



Genome organisation and response to queen mandibular pheromone in the honeybee (*Apis mellifera*).

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The defining characteristic of eusocial insects, including the honeybee (*Apis mellifera*), is the reproductive division of labour, where only one female caste is reproductively active. In the honeybee, larvae destined to become queens are fed a diet of royal jelly which leads to substantial changes in adult morphology and behaviour; queen bees are larger, live a long time and have fully active ovaries. Adult workers do retain some ability to reproduce and mechanisms have evolved to constrain reproduction in workers maintaining the strict reproductive division of labour. In worker honeybees, sterility or reproductive constraint is conditional; in the absence of queen mandibular pheromone (QMP) and brood pheromone, worker bees can activate their ovaries and lay unfertilised eggs. In previous work we have shown that QMP causes worker ovary activity to be constrained via a process involving Notch cell signalling. Here, we investigate the genome-wide response to QMP in honeybee ovaries using RNA-seq. We find that as the ovaries become active, a range of genes organised in clusters in the genome, become co-regulated. These clusters of genes occur more frequently than predicted by chance, and have complex evolutionary history, some evolving in the lineage leading to honeybees, and some ancient complexes found in all Hymenoptera. Further, using ChIP-seq against histone modifications, we have shown that these complexes are marked differently in repressed worker ovaries by common chromatin modifications, *before* the loss of QMP suggesting that these regions of the genome are prefigured to respond to the loss of QMP. The presence of gene complexes and chromatin modifications imply that the genome is poised respond to QMP, and is hard-wired to produce coordinated gene regulation in response to QMP. Such mechanisms imply that QMP responsiveness has shaped the evolution of the honeybee genome. These findings will help us understand the genomic basis of the evolution of eusociality.