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Identification of chromosome abnormalities in screening of a family with manic depression and psoriasis: Predisposition to aneuploidy

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ABSTRACT

Cytogenetic analysis is an important stage in understanding the genetic background of manic depression (MD), and may provide a valuable clue to the identification of target loci and successful search for major genes. In order to identify chromosomal regions we aimed to detect the relationships between chromosomal aberrations (CAs) and immunological markers in a family with MD and psoriasis. We used the cell cultivation and conventional G-banding. We found predominantly numerical aberrations. The most common aneuploidy was chromosome 8, followed by chromosome 22, 21, 15, X and Y. However, structural aberrations consisted of duplications, deletions, translocations and breaks, with a focus on: loci on del(1)(q12–q23), del(1)(q21.1–q24), del(1)(q21.1–q23), del(10)(p11.2-pter), der(2)t(2;4)(p25;p12), t(2;22)(p14;p13), t(19;Y)? and dup(10)(q26). The susceptibility genes of MD or psoriasis may be located on these loci. Numerical sex CAs included 4(5.8%) with 45,X, 3(4.3%) with 47,XXY, and 4(5.8%) with structural chromosome X; del(X)(q13); del(X)(p11-pter) del(X)(q21.3) and inv(Y)(q11.2). We also conducted an immunological study. According results of this study, the percentage of CD2+, CD4+ and CD8+ lymphocytes of the father were significantly higher, whereas CD4+ lymphocytes were decreased in the mother, when compared the healthy persons. The percentage of CD4 level of the son was decreased, whereas CD8+ lymphocytes were higher. The CD4/CD8 ratio of the father and the son was found to be significantly high. These results may suggest that MD and psoriasis have a significant impact on both genetic and immunological parameters.

1. Introduction

Bipolar disorder (BD) (also known as manic depressive illness, MD) affects ~1% of the population and shows strong heritability. Family, twin and adoption studies provide strong support for an important genetic component (Nurnberger and Gershon, 1992). Cytogenetic studies in psychiatry are important in view of the potential multiple etiologies of psychiatric syndromes and due to the high incidence of chromosomal aberrations (CAs) reported in diverse psychiatric syndromes. Some genetic studies have confirmed that susceptibility loci exist for BD on multiple regions of the human genome, including 4p14, 4q35, 6q24, 10p13–12, 12q24, 13q32, 16p, 18p11.2, 18q22, 20p11.2–q01.2, 21q21, 22q11–13, Xq, and Xq26 (Smyth et al., 1997; Adams et al., 1998; Maier et al., 1999; Berrettini, 2000; Blackwood et al., 2001; Craddock and Jones, 2001). In other study, we have examined the chromosomes of 80 patients with BD. Numerical and structural variations were found in 26% of the patients and in 10% of the controls. In patients, 57% and 43% of abnormalities were structural and numerical aberrations, respectively, chromosomal regions of interest include 1q32, 7q32, 8p21, 21, 22q13 loci, +ace and monosomy X (Demirhan et al., 2007). These findings suggests that some chromosomal regions may play an important role in the genetics of BD. Psoriasis is also a polygenic disorder characterized by keratinocyte hyperproliferation with hyper- and parakeratotic differentiation, epidermal influx of polymorphonuclear leukocytes, and the presence of a mononuclear infiltrate in the papillary dermis and in the epidermis. However, a genetic model for psoriasis is still far away. Matthews et al. (1996) have indicated a locus for familial psoriasis on 4q, although a possible candidate gene in this chromosomal region has not been identified. Chromosome 1q21 is a common locus with genetic linkages to both atopic dermatitis and psoriasis (Cookson et al., 2001). Also, researchers has linked psoriasis to putative susceptibility loci,

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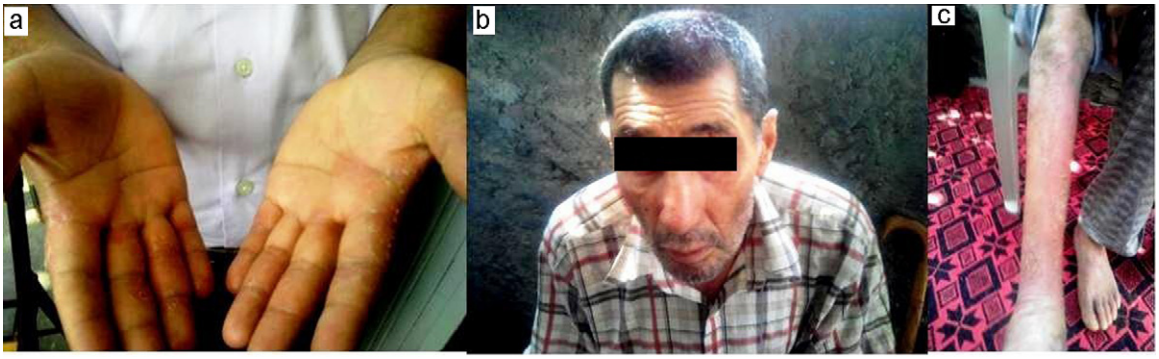

Fig. 1. Patient and his father with psoriasis together with BD. (a) Appearance of psoriatic lesion of hands of patient, (b) frontal view of face of patient's father, (c) appearance of psoriatic lesion of leg of patient's father.

