

WHSC1

Patient Description:

2 yo girl with significant failure to thrive (weight z score -4.77, length z score -2.28), developmental delay and recurrent infections and allergies. At 2 years 7 months, she has about five recognizable words but is playful and has good receptive language. She has a mildly prominent glabella and hypertelorism and had a normal brain MRI.

Disease/Syndrome Features:

Wolf-Hirschhorn syndrome (WHS) is caused by sub-telomeric deletions on chromosome 4p and occurs in around one in every 50,000 births. Deletion mapping of WHS patients has revealed a WHS critical region (WHSCR) located 2 Mb from the telomere. Of the genes located within the WHSCR, only *WHSC1* is at least partially deleted in all known cases of WHS. Still, phenotypic variability and murine models suggest that haploinsufficiency of *WHSC1* alone is not sufficient to cause WHS [Bergemann 2005].

WHS is characterized by intellectual disability, epilepsy, growth delay, and cranio-facial dysgenesis. Its specific facial dysmorphism has been referred to as “Greek (warrior) helmet face” and results from microcephaly, hypertelorism, a broad forehead, arched eyebrows, a short philtrum, and micrognathia. Patients also display hypotonia, dysgenesis of the corpus callosum, and speech delays. There is significant variability in the severity of these core phenotypes, and additional problems occur in a subset of patients. These include midline fusion defects such as hypospadias, cardiac anomalies, and cleft lip and palate, as well as skeletal defects such as club foot, clinodactyly, scoliosis, and kyphosis. Mortality rates for individuals with WHS are high in the first two years of life, reportedly between 21 and 34 percent, but patients surviving beyond two years have median life expectancies greater than thirty years [Bergemann 2005].

Protein/Pathway:

Wolf-Hirschhorn syndrome candidate 1, *WHSC1* (also known as Nuclear Set Domain-Containing Protein 2, *NSD2*, or Multiple Myeloma SET Domain Containing Protein, *MMSET*), measures 90 kb and contains 25 exons. The expression pattern and known domains of *WHSC1*, along with its implication in WHS, suggest important roles in development. *WHSC1* contains a proline-tryptophan-tryptophan proline (PWWP) domain, an HMG box domain, a plant-homeodomain (PHD)-type zinc finger, and a suppressor of variegation enhancer of zeste and Tirthorax (SET) domain. *In situ* hybridization reveals *WHSC1* expression in many fetal tissues that correspond to organs affected in WHS including the brain, jaw, and genitourinary system. *MMSET* is so-called because a translocation in a significant number of multiple myeloma cases fuses the *IgH* and *WHSC1* genes [Stec 1998].

WHSC1/MMSET/NSD2 has a complex transcriptional profile and generates at least four different proteins, MMSET I, MMSET II, MMSET III, and RE-IIBP. RE-IIBP is translated starting at exon 15 and contains the SET domain. It is universally expressed, with the highest levels found in the thymus. RE-IIBP is named because it binds to RE-II of the IL-5 promoter and suppresses its transcription. Cellularly, RE-IIBP localizes to the

cytoplasm and the nucleoli. RE-IIBP is a histone methyltransferase (HMTase), and its activity as such is abrogated by C483A or R477A point mutations in highly conserved residues of the SET domain. The HMTase activity of RE-IIBP shows greatest affinity for K27 of histone H3. Transcriptional repression by RE-IIBP is mediated by H3-K27 methylation and the subsequent recruitment of histone deacetylase (HDAC). In cell lines derived from leukemia patients, RE-IIBP expression and histone methylation are both increased [Kim 2008]. MMSET has additional HMTase activity in mediating the DNA damage response. MMSET is recruited to double-strand DNA breaks (DSB) by the γ H2AX-MDC1 pathway. Once recruited, MMSET induces methylation of H4-K20 which itself recruits p53-binding protein 1 to the DSB [Pei 2011].

Publications:

- Bergemann, A. D., Cole, F., & Hirschhorn, K. (2005). The etiology of Wolf-Hirschhorn syndrome. *Trends in Genetics*, 21(3), 188–195.
<https://doi.org/10.1016/j.tig.2005.01.008>
- Kim, J.-Y., Kee, H. J., Choe, N.-W., Kim, S.-M., Eom, G.-H., Baek, H. J., ... Seo, S.-B. (2008). Multiple Myeloma-Related WHSC1/MMSET Isoform RE-IIBP Is a Histone Methyltransferase with Transcriptional Repression Activity. *Molecular and Cellular Biology*, 28(6), 2023–2034. <https://doi.org/10.1128/MCB.02130-07>
- Pei, H., Zhang, L., Luo, K., Qin, Y., Chesi, M., Fei, F., ... Lou, Z. (2011). MMSET regulates histone H4K20 methylation and 53BP1 accumulation at DNA damage sites. *Nature*, 470(7332), 124–128. <https://doi.org/10.1038/nature09658>
- Stec, I., Wright, T. J., Van Ommen, G.-J. B., De Boer, P. A. J., Van Haeringen, A., Moorman, A. F. M., ... Den Dunnen, J. T. (1998). WHSC1, a 90 kb SET domain-containing gene, expressed in early development and homologous to a Drosophila dysmorphia gene maps in the Wolf-Hirschhorn syndrome critical region and is fused to IgH in t(4;14) multiple myeloma. *Human Molecular Genetics*, 7(7).
<https://doi.org/10.1093/hmg/7.7.1071>

Support Groups and Information:

[Liv 4 the Cure](#)
WolfHirschhorn.org

Relevant Facebook Groups (of many):

Wolff Hirschhorn Syndrome: private support group, 2.6K members

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