A structured assessment of motor function, behavior, and communication in patients with Wolf–Hirschhorn syndrome

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1. Introduction

Wolf–Hirschhorn syndrome (WHS; OMIM #194190, ORPHA #280) is a congenital malformation disorder caused by variably sized deletions of chromosomal region 4p16.3. The deletion was first described in 1961 (Cooper and Hirschhorn, 1961) and in 1965 (Hirschhorn et al., 1965) as 4p-syndrome. Later, a critical WHS region with specific key genes was described, including WHSC1, WHSC2, SLBP, LETM1, CTBP1, CPLX1, PIGG, and FGFRL1 (Battaglia et al., 2015). The prevalence of WHS is estimated to be 1:50,000 and more frequent in females than in males (2:1) (Battaglia, ).

Studies of genotype–phenotype correlation have led to the recognition of a much broader clinical spectrum than previously considered possible, including possible identification of key genes responsible for specific phenotypic features of WHS (Battaglia et al., 2015). It was an earlier common understanding of the syndrome that all individuals with WHS have severe or profound intellectual disability and minimal communication skills; however, a broader range of abilities has recently been described (Battaglia et al., 2015).

Clinical characteristics of WHS are pre- and postnatal growth delay, craniofacial dysgenesis, mild-to-profound developmental delay, limited expressive speech and language, and epilepsy (Battaglia et al., 2008). The severity of these characteristics is highly variable. Additional problems, including midline defects, occur at lower frequency in a subset of patients (Zollino et al., 2000). Typical craniofacial features include microcephaly, prominent glabella, widely spaced and prominent eyes, a “Greek warrior helmet appearance” of the nose, a broad nasal tip, a short philtrum, and downturned corners of the mouth (Battaglia et al., 2008).

Although WHS was first described half a century ago, data on behavioral features such as autism spectrum disorders (ASD) and adapted behaviors are scarce. To our knowledge, only limited data based on formal evaluations regarding these topics have been

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published (Fisch et al., 2008, 2010). Earlier studies described persons with WHS as being severely impaired physically, clinically, cognitively, and having little or no expressive speech or language (Battaglia et al., 2015; Fisch et al., 2010). Not until 2008 (Fisch et al., 2008) and 2010 (Fisch et al., 2010) were groups of higher functioning children with WHS described with a cognitive–behavioral profile. In these studies, the authors found that cognitive abilities and adapted behavior skills were lower in children with WHS than in children with other deletions (11q25, 2q37, and 8p21–23). Children with WHS were also found to have a relative strength in socialization skills (Fisch et al., 2008, 2010). One of these studies also reported a lower incidence of ASD in children with WHS than rates of autism in children with other deletions (Rutter et al., 2003). Experience with WHS at Frambu indicates that the range of abilities in persons with WHS is wider than the published research shows. Over the past years, we have been in contact with several persons with WHS who have better cognitive, motor, and communication skills than described in the literature.

Therefore, we conducted a multidisciplinary, formal evaluation of Norwegian patients with WHS. The aim of this study was to increase the knowledge about the syndrome, especially aspects about motor function, ASD, and adapted behavior, but also regarding clinical symptoms in general; however, it was not our intention to conduct a phenotype–genotype study.

2. Patient data

Two males and eight females between one and 48 years of age with a genetically confirmed diagnosis of WHS and their parents participated in this study. Deletion sizes were known for seven of the ten patients and varied between 55 Kb and 20 Mb. The chromosome coordinates were known for six of the patients; none of those six patients had the same break points in their deletion (Fig. 1).

3. Methods

This study was designed as a cross-sectional study. It follows the same study design and methods as our previously published study of patients with Kleefstra syndrome (Schmidt et al., 2015).

3.1. Recruitment

We aimed to recruit as many patients as possible from the entire country. The only inclusion criterion was a genetically confirmed diagnosis of WHS; exclusion criteria were not applied. As there is no central registry of persons with a rare disorder in Norway, potential patients were recruited through different channels. Frambu Resource Centre for Rare Disorders (Frambu) has its own registry, which is based on informed consent. Frambu is one of nine state-financed centers of expertise administered by the Norwegian National Advisory Unit on Rare Disorders. We were therefore able to send invitations to already registered families with a child or an adult with a diagnosis of WHS. Information about the study was also published on Frambu’s website (www.frambu.no) and Frambu’s Facebook site. In addition, four Departments of Medical Genetics in Norway were asked to send invitations to their registered WHS patients.

In total, eleven out of 13 families registered at Frambu with a child or an adult with the tentative diagnosis of WHS consented to participate in our study. However, the review of the genetic work-up showed that one adult did not have a genetically confirmed diagnosis of WHS. This patient was excluded; therefore, ten patients remained in the study.

3.2. Background data

A copy of the genetic work-up to confirm the diagnosis of WHS was obtained. The parents completed a questionnaire with 71 questions, including information on the demography, pregnancy, and delivery, the child’s first years of life, past and present medical situation, perception problems (vision, hearing, and pain threshold), developmental milestones, nutrition, and growth. The questionnaire was developed for the purpose of this study based on a thorough literature review on WHS.

3.3. Assessment of motor function and developmental status

All patients were subjected to a structured observation by a pediatrician (D.K.B) and a physiotherapist (B.S.H.) with emphasis on motor function and developmental status. Most of the observations occurred in the Frambu gym with access to different activities and equipment chosen specifically for this observation. Two of the observations were done in the patients’ home due to their medical situations, which avoided traveling over a long distance.

Furthermore, developmental milestone data were obtained retrospectively from the parents via the completion of the questionnaire described in the background data section.

3.4. Behavioral assessment

The Vineland Adaptive Behavior Scales II (VABS II) survey (Haukeland, 2011; Sparrow et al., 2005) is a semi-structured interview of the parents or caregivers and assesses the everyday behavioral functioning of children and adults from birth throughout life. In the present study, the Norwegian version of the scales based on Scandinavian normative data was used. We used the raw scores on the subdomains from the Scandinavian version to calculate the age-equivalent from the English version (Sparrow et al., 2005). We also used the standard scores of the adapted behavior composite score from the Scandinavian version to compare with levels of intellectual functioning from the English version (Sparrow et al., 2005).

The Social Communication Questionnaire (SCQ) is a standardized screening tool for the evaluation of communication forms and social function in children or adults to exclude an autism spectrum disorder (ASD) (Rutter et al., 2003). The questionnaire can be used from the age of four years onward, with a mental age of at least two years. Patients above the chronological age of four years were estimated to have a mental age of at least two years. Using age-

Fig. 1. Chromosome coordinates list for patients with WHS created in the Genome Browser website (http://genome.ucsc.edu).
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