Genetic factors affecting EBV Load in Transformed LCLs from the 1000 Genome Project : a GWAS on Transformation

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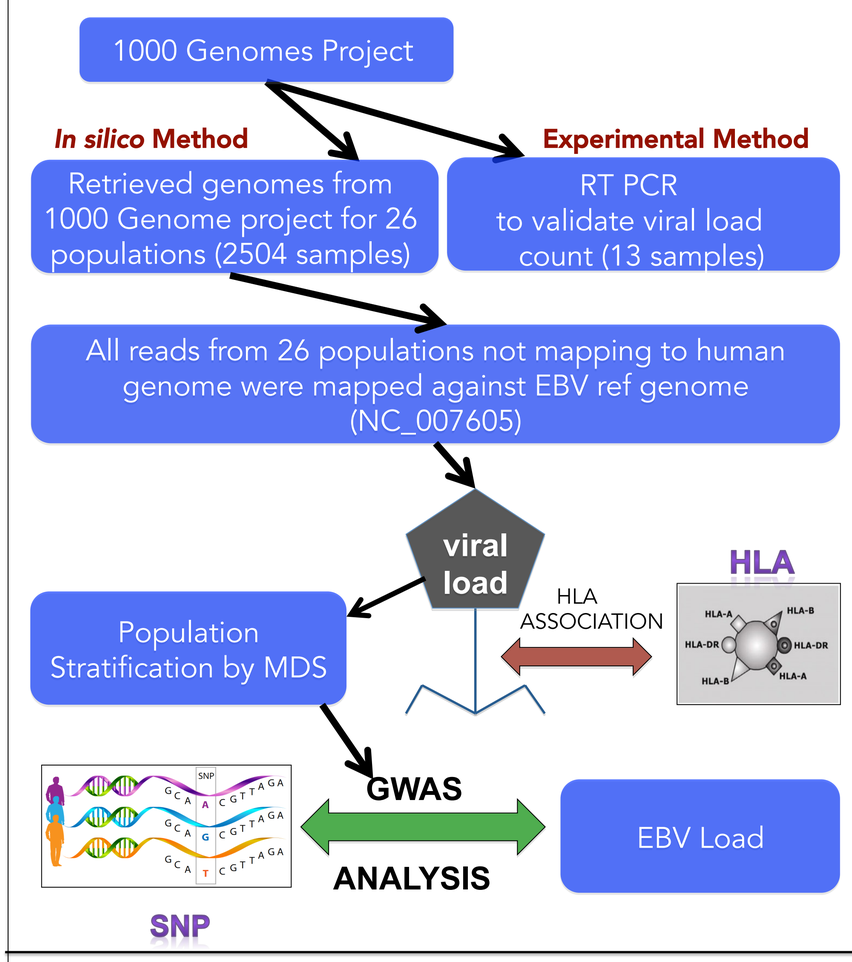
- Background of study -

- Epstein-Barr virus (EBV) infects 95-98% of adults world-wide, and causes infectious mononucleosis. EBV is also linked with severe conditions such as Burkitt's lymphoma, nasopharyngeal carcinoma and post-transplant lympho-proliferative disorder.
- It is unknown to what extent host genetic variants influence EBV load within LCL.
- We hypothesized that differences among individual LCLs in the EBV load resulting from EBV transformation may reflect different genetic susceptibility to EBV infection.

- Objective of study -

- To assess whether there are SNPs in the genome of worldwide populations from the 1000 Genomes Project that could be associated with the viral load measured in LCLs used in that project.
- To help understanding the biology of cell immortalization and of EBV-related diseases.

- Methodology -



- EBV load estimation results -

- Viral load ranges from 1-600 viral RNA copies/LCL across all populations are observed.
- Viral load shows significant differences between continents.
- Within continent, populations also show clear differences. In Europeans, for instance, IBS and CEU appeared to have higher viral loads than Finish or Tuscans **(Figure 1)**.
- No difference is observed between males and females.

