The Wnt/beta-catenin pathway regulates the expression of early embryonic stem cell genes in human parathyroid tumors.

Introduction
Evidence suggested an embryonic epigenetic signature in parathyroid tumors, with deregulated miRNAs and gene methylation. In embryonic stem cells, the Wnt/beta-catenin signaling regulates the expression of the core stemness genes, namely NANOG, OCT4 and SOX2. Though constitutive nuclear accumulation of beta-catenin has not been detected, the Wnt/beta-catenin pathway might be deregulated in parathyroid tumors, as Wnt signaling inhibitors have been found reduced.

Aim of the study
To investigate the embryonic signaling Wnt/beta-catenin – core stem cells genes in adult human tumor parathyroids.

Results
Nuclear active beta-catenin levels in parathyroid adenomas:
We investigated unphosphorylated active beta-catenin distribution by western blot in 25 typical parathyroid adenomas (Pads) ([Panel A]): beta-catenin accumulation in the nuclear protein fractions varied from the levels detected in Caco-2 cells with constitutively active Wnt signaling (9 Pads) to the levels measured in HEK293 cells with intact Wnt signaling (6 Pads) ([Panel B]) and positively correlated with AXIN2 mRNA levels (r=0.645, P=0.026) ([Panel C]).

Effects of Lithium Chloride (LiCl) treatment on stem cell markers in parathyroid adenomas (Pads)-derived cells: The Wnt/beta-catenin pathway is intimately connected to the embryonic pluripotent core circuitry. Treatment of Pads-derived cells (n=5) with 10-20 mM lithium chloride (LiCl) for 8 hours induced nuclear accumulation of beta-catenin ([Panel A]) and concomitant increases in mRNA levels of POUSF1 ([Panel B and C]) and SOX2 genes, as reported in embryonic stem cells. Nonetheless, at variance with embryonic stem cells, beta-catenin accumulation induced a decrease in NANOG mRNA levels ([Panel D]). * P<0.05

Conclusions
We firstly identified an embryonic pattern of gene expression in parathyroid tumors, where beta-catenin signaling might be involved in regulating the expression of the core stem genes. SOX2, in particular, was associated with a more severe presentation of primary hyperparathyroidism.