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Freeth, M. orcid.org/0000-0003-0534-9095, Al-Jawahiri, R. orcid.org/0000-0002-5689-3368, Smith, H. et al. (1 more author) (2021) Speech, language and communication phenotyping in rare genetic syndromes: Commentary on Speech and language deficits are central to SETBP1 haploinsufficiency disorder. European Journal of Human Genetics, 29 (8). pp. 1166-1167. ISSN 1018-4813

https://doi.org/10.1038/s41431-021-00942-6

EJHG commentary

Title: Speech, language and communication phenotyping in rare genetic syndromes: Commentary on Speech and language deficits are central to SETBP1 haploinsufficiency disorder.

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Conflict of interest statement: All authors declare no conflicts of interest.

Morgan et al. (this issue) present an important analysis of the speech and language deficit associated with SETBP1 haploinsufficiency disorder. Although it is well established that many genetic syndromes are associated with speech, language and communication (SLC) problems, there are still very many for which there is currently no information available (Stojanovik. 2021). Morgan et al.'s comprehensive characterisation of the difficulties experienced in a relatively large sample (n=31), given the rarity of the condition, will be valuable in shaping clinical, educational and parental understanding of the nature of the difficulties likely to be experienced by others with this genetic diagnosis. The genotype first approach taken by the researchers is important in specifying the impact of genomic disorders and for establishing the phenotypic range associated with genotypes (Mefford, 2009; Stessman et al. 2014) as well as more closely specifying genotype-phenotype profiles (Chawner et al., 2021). In the current study, recruitment of a cohort of individuals with SETBP1 haploinsufficiency enables Morgan et al. to clearly establish the link with childhood

apraxia of speech (CAS) which was present in 80% of the children who were verbal (65% of the cohort). Establishment of this link is important, and one which previous single case studies or case series reports were only able to speculate towards. Of the 35% of the cohort who were minimally verbal there was, nevertheless, strong intent to communicate using various approaches including sign, language, and digital devices. The authors argue that this indicates clear opportunities to develop communication further in children with SETBP1 haploinsufficiency who are minimally verbal, which is important information for clinicians, educators, and parents to have.

In the current study, Morgan et al. chose to use a range of age and ability appropriate standardised measures to assess their sample thus enabling comparison of the present cohort to other genetic syndrome cohorts. In particular, the Vineland Adaptive Behaviour Scales is widely used to characterise the difficulties experienced by other genetic syndrome cohorts (Di Nuovo & Buono, 2011). This analysis of skills and abilities other than those relating to speech and language, such as motor abilities and social skills, provides important contextual information. Such information facilitates the interpretation of results and consideration of other explanatory factors for speech and language difficulties that could otherwise have been missed. Another standardised measure used in the current study is the Children's Communication Checklist 2 (CCC-2) (Bishop, 2003). This parent-report questionnaire has widely been demonstrated to be a useful tool in differentiating between particular language profiles (Geurts & Embrechts, 2008). It has also been used to identify the profiles of various different genetic syndrome groups such as Down's syndrome (Laws & Bishop, 2004; Smith et al. 2007), Noonan syndrome (NS) and neurofibromatosis type 1 (NF1) (Pierpont et al. 2018), Williams syndrome (Laws & Bishop, 2004; Hoffmann et al. 2013) and Sotos syndrome (Lane et al. 2019) providing useful outlines of the profile of SLC difficulties in these populations.

The conclusions of previous studies on SETBP1 haploinsufficiency disorder have been tempered by reliance on retrospective examination of medical records, whereas the

collection of primary data by Morgan et al. enabled the standardised assessment of current skills. It was interesting to see that SLC difficulties were commonly observed with protracted developmental trajectories being present across the cohort. This suggests that SLC support for individuals with this diagnosis is important to consider, particularly given that difficulties seem to become more marked as the middle school years are reached. Overall, identifying specific SLC features in SETBP1 haploinsufficiency and rare genetic syndromes, more generally, leads to differentiation between similar syndromes and more tailored speech and other therapies.

Considering the range and profiles of speech, language, and communication observed in the current cohort, it would have been useful to see information from other measures to supplement the information presented to delve a little deeper into the profile of difficulties experienced. For example, a recent study by Brignell et al. (2021) considered a broad range of SLC assessments suitable for those with minimal language demonstrating the utility of direct assessment of early years development, such as the Preschool Language Scales (5th ed) (PLS-5) (Zimmerman et al. 2011) and the Peabody Picture Vocabulary Test (4th ed) (PPVT-4) (Dunn & Dunn, 2007). Assessment using the PLS-5 enabled comparison of receptive and expressive language via age-equivalence data thus demonstrating relative strengths and difficulties in the cohort and characterisation accessible to non-specialists. Further, Brignell et al. (2021) also present data from parent-reports of early SLC development, such as the Communication and Symbolic Behavior Scales (Wetherby & Prizant, 2002) which enabled identification of relative areas of strength within the cohort. Another useful metric of SLC is the presentation of domain-specific percentile scores, thus indicating absolute level of ability when considering the general population in a particular age bracket. For example, Lozano et al. (2015) provide such metrics for an individual with *FOXP1* variant. Given that readers of academic papers on particular syndromes are often reading them due to their syndrome-specific interest rather than being a topic specialist, presentation of information in an accessible manner is particularly valuable and will likely

have more impact on understanding for those having day-to-day interactions with those with the syndrome in question.

Overall, Morgan et al.'s cohort study provides valuable information for clinicians, educators, and parents when thinking about how best to support children's speech, language, and communication development and will likely encourage more targeted research into SETBP1 haploinsufficiency. Rare genetic syndromes, although individually rare, are collectively common. The growing field of rare genetic syndromes' research and increase in deep phenotyping studies will lead to better understanding of SLC, motor, developmental, and other pertinent features in rare genetic syndromes. In-depth understanding of the profile of communication and other cognitive and behavioural features of rare genetic syndromes is useful for aiding the development of diagnostic tools, SLC support, and other tailored interventions. Morgan et al.'s paper provides an excellent example of the value that can be gained by genetic syndrome phenotyping research.

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