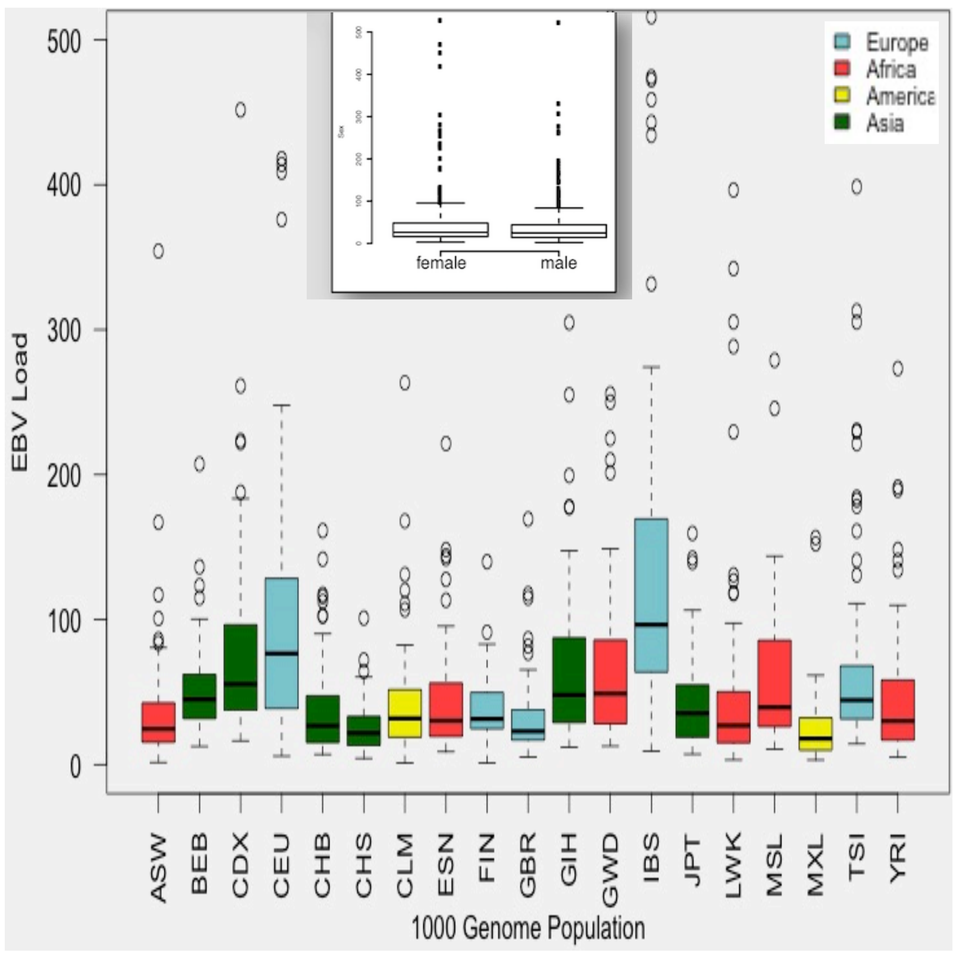


Fig:1 EBV load distribution among 1000 genome populations

- GWAS results -

SNP	Chr	BP	Beta	SE	Gene symbol	Gene feature	GWAS P-value
Top GWAS hits from all populations samples							
rs200699422	4	174352039	-0,161	0,02717	**SCRG1**	intergenic	**3.79E-09**
rs28758290	4	106030663	0,1127	0,0193	**TET2**	intergenic	**6.35E-09**
rs4976776	5	177855823	0,07717	0,01429	**COL23A1**	intronic	**7.58E-08**
rs112772351	6	36498148	-0,1074	0,02007	**STK38**	intronic	**9,89E-08**
rs17809115	17	32629296	0,1042	0,01936	**CCL11**	intergenic	**8.31E-08**
rs384592	19	23458920	0,1379	0,02474	**IPO5P1**	intronic	**7.58E-08**
Top GWAS hits from Asian populations samples							
rs80274284	1	116579977	-0,2156	0,03757	**SLC22A15**	exonic	**1.55E-08**
rs199893425	2	231404151	-0,2298	0,03928	**SP100**	intronic	**8,37E-09**
rs200655768	2	179575949	-0,2411	0,04178	**TTN**	exonic	**1.30E-08**
rs200699422	4	174352039	-0,2254	0,04107	**SCRG1**	intergenic	**6.19E-08**
rs199422217	5	156895736	-0,2264	0,04149	**NIPAL4**	exonic	**7.29E-08**
rs184202621	9	115166387	-0,2448	0,04015	**HSDL2**	exonic	**2,02E-09**
rs201672061	9	134357909	-0,2229	0,04093	**PRRC2B**	exonic	**7.68E-08**
rs112607901	16	31003411	0,1165	0,02039	**STX1B**	UTR3	**1.82E-08**

