

Supplemental Note 1: Treatment of human X-palindrome genes with conflicting annotations

There were three instances in which a gene in one arm of a palindrome was designated as protein-coding while the homologous sequence in the other arm was designated a pseudogene: *IKBKG* (protein-coding) and *IKBKGPI* (unprocessed pseudogene); *PNMA6A* (protein-coding) and *PNMA6B* (unprocessed pseudogene), and *PWWP4* (protein-coding) and novel gene ENSG00000224931 (processed pseudogene). We decided whether to include gene copies marked as pseudogenes in downstream analyses, i.e., whether their expression should be averaged with that of the corresponding protein-coding gene, as follows:

- 1) *PNMA6A* encodes a protein of 399 amino acids. *PNMA6A* and *PNMA6B* differ in their coding sequence by only a single missense substitution. The 3' UTR of *PNMA6B* is truncated, but the significance of this is unclear. Given that *PNMA6B* encodes an intact protein-coding sequence, we chose to include *PNMA6B* in downstream analyses.
- 2) *PWWP4* encodes a protein of 2061 amino acids. Novel gene ENSG00000224931 has a nonsense substitution, but contains a downstream start codon that would lead to translation of the terminal 1253 amino acids of *PWWP4*. Given that novel gene ENSG00000224931 encodes a protein encompassing more than half the length of the original protein, we chose to include novel gene ENSG00000224931 in downstream analyses.
- 3) *IKBKG* encodes a protein of 419 amino acids. *IKBKGPI* is a well-characterized pseudogene lacking the promoter and first four exons of *IKBKG* (Aradhya et al. 2001); we therefore chose not to include it in downstream analyses.