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CLINICAL REPORT

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Neural tube defects in Waardenburg syndrome: A case report and review of the literature

Joseph Hart | Kalpana Miriyala

Joan C Edwards School of Medicine, Marshall University, Huntington, West Virginia

Correspondence
Joseph Hart, Joan C Edwards School of Medicine, Marshall University, 1115 20th St #205, Huntington, WV 25703.
Email: hart.josephc@gmail.com

Waardenburg syndrome type 1 (WS1) is an autosomal dominant genetic condition characterized by sensorineural deafness and pigment abnormalities, and is caused by variants in the *PAX3* homeodomain. *PAX3* variants have been associated with severe neural tube defects in mice and humans, but the frequency and clinical manifestations of this symptom remain largely unexplored in humans. Consequently, the role of *PAX3* in human neural tube formation remains a study of interest, for clinical as well as research purposes. Though the association between spina bifida and WS1 is now well-documented, no study has attempted to characterize the range of spina bifida phenotypes seen in WS. Spina bifida encompasses several diagnoses with a wide scope of clinical severity, ranging from spina bifida occulta to myelomeningocele. We present a patient with Waardenburg syndrome type 1 caused by a novel missense variant in *PAX3*, presenting with myelomeningocele, Arnold-Chiari malformation, and hydrocephalus at birth. Additionally, we review 32 total cases of neural tube defects associated with WS. Including this report, there have been 15 published cases of myelomeningocele, 10 cases of unspecified spina bifida, 3 cases of sacral dimples, 0 cases of meningocele, and 4 cases of miscellaneous other neural tube defects. Though the true frequency of each phenotype cannot be determined from this collection of cases, these results demonstrate that Waardenburg syndrome type 1 carries a notable risk of severe neural tube defects, which has implications in prenatal and genetic counseling.

KEYWORDS
Arnold-Chiari malformation, case reports, meningomyelocele, neural tube defects, Waardenburg syndrome

1 | INTRODUCTION

Waardenburg syndrome is a genetic disorder characterized by congenital sensorineural deafness as well as striking pigmentary changes in the iris, hair, and skin, and is classified into types I, II, III, and IV. It has been repeatedly observed that spina bifida and other neural tube defects (NTDs) occur more often in patients with WS types I and III compared to the general population (Agopian et al., 2013; Pandya et al., 1996). However, though the link between WS and NTDs has been well-studied in mice models, research into the presentation in humans has been mostly limited to case studies or small case series.

The symptom is consistent with our genetic understanding of the disease—WS1 is primarily caused by *PAX3*, which is expressed in the neural crest. Additionally, the *PAX3* gene has been shown to cause NTDs at a rate of about 6% in heterozygous mice models, and 95% in homozygous models (Martin et al., 2003; Tassabehji et al., 1994). In humans, however, the frequency is largely unknown, and understanding of the clinical presentation is limited by the absence of any large

study. Only two previous publications include more than two patients with WS and clinically significant spina bifida, and neither describe the spina bifida in detail (Baldwin, Hoth, Macina, & Milunsky, 1995; da-Silva, 1991). Though there are no strong studies, there is now a large body of reported cases from which to draw insight. In this literature review and case report, we summarize the body of published cases to describe the range of neural tube defects seen in Waardenburg syndrome, and illustrate their clinical importance using the case of a patient with concomitant WS and myelomeningocele.

2 | CASE REPORT

The proband was born via c-section with a large lumbar myelomeningocele and Arnold-Chiari malformation which was repaired at 1 day of age. He also received a ventriculoperitoneal shunt at that time due to obstructive hydrocephalus. Hospital records noted talipes calcaneovalgus present at birth. There was no history of medications, alcohol, or other harmful substances used during pregnancy. His mother took no prenatal vitamins before 12 weeks gestation. He lacked motor control below the waist. At 18 months, with the use of braces he was able to stand and lean on walls. When he was 20 months old he suffered osteomyelitis of the left hip. The infection resolved with surgery and antibiotics, but he has since been wheelchair-bound. Waardenburg syndrome type 1 was diagnosed at age 1, and he was noted to have dystopia canthorum, a medial eyebrow flare (synophrys), a short, low hanging columella, and underdeveloped alae nasi. He has no hearing loss nor pigmentary abnormalities in his hair, skin, or irides. When first diagnosed, it was believed by his care team that his myelomeningocele was not related to his Waardenburg Syndrome—only when seen by our clinic at age 4 was it noted that his neural tube defect was another manifestation of his genetic disorder. At that time he received testing for ADHD using the NICHQ Vanderbilt Parent Assessment Scale, and was diagnosed with the Predominantly Hyperactive/Impulsive subtype (answering "often" or "very often" in 7 out of 9 related questions). He was further evaluated using the BASC behavioral scale, and exhibited hyperactivity and attention difficulties in the "at risk" range (60–70th percentile). Subsequent evaluation for cognitive functioning was performed using the Wechsler Preschool and Primary Scale of Inteligence-Fourth Edition. He showed low cognitive functioning across all tests, with no significant difference between subtests, indicating mild to moderate intellectual disability.