Table:1 Top GWAS hits with gene name and annotation

- 14 strong association signals (**Table 1**) from all populations and Asian populations are observed.
- Genes associated with neurological disorder, prostate cancer and Hodgkin lymphoma are frequent.
- Regions containing genes TRAK1, DKK2, PAPD7, MLN, ARHGEF10, SYT9 and LINC01255 are shared between Asian and African populations.
- The proportion of variance in EBV load explained by SNPs is 0.63 (n=1730, SE ± 0.17, P= 5.77e-15), and 0.86 (n=573, SE ± 0.02, P= 4.08e-08) for all populations and Asian populations (1.06 and 2.2 million SNPs considered in each case)

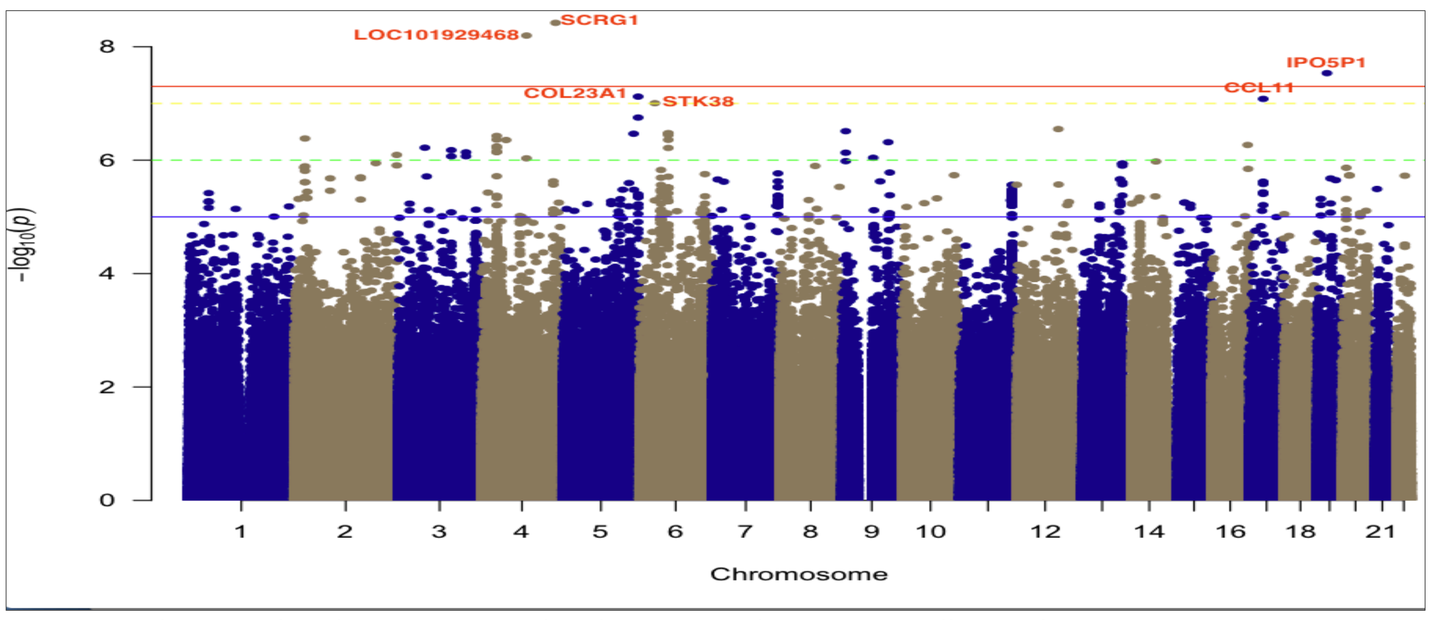


Fig:2 Manhattan plot depicting EBV load associated variants in all populations

- Conclusions -

- We identified some genetic variants associated with viral load. These might point to pathways involved in natural EBV transformation and associated infections.
- Individual and population level variation in viral load may affect individual and population risk for certain EBV-related disease.
- LCL-based models would be a good indicator of EBV load at the population-level, which would be useful in linking EBV load variation in transformed LCLs to specific genetic loci.

- References -

- Chang CM, Yu KJ, Mbulaiteye SM, Hildesheim A, Bhatia K. 2009. The extent of genetic diversity of Epstein-Barr virus and its geographic and disease patterns: a need for reappraisal. Virus Res.
- Houldcroft CJ, Kellam P. 2014. Host genetics of Epstein-Barr virus infection, latency and disease. Rev. Med. Virol.