**Please nominate 1 category that best fits your submitted abstract:**

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| [x]  Paediatric and/or congenital diseases[ ]  Maternal and/or prenatal health[ ]  Cardiometabolic diseases[ ]  Chronic diseases[ ]  Healthy aging[ ]  Cancer[ ]  Neurodegenerative diseases[ ]  Public health[ ]  Other |

**Please nominate 2-5 subject areas relevant to your submitted abstract:**

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| [ ]  Aged care [ ]  Allied health [ ]  Animal models [ ]  Biochemistry [ ]  Bioinformatics [ ]  Biomarker research [ ]  Biotechnology[ ]  Cardiovascular research[ ]  Cancer [ ]  Cell biology [ ]  Clinical research[ ]  Commercialisation [ ]  Computational biology and/or statistics [ ]  Consumer advocacy[ ]  Dentistry [ ]  Developmental biology[ ]  Drug discovery[ ]  Drug target identification and validation[ ]  Education and training[ ]  Endocrinology[ ]  Environment[ ]  Epidemiology [ ]  Genetic counselling[ ]  Genetics, epigenetic or small RNAs[ ]  Healthcare  | [ ]  Health economics [ ]  Health policy[ ]  Health promotion[ ]  Imaging and computing[ ]  Immunology[ ]  Indigenous health[ ]  Industry [ ]  Invisible illnesses[ ]  Medicinal chemistry[ ]  Microbiology[x]  Molecular biology[ ]  Neuroscience [ ]  Nutrition[ ]  Pain management[ ]  Pathology[ ]  Personalised Medicine[x]  Rare diseases[ ]  Physiology[ ]  Psychology[ ]  Public health[x]  Reproductive biology[ ]  Technology[ ]  Tele-health[ ]  Virology[ ]  Other (please specify):  |

**Variants in *SART3* are a novel cause of a syndromic Difference of Sex Development**

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**Background and Aims:** Differences of sex development (DSD) represent a major paediatric concern and can be associated with >200 congenital conditions. Clinical management of these conditions is challenging but can be guided by a genetic diagnosis to improve patient health and wellbeing. Our group employs genomic sequencing of DNA from undiagnosed patients with DSD to find novel genetic causes.

**Methods:** DNA from patients underwent exome sequencing and variant analysis. For functional analysis of variants we used the following methods: RNAi mediated knock-down in *Drosophila*; transfection assays in Hek293t cells followed by qRT-PCR, western blots and immunofluorescence; transcriptomic and proteomic profiling of human induced pluripotent stem cells (iPSCs), and differentiation of iPSCs into neuronal and gonadal cells.

**Results:** We recruited nine children from six families who have an overlapping undiagnosed syndrome including intellectual disability, global developmental delay and a subset of brain anomalies. 46,XY children have gonadal dysgenesis (female or undervirilised male sex characteristics) whereas 46,XX children appear to have functional ovaries. Exome sequencing identified recessive variants in the *Squamous cell carcinoma antigen recognized by T cells 3* (*SART3*) gene in all nine children. SART3 is an RNA-binding protein with numerous biological functions including recycling small nuclear RNAs to the spliceosome. Knockdown of the *Drosophila* orthologue, *rnp4f*, revealed a conserved role in embryonic neuronal development, and testis but not ovarian function, consistent with patient findings. iPSCs carrying patient *SART3* variants showed significant disruption to multiple signalling pathways and upregulation of spliceosome components. These showed aberrant differentiation into neuronal cells and into gonadal organoids (using our recently developed protocol) with disruption to key testis signalling components.

**Conclusions and Significance/Impact:** Collectively, these findings suggest that bi-allelic variants in *SART3* underlie a new syndromic DSD. These findings will enable additional diagnoses and improve outcomes for individuals with syndromic differences of sex development.

**Lay Title:** Genetic changes in the *SART3* gene cause a rare syndrome with brain defects and sex reversal.

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**Lay Summary:** We have identified a new congenital disorder in six families characterised by 46, XY gonadal dysgenesis (sex reversal), and neurodevelopmental anomalies including intellectual disability. We found that each affected child has two genetic changes in the *SART3* gene. We have shown that *SART3* is important in neuronal and testicular development, from fruit flies to humans. Additionally, stem cells carrying patient SART3 mutations have disrupted development into brain and gonadal cells in a dish. Our work will lead to future diagnoses for additional families. It provides a better understanding of SART3 and may open up therapeutic avenues in the future.