



Does the human leukocyte antigen's relatively homogeneous genetic background relate to better lung transplantation outcomes in Japan?[※]

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Abstract: The outcomes of lung transplantation in Japan are better than in other countries; however, the reasons for this are unclear. While the genetic background of the Japanese may be relatively homogeneous compared with those of other countries, whether this genetic similarity is related to better lung transplantation outcomes is an interesting question. We reviewed the literature to define the relationship between genetic similarity and better lung transplantation outcomes. However, it is still difficult to directly describe the relationship between genetic background and lung transplantation outcomes. As another approach, racial match or mismatch lung transplantation helps investigate whether genetic background similarity contributes to better outcomes of lung transplantation. Some reports have evaluated the impact of donor/recipient race-matching, which does not sufficiently influence patient outcomes to factor into organ transplant offers. Matching is not beneficial for African American lung transplant recipients. This may indicate that other factors influence the outcomes of these transplants. However, to discuss racial mismatch transplantation, racial disparities in organ transplantation need to be understood because the outcomes of organ transplantation differ between recipients of different races regardless of mismatched or matched organ transplantation. This makes it difficult to understand the outcome of a racially matched or mismatched lung transplantation. Meanwhile, in cadaveric liver and kidney transplantations, there is no difference in the outcomes in Japan and in other countries. In conclusion, it remains difficult to determine whether similarity in genetic backgrounds is related to better lung transplantation outcomes in Japan.

Keywords: Lung transplantation; genetic background; racial matched; unmatched lung transplantation; racial disparities in transplantation

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Introduction

The outcome of lung transplantation in Japan is better than that in other countries; however, the reasons for this may vary, and definite reasons are yet to be provided. The

genetic background may be relatively homogeneous in the Japanese people, compared with people in other countries. This genetic similarity may be related to better outcomes in lung transplantation. In this article, we reviewed studies

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to define the relationship between genetic similarity and improved lung transplantation outcomes.

There are no data on how the similarity of the genetic background could influence the outcome of lung transplantation. However, the influence of racial differences in lung transplantation could be used as a reference instead of differences in genetic backgrounds; therefore, racial match and mismatch between donor and recipient would be useful to answer this question. Therefore, we reviewed some reports describing the genetic background in Japan, racial match and mismatch between donor and recipient, issues of racial disparities in organ transplantation, differences in outcomes in other organ transplantations between Japan and other countries, and transplantation data in Korea.

Genetic background in Japan

Genetic backgrounds are more similar among Japanese people than those among people in other countries (1). According to data from the single nucleotide polymorphism (SNP) discovery project in Japan, the Japanese population has a rather small genetic diversity (2). Some studies have reported genetic differences in major histocompatibility complex (MHC), even in populations worldwide (3,4). This was observed between seemingly homogeneous populations, such as China and Japan, including northern and southern Han Chinese, who are an East Asian ethnic group native to China (5), the Hondo, who reside in mainland Japan, and Ryukyu Japanese, who reside in the Okinawa islands (6). Compared to SNPs found across the rest of the genome, SNPs located in the human leukocyte antigen (HLA) region displayed the greatest allele frequency differences between mainland Japanese (Hondo) and Japanese individuals residing in the Ryukyu Islands (7). Twenty regions outside the MHC that are highly differentiated between Ryukyu (Okinawa) and Hondo (mainland Japan) were found. Therefore, there were genetic differences between individuals from Okinawa Prefecture and mainland Japan. Mainland Japanese individuals from the six prefectures were more homogeneous than northern and southern Han Chinese individuals. The distribution of haplotypes in Japan was similar, although imputation was the most accurate for Okinawa and several mainland prefectures when population-specific panels were used as a reference. In conclusion, the distribution of haplotypes across Japan was similar except for Ryukyu (Okinawa); therefore, the genetic background in Japan, particularly among mainland-residing individuals, is similar compared with that in other countries.

Racial match and mismatch lung transplantation

Donor and recipient racial match or mismatch lung transplantation is helpful when investigating whether the genetic background similarity among Japanese people contributes to a better outcome of lung transplantation in Japan.