Figure 1 shows the family's history of Waardenburg syndrome. His father, paternal uncle, and paternal grandfather all have deafness in the left ear, dystopia canthorum, and white forelocks. The father has heterochromic irides not present in other family members. The deceased paternal great-grandfather also had facial features characteristic of WS, as well as deafness. There is no history of Waardenburg syndrome or neural tube defects on the patient's mother's side.

Genetic analysis was performed on a venous blood sample from the proband using Next Generation Sequencing. Six genes associated with WS were tested: *PAX3*, *EDNRB*, *EDN3*, *MITF*, *SNAI2*, and *SOX10*. The patient was heterozygous for a previously undocumented c.124G>C variant in *PAX3*, causing a predicted p.(Gly42Arg) substitution (GenBank RefSeq NM_181457.3). The variant was confirmed using Sanger sequencing. The patient's variant is near the N-terminus of the protein-coding region of *PAX3*, specifically inside the "paired box" DNA binding domain (National Center for Biotechnology Information, 2016). This change was analyzed using AlignGVGD, SIFT, Polyphen, and Mutationtaster, all of which predicted the variant to be damaging (Adzhubei et al., 2010; Firth et al., 2009; Kumar, Henikoff, & Ng, 2009; Schwarz, Cooper, Schuelke, & Seelow, 2014). The proband's unaffected mother was tested for *PAX3* variants using the same procedure, and no function-affecting or novel variations were identified, strongly suggesting the patient's *PAX3* variant was inherited from his affected father. The father was unavailable for genetic testing.

3 | DISCUSSION

3.1 | Spina bifida phenotypes

This case illustrates one of the most severe non-fatal spina bifida phenotypes in Waardenburg syndrome: myelomeningocele with

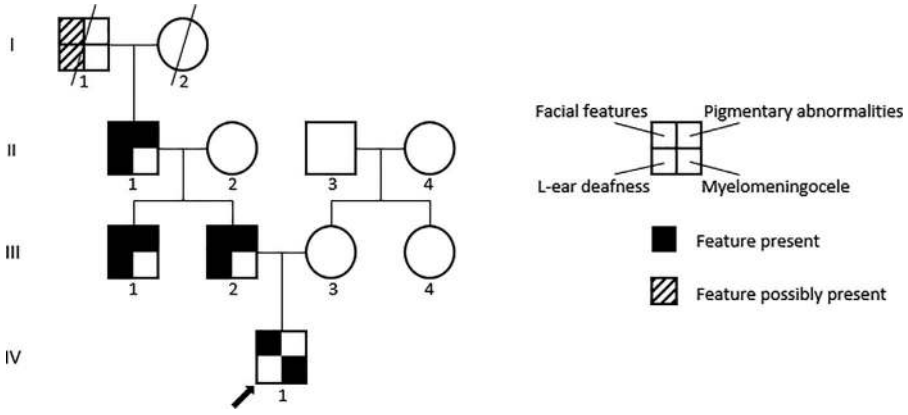

FIGURE 1 Pedigree showing WS1 and myelomeningocele in index patient (IV.1), and WS1 without neural tube defects in other members. Diagonal shading indicates individuals where history is uncertain

TABLE 1 Summary of reports of neural tube defects with Waardenburg syndrome

WS + MMC	WS + MMC + hydrocephalus	WS + SB unspecified	WS + other neural tube defect	Variant	Reference
Heterozygous cases					
2[a]			3 (sacral dimple)		de Saxe et al. (1984)
1					Narod, Siegel-Bartelt, and Hoffman (1988)
		5[e]		c.1185_1186insTGA[b], p.(Leu396X)[c]	da-Silva (1991)
2					Begleiter and Harris (1992)
	1			c.167G>T, p.(Arg56Leu)[d]	Carezani-Gavin, Clarren, and Steege (1992)
1	1				Chatkupt, Chatkupt, and Johnson (1993)
1					Moline and Sandlin (1993)
		3		c.598C>T, p.(Gln200Ter) c.954delA, p.(Gln319LysfsX62)[c]	Baldwin et al. (1995)
	1			c.598_602delCAATC[c], p.(Gln200ArgfsX2)[c]	Hol et al. (1995)
2				del. 2q35-36.2	Nye et al. (1998)
	1			der(2)inv(2)(q13q21)inv(2) (q21q24.2)ins(2)(q24.2q33q35)	Shim, Wyandt, McDonald-McGinn, Zackai, and Milunsky (2004)
		1		Splice site: IVS5 + 2 T>C	Kujat, Veith, Faber, and Froster (2007)
		1			Kfoury, Staiti, Baujard, and Benhamou (2008)
1					Seidahmed et al. (2014)
	1			c.124G>C, p.(Gly42Arg)	Hart and Miriyala (2017)
			1 (spinal dysraphism)	Deletion in PAX3	DECIPHER database search for *PAX3*. DECIPHER id 285958
Homozygous cases					
			1 (exencephaly)		Aymé and Philip (1995)
			2 (see footnote[f])	c.807C>G, p.(Asn269Lys)	Mousty et al. (2015)
Totals:					
10	5	10	7		

WS, Waardenburg syndrome, MMC, myelomeningocele, SB, Spina bifida.

