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Genetic mutation linked to walking on all fours: discovery could help answer basic questions of upright walking

Barcelona, Spain: What are the genes implicated in upright walking of humans? The discovery of four families in which some members only walk on all fours (quadrupedality) may help us understand how humans, unlike other primates, are able to walk for long periods on only two legs, a scientist will tell the annual conference of the European Society of Human Genetics today (Monday 2 June).

The quadrupedal families in Turkey previously attracted attention in 2005, when they were discovered. Now the Turkish team reports that they have found the first gene implicated in quadrupedal locomotion in these families.

Professor Tayfun Ozcelik, of Bilkent University, Ankara, Turkey, and colleagues, studied four unrelated families where some members were affected by the rare quadrupedic condition, Unertan syndrome, which is also associated with imperfect articulation of speech, mental retardation, and defects in the cerebellum, a part of the brain involved in motor control. They found that the affected individuals in two families had mutations in the gene responsible for the expression of very low density lipoprotein receptor (VLDLR), a protein which is known to be critical to the proper functioning of the cerebellum during development.

Although the families lived in isolated villages 200-300 km apart and reported no ancestral relationships, the scientists expected to find a single genetic mutation implicated in the condition. They were surprised to find that this was not the case.

“We carried out genome-wide screening on these families”, said Professor Ozcelik, “and found regions of DNA that were shared by all those family members who walk on all fours. However, we were surprised to find that genes on three different chromosomes are responsible for the condition in four different families.

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"In families A and D there were mutations in VLDLR on chromosome 9, and in family B the phenotype maps to chromosome 17 to a region that contains at least 157 genes, and we are still looking for the precise mutation. Neither region appears to be implicated for family C."

In all cases, the affected individuals were the offspring of consanguineous marriages, which suggests that if they had married outside the family they would not have had the condition. All of them had significant developmental delay in infancy. "Whereas normal infants make the transition to walking on two legs in a relatively short period", said Professor Ozcelik, "these individuals continued to move on their palms and feet and never walked upright. Although they can stand from a sitting position and maintain this upright position with flexed hips and knees, they virtually never initiate bipedal walking on their own."

It has been suggested in the past that lack of access to medical care exacerbated the effects of an under-developed cerebellum, and that this led to quadrupedality. "Although it may be true that family B lacked proper medical care, families A and D had consistent access to good medical attention, and both families sought a correction of quadrupedality in their affected children", said Professor Ozcelik. "Indeed, an unaffected member of family A is a physician, who has been actively involved in the medical interventions. In addition, the parents in family A also discouraged their affected children from walking on all fours, to no avail. We think that social factors are unlikely to be involved in the development of quadrupedal locomotion."

Mutations causing VLDLR deficiency are also found in Hutterites, a group of Anabaptists who live in colonies of North America. There, however, most of the affected individuals cannot walk at all. The neurological characteristics of the affected members of the Turkish families and the Hutterites seem similar, with the most striking difference being that the Turkish individuals are able to walk on all fours, said the scientists. They hypothesize that the Hutterites may be more profoundly affected due to the deficiency in VLDLR and a neighbouring gene, and therefore lack the motor skills even for quadrupedal locomotion.

Along with brain enlargement, speech, and the ability to make tools, upright walking has long been regarded as one of the key traits that have led to modern humans. Professor Ozcelik's team have opened a window on how mutations in VLDLR affect brain development and influence gait in humans. */more*

"It will be interesting to see if the VLDLR gene is involved in other types of cerebellar ataxias. In addition, we hope to identify the defective genes associated with quadrupedal locomotion in families B and C", he says.

Through grants from the Scientific and Technological Research Council of Turkey in Ankara, and the International Centre for Genetic Engineering and Biotechnology in Trieste, Italy, Professor Ozcelik and his colleagues are currently screening the remaining families for mutations.
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