Newly-discovered mechanism can explain the Beckwith-Wiedemann syndrome

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Researchers from Uppsala University have discovered a mechanism that silences several genes in a chromosome domain. The findings, published in today's on-line issue of *Molecular Cell*, have implications in understanding the human disorder Beckwith-Wiedemann syndrome.

In mammals the cells contain two copies of each chromosome, one inherited from the mother and one from the father. The genes on the chromosomes can either be active or inactive. If a gene is active on the maternal chromosome, the corresponding gene is usually active also on paternal chromosome.

However, in some domains of the chromosome the activity is shut down on one of the chromosomes but not on the other. The genes in these domains cannot be activated the normal way but are completely silenced. The present study shows for the first time how this silencing of several genes on a chromosome is accomplished.

The research group, led by Chandrasekhar Kanduri, has studied a domain with several silenced genes on chromosome 7 in the mouse. The corresponding domain with silenced genes is located on the human chromosome 11. When part of this domain is transcribed a long RNA molecule, Kcnq1ot1-RNA, is formed. This RNA does not give rise to any protein, instead it mediates the silencing of eight to ten genes in a much larger area on the chromosome. Based on their findings the researchers have suggested a model for how this is accomplished. The Kcnq1ot1-RNA binds to the DNA in the domain and recruits specific

enzymes that chemically modify DNA-binding proteins. This modification makes the DNA inaccessible for transcription and thereby the genes cannot be activated. In addition, the Kcnq1ot1-RNA targets the silenced domain to a specific area in the cell nucleus. There it is protected during cell division and the genes will stay silenced also in the daughter cells.

– We show for the first time how a long RNA molecule can establish and maintain silencing of multiple genes in a large domain on the chromosome, says Chandrasekhar Kanduri. The popular belief is that it is only a gene located in the same area as where the long RNA molecule is transcribed from that can be silenced.

This mechanism is important for understanding the genetic disorder Beckwith-Wiedemann Syndrome. In this condition silencing of the chromosome 11 domain does not function properly and both copies of the genes in the domain become inactive, instead of just one. Less protein is produced from the genes, leading to the excess growth characteristics associated with the syndrome: enlargement of organs in the foetus and an increased risk for tumours in the affected organs.

Source: Uppsala University