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ORIGINAL INVESTIGATION

HLA-DPB1*04:01 allele is associated with non-obstructive azoospermia in Japanese patients

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Abstract Azoospermia is defined by absence of sperm in the semen and can either be caused by obstruction of the seminal tract (obstructive azoospermia) or by defects in spermatogenesis (non-obstructive azoospermia, NOA). Previous studies reported that specific alleles and single nucleotide polymorphisms (SNPs) in the human leukocyte antigen (HLA) region were associated with NOA in East Asians. We attempt to expand upon previous findings by genotyping more HLA genes and to replicate SNP associations by focusing on Japanese NOA patients. HLA typing of six genes (HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1) was done on 355 NOA patients using SSO-Luminex assay while genotyping of two previously reported SNPs (rs498422 and rs3129878) was done on 443 patients and 544 fertile males using TaqMan assay. Association between the HLA alleles and SNP with NOA was assessed with Chi squared and logistic regression tests. We found that HLA-DPB1*04:01 [corrected p value, P_c 7.13×10^{-6}; odds ratio (OR) 2.52], DRB1*13:02 (P_c 4.93×10^{-4}, OR 1.97), DQB1*06:04 (P_c 8.94×10^{-4}, OR 1.91) and rs3129878 (p value 3.98×10^{-4}; OR 1.32) showed significant association with NOA, however, these loci are in linkage disequilibrium with each other. The conditional logistic regression tests showed that DPB1*04:01 is independently associated with NOA, confirming the involvement of the HLA region in the etiology of NOA in Japanese patients.

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Introduction

Male infertility affects approximately 1 % of the general population and 10–15 % of the cases (Male Infertility Best Practice Policy Committee 2001; Hamada et al. 2013) are caused by deficiencies of sperm in the semen, commonly known as azoospermia. This condition can be classified into two categories: obstructive azoospermia (OA) and non-obstructive azoospermia (NOA). OA is caused by physical obstruction of the seminal tracts, which prevents sperm from being present in the semen whereas NOA is due to dysfunction in spermatogenesis. NOA occurs more commonly than OA, approximately affecting 60 % of azoospermic men (Jarow et al. 1989). Although non-genetic factors such as infections and drugs may contribute to the causality of NOA, genetic components account for approximately 30 % of the cases (Lee et al. 2011). Well known genetic causalities of NOA involve chromosomal abnormalities such as Klinefelter's syndrome, and

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