Some studies have described the outcomes of donor/recipient racial matching and mismatch of organ transplantation. However, the number is small; therefore, the impact of donor/recipient race matching is unclear. LeClaire *et al.* evaluated the impact of donor/recipient race-matching using the United Network for Organ Sharing (UNOS) database from 1999 to 2018 for all solid organ transplantations, including heart, lung, liver, kidney, and pancreatic transplants (8). They sorted donor and recipient race data into matched and unmatched groups for Caucasian, African American, and Hispanic individuals and compared the outcomes between races. In lung transplantation, the Organ Procurement and Transplantation Network (OPTN)/UNOS registry reported 29,755 lung transplants, including 24,911 Caucasian recipients (83.7%), 2,515 African American recipients (8.5%), and 1,691 Hispanic recipients (5.7%). Donor-recipient race-matching in Caucasian recipients improved patient survival by 2.9% at 1 year, 2.9% at 3 years, 2.5% at 5 years, and 2.2% at 10 years. Furthermore, graft survival was also improved in this group by 3.1% at 1 year, 3.2% at 3 years, 2.9% at 5 years, and 2.4% at 10 years. In contrast, race-matched African American recipients had worse outcomes than non-matched recipients. Matched African Americans had 5.8% and 7.5% worse patient survival rates at 3 and 5 years, respectively. Hispanic recipients did not show statistically significant differences in race-matching outcomes. They concluded that race matching does not sufficiently influence patient outcomes to factor into considerations for organ transplantation. Matching is not beneficial for African American lung transplant recipients. This may indicate that other factors influence the outcomes of these transplants. The reasons for these data are still unclear; however, in terms of worse outcomes in race-matched African American recipients of lung transplantation, considerable racial disparities in organ transplantation may influence this result, as described below.

Allen *et al.* made a similar analysis about lung transplants using the OPTN/UNOS database of 11,323 patients from 1997 to 2002, of which 7,414 (65%) were race matched, including 7,104 Caucasians, 184 African Americans, 117 Hispanics and 9 Asians (9). Race matching decreased the

30-day, 90-day, 1-year, and 2-year unadjusted mortality; however, race matching decreased the risk-adjusted cumulative mortality, and race matching significantly improved survival. However, when deaths in the first year were included, race matching did not affect cumulative survival. Race matching did not influence rejection 1-year after lung transplantation. They concluded that race matching resulted in an improvement in long-term survival, which was 2 years after transplantation. However, in their data, an increased risk of death was noted among African American donors, regardless of the recipient's race. Therefore, it is important to understand data involving racial disparities in organ transplantation, which may influence this result.

LeClaire *et al.* also described donor and recipient race-matched and un-matched transplantations in other organs (8). Race-matched Caucasian recipients experienced a 1–3% improvement in mortality at most time points in liver and pancreas transplants, while no improvement in mortality was found in Hispanics. Matched African American liver transplant recipients showed a 4–6% improvement in patient and graft survival. However, in pancreas transplants, African Americans had worse outcomes with race-matching, as patient survival in the matched group was worse by 7.1% at 5 years, while graft survival was worse by 6.8% and 9.5% at 3 and 5 years, respectively. In heart transplants, there was no statistically significant survival benefit from donor-recipient race matching among any ethnic groups.

Yamada *et al.* performed an analysis of the number of HLA mismatches between donors and recipients after lung transplantation (10). They concluded that the number of HLA mismatches between donors and recipients after lung transplantation does not correlate with acute cellular rejection or with overall survival. In contrast, HLA mismatch is correlated with the development of chronic lung allograft dysfunction and should, therefore, be considered a risk factor. Therefore, HLA similarity may not influence the overall survival in lung transplantation.

In conclusion, based on some reports describing the impact of donor and recipient race-matched and unmatched transplantation, HLA similarity possibly does not influence outcomes, at least in lung transplantation.

Racial disparities in organ transplantation

To discuss racial mismatch transplantation data, racial disparities in organ transplantation need to be understood

because the outcomes of organ transplantation differ between recipients of different races regardless of mismatched or matched organ transplantation. In lung transplantation, being male or Caucasian had an outcome favoring lung transplant allocation compared to an appropriately matched person of another sex or race (11). Therefore, there are disparities in the allocation for lung transplantation. In terms of outcome after lung transplantation, there was a significant difference in, at least in the historical era. However, according to data, lung transplant survival improved in the modern era between Caucasians and non-Caucasians (12). However, further examination is necessary because there are only a few reports using relatively old data.

A few reports have evaluated racial disparities in heart transplants. According to Centers for Disease Control and Prevention's (CDC) reports, African American patients have significantly higher rates of heart disease-related mortality in the United States (13). Similar to lung transplantation, the proportion of African American patients listed and transplanted for the heart was lower than the national proportion of African American patients (13.4%) (14). However, heart transplant listing and transplantation in African American patients have gradually improved, especially since the early 2000s.

