Patients with GH Insensitivity and IGF-1 Resistance Harbour Copy Number Variants Causing a Silver-Russell-Like Phenotype

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Introduction: Our Centre is an international referral centre for genetic analysis of children with short stature (SS) and features of GH or IGF-1 insensitivity. Following candidate gene and whole exome sequencing, the genetic diagnosis for ~50% of patients remained elusive. Copy number variation (CNV, **Figure 1**) is associated with idiopathic SS, small for gestational age (SGA) and Silver-Russell syndrome (SRS) phenotypes but not previously with GH or IGF-1 insensitivity. SRS is heterogeneous with 40% patients having unknown molecular aetiology. Classically SRS is due to 11p15 LOM or UPD(7)mat but SRS features have been reported with CNVs. We hypothesised that CNVs contribute to the phenotype in our undiagnosed cohort.

Methods: Comparative Genomic Hybridisation (CGH) was performed with oligonucleotide array using ~60,000 probes in 50 patients (31M, mean age 6.7 years, range 1.1-16.5 years, mean height SDS -3.93, range -1.58 to -7.44 SDS). Population polymorphisms were filtered out and each CNV was assessed for pathogenicity in the context of each patient's presenting phenotype.

Results: Significant CNVs were identified in 8/50 (16%) patients (7M, 7 GHI, 1 IGF-1 insensitivity, **Table 1**). 6/8 had CNVs previously reported in SRS phenotypes. Many of the patients had features of SRS but the majority did not fulfil the Netchine-Harbison Clinical Scoring System (NH-CSS) criteria for SRS diagnosis (**Table 2**). This requires fulfilment of 4/6 criteria or 3/6 in addition to a genetic diagnosis associated with SRS.

Figure 1. Schematic of Copy Number Variation (CNV)

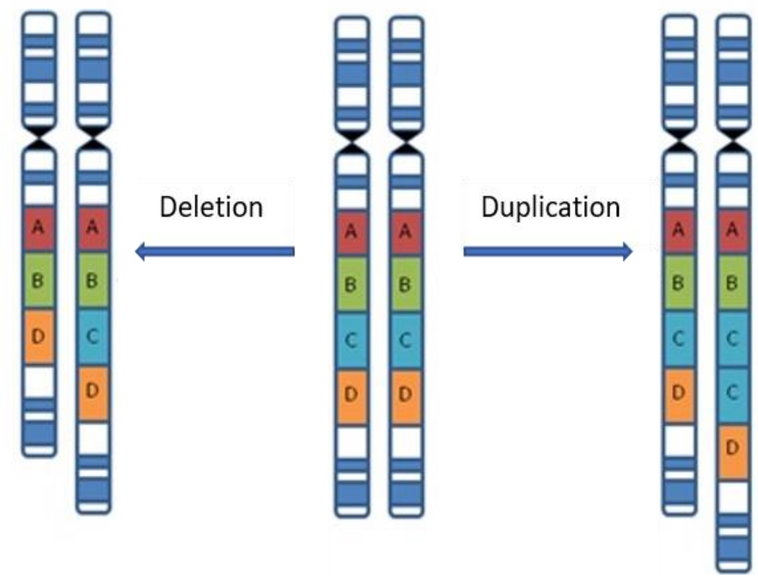

Table 2. Netchine-Harbison Clinical Scoring System (NH-CSS)

1. **SGA (Birth weight and/or birth length)**
2. **Postnatal growth failure**
3. **Relative macrocephaly at birth**
4. **Protruding forehead**
5. **Body asymmetry**
6. **Feeding difficulties and/or BMI <2 SDS**

Table 1. CNV and phenotype details of the patients

	CNV	Genetic change previously associated with SRS	Number NH-CSS criteria met	Additional details
1	1q21 deletion	Yes	2	Small triangular face with arched palate. Hypoglycaemic episodes. SRS testing negative*
2	1q21 deletion	Yes	1	Sibling of patient 1
3	12q14 deletion	Yes	2	Triangular face, pointed chin, long lashes, high pitched voice. IGF-1 insensitivity.
4	Multiple 7q deletions	Yes (7q21 deletion)	2	Low set ears, triangular face, delayed motor development. SRS testing negative*
5	1q21 deletion	Yes	3	Bilateral clinodactly
6	7q21 and Xp22 duplications	Yes (Xp22 duplication)	2	No dysmorphic features, normal intelligence
7	15q11 deletion	No	3	Triangular face, midface hypoplasia, hypoglycaemic episodes. SRS testing negative*
8	5q12 deletion	No	1	Delayed puberty, learning difficulties

*** SRS testing for 11p15 LOM +/- UPD(7)mat negative**

Conclusion: Our short stature cohort was enriched for low frequency CNVs. Interestingly, 7/8 patients with CNV defects had features of SRS. 15q11 deletions have not previously been associated with SRS. Consistent with previous reports, the SRS phenotype in our patients with CNVs appears milder than in classic cases due to 11p15 LOM or upd(7)mat and only 2/8 were born SGA. Our study contributes to the emerging SRS-like phenotype and emphasises the importance of CNV testing in short stature patients, especially those with SRS features.

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