SSBP Syndrome Sheets

Wolf-Hirschhorn Syndrome

Wolf-Hirschhorn syndrome (WHS) is a multiple congenital malformation syndrome first described in 1965 independently by Cooper and Hirschhorn and by Wolf, which presents with a broad range of clinical manifestations. It is caused by a partial loss of genetic material at the telomere of the short arm of chromosome 4 and, specifically, from a deletion of the terminal 2 Mb of the 4p16.3 region (**Figure 1**) although the hemizygosity can be variable in size and ethiology. The high variability present at both clinical and molecular level can cause difficulties in diagnosis of WHS.

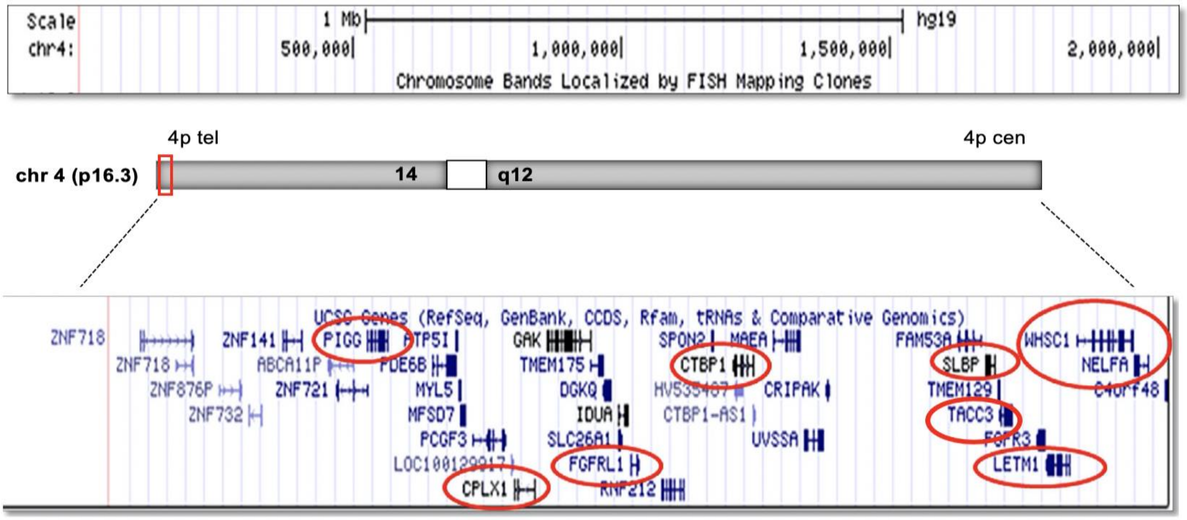

Figure 1. Diagram showing the distal region of chromosome 4p, where candidate genes for seizures and craniofacial features map (LEMT1 and WHSC1; Zollino et al., 2003; Rodrıguez et al., 2005). [Diagram was modified from Battaglia et al., 2015]

Genetics and Molecular Biology

The genotype often arises from an unbalanced translocation event (t4;8) (p16;23). Most often, however, the genotype is produced by a *de no*vo mutation. The mechanism(s) which produce the deletion are not known, but recent studies suggest that genes within sub-telomeric regions are likely to be involved in deleterious chromosomal rearrangements. Deletion size in WHS varies; it is most often telomeric, but it can also be interstitial. It is usually detected by conventional karyotyping or fluorescence *in situ* hybridization (FISH) (50-60%). *de novo* microdeletions account for approximately 25–30% and, unbalanced translocations (*de novo* or inherited) and complex genomic rearrangements, as ring 4 chromosome, are observed in approximately 15% if the cases (Battaglia et al., 2001; 2009; Lurie et al., 1980). However, it has been suggested that the prevalence of unbalanced translocations leading to WHS is underestimated as they could be missed by karyotyping and FISH (South et al., 2008). Submicroscopic deletions are also observed in WHS and often identified by multiplex ligation-dependant probe amplification (MLPA) and/or by CGH arrays (Ho et al., 2016; Wright et al., 1997). The size of the deletion has been associated with the severity in the phenotype and results, in part, to the wide variability of the clinical presentation. For a complete WHS diagnosis in the proband, chromosomal analysis is recommended also for the parents, in order to establish the risk of recurrence of other family members.

Twelve genes identified by the human genome project between 1.2 and 2.0Mb from the telomere of 4p, five (WHSC1, WHSC2, TACC3, SLBP and HSPX153) are suspected of encoding proteins involved in mRNA processes or transcription.

