Describe some evolutionarily important mutations in developmental genes that have occurred during human divergence from other apes. State how they are thought to have affected our phenotype and use examples of changes in both coding and regulatory regions of genes.

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Humans are just another branch of great apes, we are genetically closest to chimpanzee as somewhere between 5 and 6 million year ago we shared a common ancestor which does not leave a large amount of time for genetic change. This means that the fact that 96 percent of human and chimp being directly comparable does not come as a massive surprise, but there are at least 35 million single base pair changes 5 million larger base pair changes. Some of these changes are in developmental genes that have occurred during human divergence, which is the first phase of becoming different from chimpanzees, the second phase is the changes associated with colonisation out of Africa and the 3rd phase is recent evolution since farming. This essay will focus on this first phase, specifically focussing on big brains, speech, weaker bodies and immune systems.

We have many regulatory regions changes, human evolution has been rapid, bringing us a bigger brain and a weaker body, compared to chimps. The things that seem to be the main difference are not the coding sequences but the changes in the regions responsible for regulation. This could be justified by the areas of genomes that are highly conserved in many species but lost in humans these are called hConDels, importantly the majority of these were also lost in the Neanderthal genome. Only one of the found hConDels was a protein coding region, all the others were shown to be regulatory elements that controlled gene expression of nearby genes which included steroid hormone receptor genes, neural function genes, hindbrain genes, cerebral cortex genes, fibronectin type-3genes etc, which were found using Genemoic Region Enrichment of Annotations Tool (GREAT). These 'H ConDel' include a region near GADD45G, an enhancer region mutated in humans. GADD45G is related to neural stem cell apoptosis. Our mutation allows us to not enhance GADD45G, so we are able to have increased proliferation in our SV2 and create bigger brains compared to mice and chimps. Variants of Abnormal Spindle-like, Microcephaly-associated (ASPM) control neural progenitor proliferation and have arousal with written language and mutations can cause microcephaly, showing the link between brain size and language. Mcph1 transferred into chimps (7 amino acid change that causes it to be more transcriptionally active in humans) saw reduction of myelination and CNS immaturity. Mutation in humans causes microcephaly so maybe it is related to increasing NSC progenitor pool. Going back to hConDels the fact that there was a deletion event of a hConDel around an androgen receptor on the X chromosome means we don't have penis spikes, which are conserved in chimpanzees and mice, I would argue to be a minorly contributing factor to our massively expanding population over chimps. Brain size has also been linked to Human Accelerated Regions (HARs), which are regions where expression of a gene has been enhanced in humans. Analogues for DNAse1 hypersensitive regions suggest that most HARs function as enhancers and HiC and 3CC demonstrated associations between these regions and genes controlling brain size. HAR1A and HAR2B are HARs that are active during brain development. These unique HARS may explain the increase in growth velocity and volume in human embryonic brains vs chimps which, at 32 weeks, develop at a rate of 26cm3/week and 4.1cm3/week respectively. HAR1A has also been associated with auditory hallucinations when mutated, perhaps showing that this is the evolutionary cost of our larger brains. Human Accelerated Regulatory enhancer 5 up-regulates F2d8 associated with WNT/Beta-catenin signalling increasing NSC proliferation and gives us a large cortex. Thrombospondin 4 expression is increased due to HARs allowing us greater synaptic complexity

but also binds to Amyloid Beta plaques in Alzheimer's, signs of development cost. Another type of development cost was suggested by Matsuazwa from Kyoto universities primate research institute, which is that chimpanzees have a near photographic short term memory that was very useful for quick decision making for things like determining ripe vs unripe food or identifying the numbers of friends vs foe, while humans gained linguistics and abstraction. So, they suggest that humans were pushed away by these chips because of their ability to quickly combat or run from whatever they need to. What we also need to remember is that hConDels did not only give us bigger brains but also affected our steroid hormones, reducing our body size and made us generally weaker as well, but we gained our big heads and language. Language has been associated with FOXP2 a transcription factor which is very highly conserved, chimps and gorillas and macaques only have 1 amino acid difference compared to mice, but we have 2 amino acid changes. The evidence that these amino acid changes allowed us to speak are knock out mice that cannot squeak to their mothers. Other animals that have mutated this gene can also "speak" like birds which communicate to each other, which chirp and listen to each other's, similarly bats have mutations. It seems to cause changes in area of the brain (which in birds is called area X) that are linked with linguistics all from this amino acid change, and it seems that the FoxP2 in birds can be associated with vocal plasticity.

Our larger heads are at direct odds with bipedalism, our primary form of movement which is different from chimps and requires small narrower hips and therefore a narrower birth canal. This resulted in requiring our children to be born "premature", with the cognitive ability over the chimps initially. A chimp neonate has a cognitive ability of a 1-year old child we also maintain lactase persistence into adulthood, allowing the ability to digest lactose. Both of which are neotenous traits but gave us an advantage meaning that we can digest milk (e.g. dairy farming) and allowing our huge heads to develop, and our bodies to sort of "catch up", while we are growing outside our mothers.

Copy number variation also differs between us and chimps. For many genes we have more copies, which confers some advantages. Human population diversity means genes are also duplicated in certain groups like SULT1 which is higher numbers in Indian populations and may confer resistance to cancer as mutations increase cancer risk. CCL3 copy number increase causes HIV resistance. This can reflect society and culture as AMY1 amylase gene is highest in people with starchier diets. Alternative splicing differs too, we splice out Exon4 of GST02 allowing us better pathogen response by reduced enzyme activity. Gene duplication has also occurred in our eyes with opsin gene duplication.

Interestingly there are more than 200 alleles of Major Histocompatibility Complex genes in humans that occurred before divergence from chimps, these cells allow us to recognise cells that are not ours. Our T cells also differ chimpanzee T-cells, which have sialic acid conjugates that dampen immune response to prevent an overreaction of the immune response. The mutation in the caspase 12 gene also dampened the immune response, however it has come with several drawbacks including autoimmune diseases, multiple sclerosis, rheumatoid arthritis etc. This immune system changes likely came about with us encountering new pathogens, making it useful at the time, but potentially overcharged now.

In conclusion although the changes in the genome are small in terms of percentage they have dramatic affects, as they are more often than not in regulatory regions that can have great affect. These great affects always seem to come with some sort of trade off and one of the key things I took away from all of this was from a talk by Carroll where he raised the point that being the fittest is always conditional and precarious, acting only in the present, who knows what adaptations will come.