Genomic Med. (2008) 2:167–169
DOI 10.1007/s11568-009-9111-8

ABSTRACTS

Genome variation, diversity and evolution

014: Evolutionary dynamics of the human Y chromosome

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Y chromosomes, whose absence or presence determines the sex in humans, carry few functional genes and an abundance of repetitive junk DNA. Sex chromosomes arose from ordinary autosomes but the Y chromosome degenerates due to its lack of genetic recombination. For example, the human Y chromosome originated about 150–200 million years ago and most of it's originally >1,000 genes have since been lost. This has led several researchers to propose that men will go extinct because of Y chromosome degeneration. By assuming that the human Y chromosome degenerates at a constant rate, some authors predict that the human Y chromosome will lose its last gene within the next 125,000–10 million years, leading to the extinction of males. However, the assumption of a constant rate of degeneration is not based on an evolutionary model. Both positive and negative selection models have been proposed to account for the loss of functional genes on a non-recombining Y chromosome, and I develop dynamic evolutionary models to predict the rate of Y degeneration over evolutionary time. I show that the rate of degeneration is not constant over time, but instead declines steadily due to the steady decrease in the number of active genes on a degenerating Y chromosome. Interestingly, strikingly different evolutionary dynamics are predicted for positive and negative selection models; negative selection is the dominant process in the very initial stages of Y chromosome evolution, while positive selection becomes most important at intermediate stages of degeneration. Using these models, together with estimated mutation and selection parameters for humans, I show that the human Y will likely retain most of its genes after another 300 million years of evolution. This contradicts recent predictions of the forthcoming loss of all functional genes on the human Y within 10 MY.

015: Genomic Studies on Indigenous African Populations

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Introduction: Africa is the origin of humankind, yet very little research is reported off this continent with respect to this phenomenon, and the related genomic diversity here. With the vast number of large-scale genome sequencing projects that have been embarked on, and even more initiatives to conduct large scale genome wide SNP-typing of populations around the world, it is worthwhile inventorising the progress with regards to genomic research on the African continent. With this as a backdrop we present our original research on five indigenous Southern African populations using high density genome-wide SNP (6) analysis.
Methods and Materials: This research involved (1) reviewing the expansive genetic and genomic research on the African continent, and (2) conducting a genome-wide SNP analysis of five indigenous Southern African population groups, using the Affymetrix SNP6 system. The subjects were chosen to represent Eastern and Western Bantu migrations, as well as the original San population.
Results and Discussion: Genetic studies in Africa have dealt generally with monogenic disorders; e.g., haemaglobinopathies in central and North Africa, and neurodegenerative conditions in North Africa. More recently, expansive studies have begun looking at susceptibility to infectious diseases including HIV/AIDS, Tuberculosis, Malaria, Leishmaniasis, Leprosy, Schistosomiasis, and Trachoma. A growing number of studies are currently aimed at non-communicable diseases such as diabetes and hypertension. In addition to investigating predisposition to disease, several studies on worldwide human relationships using high density genome-wide SNP variations has supported evidence of a single human origin in sub-Saharan Africa. Our original research on a significant number of subjects from five indigenous populations from the Southern-most part of the African continent provides significant support for human origins south of the Sahara, and provides a means for dissecting population structure much more incisively. There is genomic evidence of significant selection pressures correlating with population migration to the southern tip of Africa.
Conclusion: The genetic dissection of indigenous African populations is growing at a significant pace. Useful information on population structure and linkage disequilibrium intervals will inform future studies here in the Southern part of Africa, aimed at mapping genotypic features against complex phenotypes.

016: The Mexican Genome Diversity Project: Analysis of genetic structure in Mestizo and Amerindian populations of Mexico

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Most of Mexico's population is represented by Mestizos resulting from admixture of Amerindian, Spaniards and, in a lesser extent, African populations. This admixture process has led to particular genomic ancestry structure. To optimize the use of the human genome information to improve healthcare in the Mexican populations, we are systematically evaluating the genomic variability of the Mexican Mestizo population. We genotyped 300 self-defined Mestizos from six regions [Guanajuato (GUA); Guerrero (GUE); Sonora (SON), Veracruz (VER); Yucatan (YUC) and Zacatecas (ZAC)] using the Affymetrix 100 K SNP array set. Heterozygosity (HET) values, Fst and principal component analysis were determined. HET was higher in Mexican subpopulations compared to the Asian HapMap samples, SON showing the highest (0.287) and GUE the lowest (0.274). Fst values from five of six pairwise comparisons between Mestizos (SON-GUE: 0.019, SON-VER: 0.013; SON-YUC: 0.012; SON-GUA: 0.011; SON-ZAC: 0.006) where higher than those of the Japanese–Chinese samples of the HapMap (JPT-CHB: 0.007). PCA separated HapMap samples in three clusters. Mestizos showed a wide distribution between the CEU and other source of variation not present in HapMap data. To demonstrate that the Amerindian population represents the third ancestral component in the Mestizo population, 33 Zapotec (ZAP) Amerindian samples were included in the analyzes. Fst values showed that GUE and VER are the most similar to the Amerindian sample (ZAP-GUE: 0.032; ZAP-VER: 0.038) and SON the most different (ZAP-SON: 0.082). Fst values for the SON-ZAP comparison was higher than all comparisons between Mestizos and CEU or Asian samples. As expected, the highest Fst value was obtained in the African–Amerindian comparison (ZAP-YRI: 0.238). PCA analysis showed that the ZAP clustered between the CEU and the Asian population. Mestizos from GUE and VER were closely located to the ZAP cluster, while samples from SON were located at the other end of the distribution, closer to the CEU. Our results indicate significant heterogeneity between populations within Mexico, as well as between Mexicans and the HapMap populations. We are including additional Mexican Amerindians and increasing the SNP density to better understand the admixture process of the Mexican Mestizo population, and develop more suitable tools to analyze the genetic bases of complex diseases in the Mexican populations.