Recent exome sequencing analyses led to the identification of two genes within the (WHSCR): the WHS candidate gene 1 (WHSC1), also known as nuclear receptor-binding Set Domain-protein 2 (NSD2), contained only partly within the WHSCR (Derar et al. 2019), and WHS candidate gene 2 (WHSC2), also known as Negative Elongation Factor Complex Member A (NELFA), entirely contained within the WHSCR (Cyr et al. 2011). Specifically, two minimal critical regions, have been identified corresponding to the smallest region, whose haploinsufficiency leads to the core WHS phenotype (Rauch et al. 2001; Zollino et al. 2003; Rodriguez et al. 2005). Furthermore, WHSC1 and SLBP genes, are both involved in histone metabolism, and therefore might affect the expression of other genes. Hence, it is likely that some of WHS pathology results from the combined effects of haploinsufficiency in more than one of these genes and generating significant biological changes in the expression of the correspondent target genes.

Prevalence and Mortality

The genotype is relatively rare – estimates of its prevalence range from 1:20,000-50,000 live births with a 2:1 female-to-male ratio (Maas et al., 2008). Mortality rate in the first two years of life is high [~21%]. However, the median life expectancy for those who survive is greater than age thirty years. Nonetheless, life expectancies are far greater for other microdeletion cases than for WHS.

Physical, Behavioral and Neuropsychological Features

Clinical characteristics of the phenotype include growth delay, hypotonia, unusual idiosyncratic distinctive craniofacial appearance - "Greek warrior helmet" – that are the combined result of microcephaly, broad forehead, prominent glabella, hypertelorism, high arched eyebrows, short philtrum and micrognathia. In addition, are variable observed clinical manifestations severe feeding difficulties, and congenital anomalies like skeletal anomalies, heart lesions, oral facial clefts, senso-neural deafness, and genitourinary tract defects (Battaglia et al. 2001, **Figure 2**).

Figure 2: Typical facial features including the Greek warrior helmet, frontal bossing, sparse scalp hair, low set ears, broad nasal bridge, hypertelorism, epicanthic folds, high forehead, proptosis and

ectropion, indicative of WSH syndrome. Ptosis in pt. no. 8, 9 and 10; squint in pt. no. 7 and 9; upward eyelid slanting in pt. no. 1, 2, 5, 8 and 10; downward eyelid slanting in pt. no. 3, 6, 7 and 9 [Mekkawy et al. 2020]

Most individuals with WHS are prone to seizures, have mild to profound intellectual disability, attention deficits and limited, if any, expressive speech, and language. Children with WHS are more severely impacted (~ 65% are profoundly ID) in both general cognitive ability and overall adaptive behavior skills compared to children with other microdeletions. Among less severely affected children, i.e., those who have expressive language, the profile of mean cognitive abilities and deficits is relatively flat and extends to all cognitive areas tested: verbal, quantitative, and abstract/visual reasoning, and short-term memory. Interestingly, and despite their limitations in cognitive ability and overall adaptive behavior, children with WHS exhibit relative competence in socialization skills compared to their abilities in other adaptive behavior domains (Fisch et al. 2010). On the other hand, they often have significant social problems, as assessed by the Conners Parent Rating Scale and Child Behavior Checklist. Limited attention span among children with WHS likely has a negative impact on their short-term memory skills. To that extent, these difficulties are not unique to the WHS phenotype. The proportion of children with WHS with autism or autistic-like features is significantly lower than the rates of autism found in the other sub-telomeric disorders such as 2q37, 8p23 and 11q22-25 (Jacobsen syndrome).

Although the variability in the broad range clinical manifestations observed in WHS, can be in part explained by the extent of the deletion, it is more likely that a synergistic effect of the haploinsufficiency of the genes mapping within the deleted area and additional factors including genetic backgrounds, allelic variation in the non-deleted regions of the other chromosome 4 and unbalanced translocation (Zollino et al. 2000; South et al., 2008) lead to the observed heterogeneous phenotype.

Updated in 2022 by Flora Tassone

References

Battaglia A, Carey JC, Wright TJ: Wolf – Hirschhorn (4p-) syndrome. Adv Pediatr 2001; 48: 75– 113.

Battaglia A, Filippi T, South ST, Carey JC. Spectrum of epilepsy and electroencephalogram patterns in Wolf-Hirschhorn syndrome: experience with 87 patients. Dev Med Child Neurol 2009; 51:373–80.

Battaglia A, Carey JC, South ST. Wolf-Hirschhorn syndrome: a review and update. Am J Med Genet C Semin Med Genet 2015;1 69:216–23.

Cyr AB, Nimmakayalu M, Longmuir SQ, Patil SR, Keppler-Noreuil K, Shchelochkov OA. A novel 4p16.3 microduplication distal to WHSC1 and WHSC2 characterized by oligonucleotide array with new phenotypic features. Am J Med Genet Part A. 2011; 155:2224–2228.