However, few reports have evaluated racial disparities in the outcomes of heart transplants. These reports described that the authors focused on early post-transplant outcomes stratified by race and suggested adverse post-transplant outcomes for the African American population (15,16). In another report, African American race was identified as a risk factor for poor post-transplant survival (17). Trivedi *et al.* evaluated race along with different transplant eras and observed that African American patients had historically poor survival. However, in recent years, heart transplantation survival in the United States has improved and has become comparable to the rest (18). The reasons for this may have been the general improvement in care, better compliance with immunosuppression, reliable insurance coverage, and increased awareness about reducing racial disparities.

In other solid organ transplantations, racial disparities in recipients have been reported in terms of outcome. As with heart and lung transplantations, few studies have performed chronological comparisons (11,19). These studies showed that racial disparities have reduced in kidney transplants in recent years. However, for lung and liver transplants, non-Hispanic African American patients still have poor outcomes (11,19,20).

Therefore, the influence of racial disparities in organ transplantation must be considered in the evaluation of racial-matched and unmatched solid organ transplantation.

Comparison of transplantation outcomes between Japan and other countries

Comparison between other countries and Japan is helpful in understanding the effect of HLA similarity on the outcome of organ transplantation.

In terms of liver transplantation, comparing the outcomes of liver transplantations in Japan and other countries are difficult because the number of living donor transplantations in Japan is higher than that in other countries. In some previous reports, the survival rates between parts of the United Kingdom and Japan were similar. The 1-, 5-, 10-, and 20-year patient survival rates were 98%, 95%, 87%, and 62% in the United Kingdom and 100%, 96%, 88%, and 62% in Japan, respectively (21). Meanwhile, in Japan, patient survival was 89.1%, 85.2%, 82.9%, 75.4%, and 70.7% after 1, 3, 5, 10, and 15 years, respectively, following liver transplantation from cadaveric donors, and 85.0%, 80.9%, 78.5%, 73.2%, 68.5%, 65.7%, and 64.6%, after 1, 3, 5, 10, 15, 20, and 25 years, respectively, following liver transplantation from living donors (22). According to these data, we may tentatively conclude the following. The outcome of liver transplantation in Japan might be worse than that in the United Kingdom and Canada. However, the overall survival in the United States and Europe may be poorer than that in the United Kingdom (22-24). Nevertheless, it is still difficult to evaluate the outcomes of liver transplantation because the number of living donor transplantations in Japan is higher than that in other countries.

In terms of kidney transplantation, the situation is similar to that of liver transplantation in terms of a greater number of living donor transplantations and fewer cadaveric transplantations compared to other countries. In cadaveric kidney transplantation, there is no difference in the outcomes between Japan and other countries (25).

Based on these data, it is still difficult to conclude that the similarity of genetic backgrounds may be related to better outcomes of solid organ transplantation.

Outcomes in other countries with relatively homogeneous genetic backgrounds such as Japan

Organ transplantation in Korea is similar to that in

Japan. Additionally, the HLA similarity of Korean people is similar to that of Japanese people. As described, the HLA of the Japanese population is more homogeneous than those of people from other countries. Koreans also have a more similar HLA background compared to other European countries (26-28). Based on these data, if the HLA background is closely related to the outcome of lung transplantation, the outcome in Korea is expected to be better than that in other countries. However, the postoperative 1-, 3-, and 5-year survival rates published by The Korean Network for Organ Sharing (KONOS) were 61.8%, 52.3%, and 45.3%, respectively. These values are much lower to those of the International Society for Heart and Lung Transplantation (ISHLT) and Japan (29). The poorer outcome in Korea has been influenced by some negative effects, such as the requirement of extracorporeal membrane oxygenation (ECMO) or mechanical ventilation in half of the recipients, low rate of usability of the donor's lung, and more frequent indications of idiopathic pulmonary fibrosis (IPF) (30). Based on these data, it is still difficult to relate the similarity of genetic backgrounds to better lung transplantation outcomes.

Conclusions

From the literature, it remains difficult to conclude that similarity in genetic backgrounds is related to better lung transplantation outcomes in Japan.

The mystery of better outcomes due to the similar genetic background of the Japanese population could not be determined. However, such an investigation is difficult when aiming to define the effect of genetic background because the outcome of lung transplantation could be influenced by many factors. In the future, the effect of genetic background on lung transplantation should be determined by other studies. In conclusion, the improved lung transplantation outcomes in Japan are influenced more by other factors other than the similarity in genetic background.

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