017: Population history of North Eurasia revealed by X-chromosome ZFX haplotypes

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To reconstruct the origin and evolution of human populations in North Eurasia we investigated the genetic diversity in 23 population samples (about 1,300 individuals totally) using X chromosome lineages. SNP markers in a single 50 kb linkage disequilibrium region of ZFX gene was used to trace the X chromosomal population history. Forty-one ZFX haplotypes were found in populations of North Eurasia, belonging to three major clusters (see cluster definitions below). North Eurasian populations are less divers with respect to X-chromosomal haplotype (gene diversity within populations 0.65–0.80) and less differentiated (Fst = 3%) compared to Y lineages. But the regional differentiation demonstrates the same picture: the highest level of between-population genetic differences was observed in isolated populations of North East Asia, whereas European and Central Asian populations are almost undifferentiated by ZFX lineages. Three clusters of population are formed in the space of two-first principal components. The most distant cluster consisted of African Yoruba population, and North Eurasian populations are joined into two clusters, one of which consisted mainly of Caucasoid populations, whereas Siberian and South-East Asian Mongoloids form the second. The positions of populations in the PC1/PC2 space strongly correlate with geographic distances between populations. The population clustering by X and Y gives, to a first approximation, a similar picture, and matrices of genetic distances between populations for X and Y haplotypes significantly correlates. Strong linkage disequilibrium was observed between all ZFX SNPs, which formed the single LD block in all studied populations. North Eurasian ZFX haplotypes belong to 2 main clusters, both originated from the same African root (cluster A). Two major haplotypes were observed within the cluster B, and the single founder haplotype of cluster C was found. The structure of root haplotype was estimated by comparing human and chimpanzee (Pan Troglodytes) ZFX gene sequences. The founder of the whole tree was found with low frequency in African population, and haplotypes within 1–2 mutations distances (cluster A) from founder were observed mostly in Africans. The presence of 2 different clusters in Europeans and Asians probably provides the evidence of two population expansions outside Africa. This work is supported by RFBR grants ##06-04-48274 and 07-04-01629.

018: Population structure inference and genetic matching in European samples using genome-wide marker sets

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Genetic association studies can be confounded by population stratification. Genetic matching, such as between cases and controls, by use of large numbers of genetic markers can prevent systematic ancestry differences. Here, we compare the genetic structure of European populations using more than 2,400 samples with genome-wide single nucleotide polymorphism (SNP) data from 23 different regions. Furthermore, we investigate if a small number of ancestry-sensitive markers (ASM) are sufficient to allow a genetic matching in European sample sets with the same accuracy as the complete, genome-wide marker set. Our results indicate that, besides a small number of highly informative markers, the great majority of markers contribute only little, but independent information for matching and a large number of markers are required for reliable matching within Europe.

019: Structure of Japanese population based on SNP genotypes from 7,003 individuals in comparison to other ethnic groups: Effects on population-based association studies

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Because population stratification can cause spurious associations in case-control studies, understanding the population structure is important. Here we examined the population structure of 7,003 Japanese individuals using the genotypes for 140,387 SNPs by 'Eigenanalysis', along with 60 European, 60 African and 89 East Asian individuals in the HapMap project. Most Japanese individuals fell into two main clusters, Hondo and Ryukyu clusters, which may reflect the descendents of the Yayoi and Jomon populations, respectively, in ancient Japan. The highly differentiated regions between Hondo and Ryukyu clusters were found in HLA region in chromosome 6, and particular regions in chromosomes 4 and 9. Two non-synonymous SNPs, one of them is in the EDAR, which is associated with Asian hair thickness and the other in ABCC11, which is associated with dry ear wax, showed significantly different genotype frequencies between Hondo and Ryukyu clusters. Genetic differentiation was observed even among different regions in Honshu Island, the largest island of Japan. Simulation studies showed that the inclusion of different proportions of individuals from different regions of Japan in case and control groups can lead to an inflated rate of false positive results when the sample sizes are large.