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J.Biomed.Transl.Res
ISSN: 2503-2178

JOURNAL OF BIOMEDICINE AND TRANSLATIONAL RESEARCH

Letter to The Editor

Focal area of a high rate of fragile X in Indonesia: a long term follow up

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Article Info
History : **Received :** 23 Dec 2019; **Accepted :** 31 Dec 2019; **Available :** 31 Dec 2019
Permalink/ DOI: https://doi.org/10.14710/jbtr.v5i2.68951

Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability (ID) and a leading cause of autism spectrum disorder (ASD). FXS is caused by an expansion of CGG repeats >200 in the 5′ untranslated region of the promotor region fragile X mental retardation 1 gene (*FMR1*), which is located on *Xq27.3*. The abnormal CGG expansion leads to methylation and transcriptional silencing of the *FMR1* gene, resulting in a reduction or loss of fragile X mental retardation 1 protein (FMRP) and causes long, thin, and immature dendritic spines, which lead to deficits in cognitive function, behavioral problems, and learning ability(1).

The length of CGG repeats in the *FMR1* gene is recently divided into four types: (1) individuals with 6–44 CGG repeats are normal, and the most common sizes are 29 and 30 copies; (2) 45–54 CGG repeats are called “gray zone” or intermediate alleles; (3) premutation alleles are in the range of 55–200 CGG repeats; and (4) CGG repeats >200 are considered full mutations(2). Molecular diagnosis in genetic diseases is not commonly used in Indonesia. Therefore the causes of intellectual disability cases have rarely been explored genetically, including FXS.

In our cohort of Indonesian ID population, the prevalence of FXS is 1.7%, with the detail prevalence 1.5% in males and 2% in females (3), while prevalence in general population worldwide around 1:5000–7000 in men and 1:4000–6000 in female (4). Our previous study in 120 unselected males in the isolated Hiri Island (Molucca, East Indonesia) found four alleles with 55-57 *FMR1* CGG repeats, giving the 3.3% prevalence of fragile X permutation (5).

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Semin, a district with 55,000 inhabitants located at Yogyakarta province, island of Java is known as an area with many ID cases (estimated number of cases ~400). Most cases were familial and inherited by female lineage. In the year 2000 we did our first investigation for 47 ID cases at the special school and 76 ID cases at home visit nearby the school in this rural area. There were 12 families with more than 2 affected children in each family. Two male students and 6 other family members were randomly chosen for cytogenetic and molecular diagnosis. All were positive FXS, therefore, cascade testing has been undertaken subsequently. Afterwards, a large-multi-generational family pedigree with many affected individuals with FXS was diagnosed molecularly. These 2 male students actually were members of this large pedigree. The origin of fragile X mutations in this large pedigree was actually from one ancestor. Further molecular studies were carried out to confirm if there is a high rate of fragile X in this region. We found 16 nuclear families, with 25 affected males, 17 affected females, 27 premutation females carrier and 6 premutation males carrier and, interestingly, 45% of the ID students at school were FXS. This is the first reported area with many Fragile X cases in Indonesia, after the new cases finding in 1994 (6). Surprisingly we found many affected females with various clinical features, this is confirmed with X-linked dominant pattern of inheritance.

After almost 10 years of our screening program, these FXS families have been traced back and followed up. We found some nuclear families with many full mutation females who have married and inherited FXS children. The parents almost never have formal education (not graduated from elementary school) and little exposure to any media, while their affected children were educated at the special school in the village. Eight out of ten females with FXS have been married; three have no child, while the other 5 females (62.5%) have children with at least 1 affected with FXS. Marriage for females with FXS and ID with low educational background is not frightening to

the family and is acceptable in this rural community. This is related to the cultural background and ignorance about the problems that these females can have including raising children with FXS.

The school and village were revisited again 5 years later and found to have 6 additional nuclear families with 5 affected males, 5 affected females, 5 premutation females carrier and 5 premutation males carrier (3). Recently in our last visit to the school, the screening from 68 ID students by physical examination and interview revealed that there was no additional new FXS students except 2 adult males and 2 females from the previous data.

Genetic counseling is important in dealing with family suffered from inherited diseases. The goal in counseling sessions is to develop an understanding of the genetics of FXS and the high risk of an affected child, however this is challenging in families of a low educational and socioeconomic background. Prenatal diagnosis especially for FXS as a prevention of having more affected children in Indonesia cannot be offered, although advanced molecular techniques have already been introduced. Nevertheless, over the past two decades our surveillance (continuing follow up includes *FMR1* screening of new carrier offspring) has shown a decrease of affected cases. This might due to improvement of their awareness about FXS through long term follow up.

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