Title:

Whole exome sequencing can identify defects not detected by candidate gene sequencing in patients with short stature and features of growth hormone insensitivity (GHI)

Abstract: (Your abstract must use Normal style and must fit into the box. Do not enter author details)

Background GH insensitivity (GHI) encompasses growth failure, low serum IGF-1 and normal/elevated serum growth hormone (GH) (basal level >5µg/L and/or peak on provocation testing >10µg/L). In a significant number of children the molecular cause is unknown.

Objective To investigate the genetic etiology of GHI in a cohort of children by candidate gene (CGS) and whole exome (WES) sequencing.

Methods 109 patients (61 M, median age 6.5 yr [range 0.4-17.0]) with a phenotype consistent with GHI (mean height SDS -4.8; mean IGF-1 SDS -2.7) were accepted for genetic investigation since 2008. CGS was undertaken for *GH-IGF1* axis [*GHR, STAT5B, IGFALS, IGF1*] and 3M [*CUL7, CCDC8, OBSL1*] genes and WES was performed in unsolved cases (to date, 53 patients). A bioinformatic pipeline was developed to interrogate the WES data and identify potential causative genetic variants.

Results CGS identified homozygous mutations in the following genes in 36 patients: *GHR* [26], *IGFALS* [3], *OBSL1* [6] and *CUL7* [1]. WES identified changes in 13 patients: compound heterozygous *IGFALS* [1], homozygous *GHR* [5], heterozygous *PTPN11* [2], homozygous *CCDC8* [3], homozygous *CUL7* [1], and heterozygous *SOS1* [1]. 14 of these genetic variants are novel. In 2 subjects who were small for gestational age (birth weight SDS -2.3 and -1.8) hypomethylation in the imprinting control region 11p15 or mUPD7 was demonstrated confirming Silver Russell Syndrome (SRS). Mining the WES data of patients without a genetic diagnosis identified 24 candidate genes having deleterious variants in more than one GHI patient.

Conclusions A genetic diagnosis was obtained in 51 (47%) patients. These included 14 novel variants. Importantly, WES identified 13 mutations in known genes, which had not been detected on CGS. Diagnoses with phenotypes overlapping with GHI included SRS, 3M and Noonan syndrome. Variants in novel genes with potential impact on growth have been identified and are under further investigation.