SSBP Syndrome Sheets

Wolf Hirschhorn Syndrome

First description

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 complex clinical manifestations and variability, but also with a variability both in terms of deletion size and causal process. 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 etiology. The high variability present at both clinical and molecular level can cause difficulties in diagnosis of WHS.

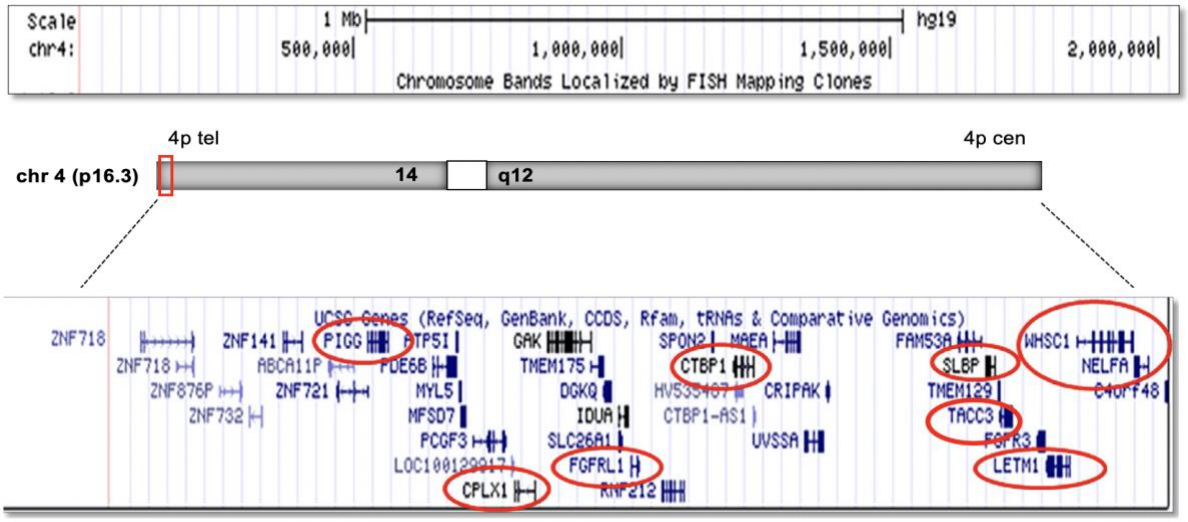

Figure 1. Diagram showing the distal region of chromosome 4p, where candidate genes for seizures and craniofacial features map (LEMT1 and WHSC1; Zollino et al., 2003; Rodrıguez et al., 2005). [Diagram was modified from Battaglia et al., 2015]

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 novo 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%) but chromosomal microarray analysis (CMA) is considered the gold standard technique for WHS diagnosis. 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. Taken all together these observations point toward a mandatory use of several genetic investigations (CMA, MLPA, FISH, karyotype) for a complete diagnosis of WHS, in addition to chromosomal analysis of the parents for assessing the risk of occurrence of other cases in the family. A combination of MLPA with CMA can provide a comprehensive approach to diagnosing WHS, ensuring that both large and small deletions are detected.

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, behavioural, 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).

Most individuals with WHS are prone to seizures, have mild to profound intellectual disability, attention deficits and limited, if any, expressive speech, and language. The appearance of epilepsy [Battaglia et al., 2015], in about 90-100% of the WHS cases, usually occurs in the first 3 years of life. It can be triggered by fever in about 70% of the cases [Battaglia et al. 2008] or due to a synergism with additional genes [Bi et al., 2016].

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).
Interestingly, children who have an heterozygous deletions of the distal short arm of chromosome 4 that includes the NSD2 gene tend to present a milder spectrum of skeletal abnormalities, and exhibit fewer seizures.

In summary, WHS is a complex genetic disorder with a known genetic etiology, variable expressivity, and penetrance, thus a wide spectrum of clinical involvements and clinical manifestations are observed. 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. Although the common features include intellectual disability, facial features, growth delays, and seizures are common, recent studies have underlined the existence of milder phenotypic forms, such of those in which the NSD2 gene is involved.

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