Abstract Title: Human Sex-Reversal as a paradigm to understand cell fate choice and gene regulatory mechanisms

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Abstract: Mammalian Sex-Determination (SD) is a tightly controlled, highly complex process where the bipotential gonad forms either a testis or an ovary. The fetal gonad contains a single multipotent progenitor cell population that generates the first somatic cells lineages of either the testis (Sertoli cells) or ovary (granulosa cells). SD serves as a unique paradigm to study gene regulatory elements (GREs) and gene regulatory networks (GRNs) involved in cell fate choice and the maintenance of cellular identity. We have identified many factors involved in human SD by the genomic analysis of >1000 individuals who are sex-reversed (XY gonadal dysgenesis or XX individual with testis). These mainly consist of transcription factors or cofactors. Using this data, we established that the sexual identity of the gonad (testis versus ovary) is specified by mutually antagonistic GRNs and these GRNs are required to maintain the identity of the gonad. At a mechanistic level it is unclear how these GRNs operate in human embryogenesis to specify and to maintain the gonad identity.

Despite extensive genomic analysis, variants in the coding sequences of SD genes explain only about 50% of sex-reversal cases. The remaining cases of sex-reversal could be due to variants in GREs. This would be unusual, since gene regulation during embryonic development is dominated by multiple enhancers with overlapping spatiotemporal activities. Their redundancy serves not only to improve the robustness of gene expression by maintaining expression levels above critical thresholds but also prevents the deleterious effects of mutations in individual enhancer elements. Consistent with these observations, human developmental disorders that can be attributed to disrupted enhancer elements are rare. However, our emerging evidence indicates that the pathologies of sex-reversal are an exception and provide a unique model to understand GREs and GRNs in human development.

I will present data showing sex-reversal involving GREs at three loci (SRY - Y chromosome, SOX3 - X chromosome and SOX9 - Chr 17). Remarkably these sex-reversing variants include point mutations. As we expand this analysis genome-wide to accurately define both GRE/GRNs regulating SD, we believe this will provide an informative general model of the regulation of gene expression and cell fate decisions during human development.

Area of expertise: genetics, sex-determination, stem cell biology