Derar N, Al-Hassnan ZN, Al-Owain M, Monies D, Abouelhoda M, Meyer BF, et al. De Novo Truncating Variants in WHSC1 Recapitulate the Wolf-Hirschhorn (4p16.3 Microdeletion) Syndrome Phenotype. Genet Med. 2019;21(1):185–188.

Fisch GS, Grossfeld P, Falk R, Battaglia A, Youngblom J, Simensen R. Cognitive-behavioral features of Wolf-Hirschhorn syndrome and other subtelomeric microdeletions. Am J Med Genet C Semin Med Genet. 2010 Nov 15;154C (4):417-26.

Hirschhorn K, Cooper HL, Firschein IL. 1965. Deletion of short arms of chromosome 4–5 in a child with defects of midline fusion. Humangenetik 1:479–482.

Ho KS, South ST, Lortz A, Hensel CH, Sdano MR, Vanzo RJ, Martin MM, Peiffer A, Lambert CG, Calhoun A, Carey JC, Battaglia A. Chromosomal microarray testing identifies a 4p terminal region associated with seizures in Wolf-Hirschhorn syndrome. J Med Genet. 2016 Apr;53(4):256-63.

Lurie IW, Lazjuk GI, Ussova YI, Presman EB, Gurevich DB: The Wolf –Hirschhorn syndrome. Clin Genet 1980; 17: 375– 384.

Maas, N. M. C, Van Buggenhout, G, Hannes, F, Thienpont, B, Sanlaville, D, Kok, K, Midro, A, Andrieux, J, Anderlid, B. M, Schoumans, J, Hordijk, R, Devriendt, K, Fryns, J. P, & Vermeesch, JR (2008). Genotype-phenotype correlation in 21 patients with Wolf-Hirschhorn syndrome using high resolution array comparative genome hybridization (CGH). Journal of Medical Genetics, 45, 71–80.

Mekkawy MK, Kamel AK, Thomas MM, Ashaat EA, Zaki MS, Eid OM, Ismail S, Hammad SA, Megahed H, ElAwady H, Refaat KM, Hussien S, Helmy N, Abd Allah SG, Mohamed AM, El Ruby MO. Clinical and genetic characterization of ten Egyptian patients with Wolf-Hirschhorn syndrome and review of literature. Mol Genet Genomic Med. 2021 Feb;9(2): e1546.

Rauch A, Schellmoser S, Kraus C, Dörr HG, Trautmann U, Altherr MR, et al. First known microdeletion within the Wolf-Hirschhorn syndrome critical region refines genotype-phenotype correlation. Am J Med Genet. 2001;99(4):338–342. doi: 10.1002/ajmg.1203.

Rodríguez L, Zollino M, Climent S, Mansilla E, López-Grondona F, Martínez-Fernández ML, et al. The new Wolf-Hirschhorn syndrome critical region (WHSCR-2): a description of a second case. Am J Med Genet A. 2005;136(2):175–178.

South ST, Whitby H, Battaglia A, Carey JC, and Brothman AR. Comprehensive analysis of Wolf–Hirschhorn syndrome using array CGH indicates a high prevalence of translocations. Eur J Hum Genet. 2008 Jan;16(1):45-52.

Zollino M, Lecce R, Fischetto R, Murdolo M, Faravelli F, Selicorni A, et al. Mapping the Wolf-Hirschhorn syndrome phenotype outside the currently accepted WHS critical region and defining a new critical region, WHSCR-2. Am J Hum Genet. 2003;72(3):590–597.

Zollino M, Di Stefano C, Zampino G, Mastroiacovo P, Wright TJ, Sorge G, Selicorni A, Tenconi R, Zappalà A, Battaglia A, Di Rocco M, Palka G, Pallotta R, Altherr MR, Neri G. Genotype-phenotype correlations and clinical diagnostic criteria in Wolf-Hirschhorn syndrome. Am J Med Genet. 2000 Sep 18;94(3):254-61.

Wolf U, Reinwein H, Porsch R, Schroter R, Baitsch H. 1965. Defizien an den kurzen Armen eines Chromosoms Nr 4. Humangenetik 1:397–413.

Wright TJ, Ricke DO, Denison K, Abmayr S, Cotter PD, Hirschhorn K, Keinanen M, Mcdonald-Mcginn D, Somer M, Spinner N, Yang-Feng T, Zackai E, Altherr MR. A transcript map of the newly defined 165 kb Wolf-Hirschhorn syndrome critical region. Hum Mol Genet 1997; 6:317–24.