Fox-O Hunting:
FOXO3A, a novel longevity gene in humans

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Human longevity is influenced by multiple genetic, epigenetic and environmental factors. The genetic component to this phenotype is estimated at 25-32%. Until recently, only variation in the apolipoprotein E gene (*APOE*) was found to be consistently associated with longevity in diverse populations. Although numerous case-control candidate gene studies have been performed and associations of the longevity phenotype with biologically plausible genes have been described, results from these experiments have proven difficult to validate. In September 2008, Willcox et al. published a study describing the association of genetic variation in the *FOXO3A* gene (an evolutionarily conserved key regulator of the insulin-IGF1 signaling pathway) with human longevity. The important role of this "master regulator" in diverse biological pathways including stress resistance, apoptosis, immunoregulation and inflammation renders *FOXO3A* a very convincing candidate. However, the Willcox' results were tentative as they had not been replicated in an independent population. Therefore, we have investigated 16 known *FOXO3A* single nucleotide polmorphisms (SNPs) in our collection of 1762 German centenarians/nonagenarians and younger controls. Our results provide conclusive evidence that polymorphisms in this gene are indeed associated with the ability to attain exceptional old age. Furthermore, we observed that the *FOXO3A* association was considerably stronger in centenarians than in nonagenarians, highlighting the importance of the oldest old for genetic longevity research. In a subsequent study, Anselmi et al. validated the *FOXO3A* association in a sample of centenarians from Southern Italy. However, so far no functional SNPs in the *FOXO3A* gene have been reported that are known to influence the longevity phenotype. A strategy for the identification of causative variants (rare and/or common) will be presented and discussed. The work has been supported by the DFG Cluster of Excellence "Inflammation at Interfaces".