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TITLE: Germline variants in individuals of low and high nevus count

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ABSTRACT BODY:

Body: We report on a prospective case-control study of melanoma and nevi in South-East Queensland, combining an assessment of pigmentation characteristics, dermoscopically-assessed nevus subtypes together with genotype comparisons and melanoma risk for 1032 individuals. Saliva-derived DNA was collected from volunteers and has been subject to genotyping at over 500K SNPs using an Illumina CoreExome Chip. Currently we have genotype information for 493 melanoma patients, 146 individuals with familial association and 393 non-melanoma/healthy controls. In this first-in-kind study, we have captured dermoscopic images of ~25,000 nevi >5mm in diameter and in an interim analysis, the dominant nevus subtype pattern was 'nonspecific' followed by 'reticular', with a minority having a 'globular' pattern. Interestingly, we have found 17 participants in our cohort harbour the SUMOylation deficient *MITF* E318K mutation. Using our combined phenotypic data, it is clear that these carriers are not only affected with melanoma (70%) or have a family history of melanoma (18%) but they also have significantly higher total nevi counts (TNC) on average than the controls. Additionally, of the six genes identified in a recent meta-analysis of nevus GWAS, we have replicated four including *IRF4*, *MTAP*, *PLA2G6* and *LMX1B*. The most striking of these was the *IRF4* SNP rs12203592*C/T (P<10⁻⁷), which was associated with a decrease in globular nevus counts (P<10⁻⁶). To discover additional rare variants influencing nevus traits, we have conducted an analysis by performing whole exome sequencing (WES) on 62 individuals with extremes of nevus phenotypes. In this pilot WES study, we compared the allele frequencies of 30 individuals with low TNC (Mean of 0.4 >5mm) with 32 high TNC (Mean of 120.8 >5mm). Thus far we have discovered a 10-fold excess of variant alleles in the high TNC group, including a novel *TERT* non-coding flanking variant.

PRESENTATION TYPE: Oral Only

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Other Category:

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