

Title: Disorders of *GNAS* Inactivation *GeneReview* – Additional Transcripts of the *GNAS* Complex Locus

Authors: Haldeman-Englert CR, Hurst ACE, Levine MA

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Additional Transcripts of the *GNAS* Complex Locus

The following alternative *GNAS* first exons and the NESP antisense exons depicted in the Figure 1 schematic are associated with promoters that contain differentially methylated regions (DMRs), each of which is methylated on the nonexpressed allele.

- Upstream of *GNAS* exon 1 each of three alternative first exons can splice onto *GNAS* exons 2–13 to create novel coding and noncoding transcripts. When the first exon is:
 - NESP: this transcript is expressed only from the maternal allele utilizing an alternative promoter. The NESP coding region does not overlap that of *GNAS*; it encodes the neuroendocrine secretory protein 55 (NESP55), which shares no protein homology with $G\alpha$.
 - XL (extra large): the coding transcript (also known as GNASXL) is expressed only from the paternal allele and has overlapping open reading frames that encode the isoforms XLas and ALEX, two proteins that are interacting cofactors that are principally expressed in neuroendocrine cells. XLas can function as a $G\alpha$ -like protein.
 - A/B: the noncoding transcript is paternally expressed.
- *NESP* AS (antisense) transcript (officially known as GNAS-AS1) comprises five exons that flank NESP. It is expressed only from the paternal *GNAS* allele, is not translated, and has no known function.