2p12–p13, 8q24.11 and 20p13 (Trembath et al., 1997), and on chromosomes 1q, 2p, 4q, 6p, 8q, 16q, 17q, and 20p (Tomfohrde et al., 1994; Matthews et al., 1996; Nair et al., 1997; Trembath et al., 1997; Capon et al., 1999). Finally, four genes were recently described with respect to regeneration and hyperplasia of keratinocytes in psoriasis by Rivas et al. (1997). Knowledge regarding expression of these genes in psoriatic skin might elucidate further the factors that control keratinocytes in psoriasis.

We have identified a family with MD and psoriasis, and decided to study the significance of CAs, selected immunological markers and chimerism. The relationships between CAs or immunological markers and MD illness or/and psoriasis were evaluated. Persons with tetragametic chimerism sometimes also have patchy skin or eye pigmentation (Sybert, 1994). Therefore, we also decided to study the tetragametic chimerism in peripheral blood and skin tissue. Depending on these findings it was thought that because both brain and skin originate from same embryonic layer, ectoderm, it is plausible that the patient is suffering from an autoimmune disease like systemic lupus erythematosus which shows symptoms of neurologic diseases together with autoimmune damages effecting many organs and tissues. However, it is also possible that the psoriasis and MD coexist in our cases.

2. Materials and methods

2.1. Subjects

The 27-year-old son (patient) suffered from over-speaking, crying and lack of appetite in his age of 21. He was first referred for BD-major depressive episode and treated with antipsychotic medications at that time. After successful 21 days treatment in hospital, patient was discharged from hospital and joined his normal daily life. After this treatment, patient continued his job as a police officer and did not encounter any problem when performing his duty for a period of time. Since then, patient was suffered from 4 psychotic episodes in different time intervals. Recently, patient was admitted to hospital and demanded help for thoughts such as "I am being chased by anyone else, my six years old nephew will be a great person in the future, secret persons are hindering my nephew and I am assigned as a selected person for protecting my nephew". Because of this paranoid talk, patient was again accepted to hospital and treated. At the end of treatment period, patient was diagnosed with bipolar affective disorder-psychosis featured mania and treatment was begun. The father of patient was also diagnosed with bipolar affective disorder-psychosis, but the mother of the patient was normal, both physically and psychologically. As elements of this treatment, lithium carbonate and valproic acid were used on the basis of 1200 mg/day and 1000 mg/day, respectively. During the treatment, patient again made paranoid statements, saying "my co-workers that I formerly worked with them in Istanbul are chasing me under altered appearance". At the same time, it was observed that the patient was hiding his hands (Fig. 1). Also, pedigree of patient's family is shown in Fig. 2.

2.2. Cytogenetic analysis

In this study, patient and his parents were examined both cytogenetically and immunologically. For eliminating ethical concerns, informed consent document has been obtained from patient and his parents. As parts of cytogenetical study, chromosomes were prepared from cultured skin fibroblasts and phytohemagglutinin-stimulated lymphocytes in prometaphase and metaphase and stained according to standard protocols. Skin fibroblast samples were obtained from the patient. All samples were mechanically minced and enzymatically disaggregated by digestion with trypsin–EDTA (Biological Industries) for one hour. After digestion, BioAMF1 medium (Biological Industries) supplemented with its supplement, penicillin–streptomycin (Biological Industries), gentamycin (Biological Industries) was used for culture. Long-term cell culturing method was performed for proliferation of malignant and non-malignant cells. After enough proliferation (average 10 days), standard cytogenetic techniques were used for harvesting and slide peparation. GTG-banding was achieved by trypsin-giemsa. Karyotype was determined by analyzing at least 72 metaphases from the skin fibroblast cells for the patient. If there were not enough metaphases, observed plaques were evaluated. 100–200 metaphases were counted for the patient and parents.

2.3. Demonstration of chimerism by analysis of short tandem-repeat microsatellite markers

Genomic DNA was extracted from 200 μL peripheral blood and skin tissue obtained from the donors (the mother, father and son) using Qiagen DNA Blood Mini Kit following manufacturer's

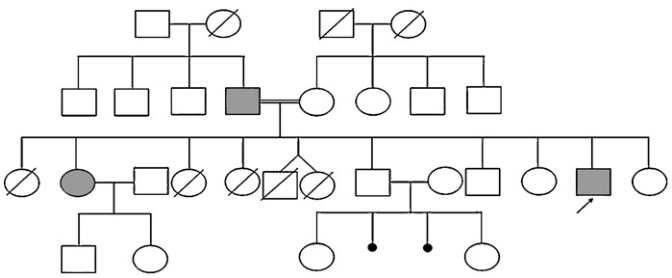

Fig. 2. Pedigree of patient's family.