27].

Micronucleus (MN) analysis offers advantages over the traditional analysis of chromosomal aberrations (CA). Detecting CA in metaphase cells (using agents such as DEB or MMC) can be labor-intensive and requires highly experienced specialists. Furthermore, MN analysis can be automated using various methods, such as flow cytometry and automated fluorescence microscopy. While this appears to be a reliable method, further research is needed to evaluate the sensitivity and specificity of the test in patients with CA and in parents with other genotypes or mutated *FANC* genes[28].

Conclusion

Fanconi anemia (FA) is a rare hereditary disorder characterized by marked clinical and genetic heterogeneity, which significantly complicates timely diagnosis. Literature analysis indicates that diagnosis based solely on clinical presentation is impossible, as a

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substantial proportion of patients (up to one-third) may lack congenital anomalies and hematological manifestations until adulthood. This necessitates the use of laboratory diagnostic methods; the gold standard remains the analysis of chromosomal breakage induced by DNA-crosslinking agents such as diepoxybutane (DEB) and mitomycin C (MMC).Advances in molecular cytogenetics have significantly expanded diagnostic capabilities for FA. The implementation of FISH and comparative genomic hybridization (CGH) has enabled the detection of clonal chromosomal abnormalities—specifically partial trisomies and tetrasomies of the long arm of chromosome 3, as well as monosomy 7—which are associated with progressive bone marrow failure and an increased risk of transformation into myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). A key advantage of these methods is the ability to analyze interphase cells without the need for culture, a particularly important feature in FA given the reduced mitotic index. Furthermore, micronucleus (MN) analysis offers a promising, automatable method for assessing genomic instability that holds prognostic value in hematological malignancies.Nevertheless, a number of unresolved challenges remain. The phenomenon of somatic mosaicism, resulting from the reversion of pathogenic mutations in hematopoietic stem cells, can lead to false-negative diagnostic results and necessitates the refinement of analysis protocols. Furthermore, despite the evident link between the chromosomal abnormalities identified and disease progression, further prospective studies are required to determine the prognostic significance of specific biomarkers and their potential role as targets for targeted therapy.

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