COMMON FRAGILE SITES INDUCED BY FOLATE DEPRIVATION, BRDU AND APHIDICOLIN: THEIR FREQUENCY AND DISTRIBUTION IN JAPANESE INDIVIDUALS

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Summary The frequencies and distribution of common fragile sites in normal Japanese individuals were studied using lymphocyte chromosome preparations from cultures under folate deprivation, 5-bromodeoxyuridine (BrdU) or aphidicolin treatment. Defining the 4% level of total breaks as a cut-off point, 13 folate-sensitive, 20 BrdU-induced and 8 aphidicolin-induced sites were identified in one or more individuals studied. After eliminating overlapping, 28 fragile sites were identified. Of these, 23 have been reported, while the other five have not been described. Of the latter, those at 4q34 and 6q22 were each found in only one individual. The site at 3q26.2 has not been reported but one at 3q27 has been identified. Excluding these three sites as inconclusive, there remain two sites hitherto undescribed: 1) a folate-sensitive site at 17q21, found in two of eight individuals studied, and 2) a BrdU-requiring site at 13q31, found in five of eight individuals.

INTRODUCTION

Chromosomal fragile sites are now classified into three groups based on their frequencies in the general population (Hecht, 1986): rare, present in less than 1% of the general population; polymorphic, 1-50%; and common, over 50%. While we agree with the classification, the frequencies of fragile sites vary considerably depending on the means of their induction. We will thus use the term "common" to include both polymorphic and common fragile sites.

Common fragile sites (c-fra) are inducible at low frequencies under culture conditions that induce thymidylate stress (folate and thymidine deprivation, methotrexate or fluorodeoxyuridine treatment), and by 5-bromodeoxyuridine (BrdU) or...
5-azacytidine treatment, while they are induced at high frequencies by treatment with aphidicolin, aphidicolin plus ethanol, caffeine, or by a combination of these with other conditions (cf. Sutherland and Hecht, 1985; Kuwano and Kajii, 1987, for references).

Reports on c-fra sites in Caucasians have included those induced by folic acid deprivation (Sutherland, 1979; Yunis and Soreng, 1984; Marlhens et al., 1986), by treatment with methotrexate (Barbi et al., 1984), fluorodeoxyuridine (Barbi et al., 1984; Daniel et al., 1984; Yunis and Soreng, 1984; Rao et al., 1988), 5-bromodeoxyuridine (Sutherland et al., 1985), 5-azacytidine (Sutherland et al., 1985), caffeine (Yunis and Soreng, 1984), or aphidicolin (Glover, 1984; Craig-Holmes et al., 1987; Rao et al., 1988). Little has been known of their individual or racial difference.

This report will deal with c-fra sites in Japanese individuals induced by folate deprivation, BrdU and aphidicolin.

MATERIALS AND METHODS

Heparinized whole blood samples from healthy Japanese individuals were cultured for 4 days in Eagle's minimum essential medium (MEM) containing 5% fetal calf serum, 4% phytohemagglutinin, penicillin and streptomycin.

In one group, blood samples from eight healthy individuals, four males and four females, ranging in age from 7 to 31 years (Subjects 1–8), were cultured in MEM without folic acid or thymidine. Additional samples from the same individ-