



## S8.O.2

### **Deciphering a biological adaptation in the Andamanese people**

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Recently, we analyzed signatures of positive selection using whole-genome sequences from the Andamanese, a pygmy population indigenous from the Andaman Islands, and several mainland Indian populations. Among the top 20 most differentiated non-synonymous SNPs detected under a hard selective sweep model in the Andamanese, we identified the R990G substitution (rs1042636) in Calcium-Sensing Receptor (CaSR) gene as a potential adaptive variant to experimentally follow up. Notably, in vitro studies had already shown that the derived allele of the R990G substitution results in a gain-of-function of the receptor. CaSR has a critical role in calcium homeostasis by directly regulating the urinary calcium excretion and the parathyroid hormone (PTH) secretion. The gene is also expressed across a wide range of tissues and has been described to be involved in many other diverse biological functions. Since no direct adaptive phenotype could be linked to the detected signatures of adaptation, we generated a knock-in mouse for the R990G substitution using the CRISPR-Cas9 technology. To assess the phenotypic impact of the substitution, we explored for potential differences related to the CaSR functions between the homozygote carriers of the ancestral and derived alleles that could result adaptive in the Andamanese. Preliminary results point to unequal fat accumulation and differential weight, with R990G homozygotes showing greater weight and more fat accumulation. Such features could facilitate an earlier sexual maturation in agreement with the hypothesis that the pygmy phenotype could result from selection for an early onset of reproduction since they live in a particularly hostile environment.