All variants are in *PAX3*. Hart and Miryala (2017) and Mousty et al. (2015) use reference sequence NM_181457.3. Baldwin et al. (1995) and Hol et al. (1996) use NM_181457.2. Other cases do not list a reference sequence.

[a]Clinical information reported by Kromberg and Krause (1993)

[b]Genetic information reported by Baldwin et al. (1995).

[c]Genetic information reported by Pingault et al. (2010).

[d]Genetic information reported by Hoth et al. (1993).

[e]These cases were reported as "spina bifida aperta" which could refer to either meningocele or myelomeningocele.

[f]Patient 1: holoprosencephaly and an incurved spine. Patient 2: small choroid plexus, incurved spine, and lag between D9 and D10 vertebrae.

hydrocephalus. Among the general population, myelomeningocele occurs in 1 out of 800 live births, while meningocele is more rare, at 1 out of 5,000 live births (Laurence & Tew, 1971; Persad, Van den Hof, Dube, & Zimmer, 2002). In our review, we found 15 reported cases of WS with myelomeningocele (including the patient reported here), distributed among 13 different families. Five of these cases also included hydrocephalus that required surgery in the first week of life, or were else fatal. Among the publications that specified the subtype of spina bifida, none reported a meningocele. This is surprising—if the pattern from the general population held, we would expect around three cases.

Many publications describe patients as having "spina bifida" without further clarification. Spina bifida is a category of birth defects, and encompasses a broad range of clinical severity: spina bifida occulta comprises the vast majority of cases, and is of little clinical significance, while meningocele and myelomeningocele can be fatal, or cause lifelong disability. Thus there is opportunity for confusion, as many authors will use the term "spina bifida" only when referring to a severe variant such as meningocele or myelomeningocele. In the WS literature there are very few reports of spina bifida with no clinical significance. To our knowledge, only one study lists any such cases, reporting three related patients with WS who had sacral dimples, possibly indicating spina bifida occulta. We found no study reporting a patient with WS and a confirmed case of spina bifida occulta. Given its much higher prevalence in the general population, we were surprised to find it mentioned so rarely in the WS case literature, even accounting for its lesser clinical importance. It is possible and even likely that the less severe NTDs are less frequently reported, but even so these findings highlight the clear link between WS and severe neural tube defects. A detailed breakdown of the cases can be found in Table 1.

More severe neural tube defects have been reported in patients with WS3 caused by homozygous *PAX3* variants. In our literature review, we found five cases of confirmed or suspected homozygous PAX3 variants, three of which had neural tube defects (Aymé & Philip, 1995; Mousty et al., 2015; Wollnik et al., 2003; Zlotogora, Lerer, Bar-David, Ergaz, & Abeliovich, 1995). Four of these were confirmed via genetic analysis. Aymé and Philip reported a fetus found to have exencephaly and an incurved spine, a phenotype which very closely resembles the curved tail found in *splotch* mice (Aymé & Philip, 1995; Copp, 1994). More recently, Mousty et al. (2015) reported two fetuses with confirmed homozygosity. The first demonstrated holoprosencephaly and an incurved spine, while the second exhibited a small choroid plexus, an incurved spine, and a lag between D9 and D10 vertebrae. In all three of these cases, pregnancy was terminated by week 15. These cases were reported due to the interesting element of homozygosity, but it is possible such defects occur in heterozygous individuals as well.

Throughout the WS case literature, we found that many of the affected families reported spontaneous abortions. From the limited information available, it is impossible to discern if the spontaneous abortion rate is higher than in the general population. However, it is possible that many WS-related neural tube defects fatal during pregnancy or early in life go unreported as these individuals are usually not assessed for WS.

The phenotype of a patient with WS type 1 appears to be influenced by their genetic background, but individual *PAX3* variants do not appear to play a large role. Patients with WS who share similar variants in the same *PAX3* codon frequently do not have the same clinical presentation, yet cases with monozygotic twins have demonstrated striking similarities between the two affected patients (Pandya et al., 1996). Outside of monozygotic twins, though, there is considerable variability in phenotype even within families, and two studies have concluded there is little correlation between genotype and phenotype in WS type 1 (Baldwin et al., 1995). This pattern appears to hold true for spina bifida as with most other WS symptoms. In the cases we reviewed, most of the patients studied had a family history of WS, without any history of neural tube defects. In larger families with multiple NTDs, spina bifida exhibited variable penetrance. From the evidence available, it is apparent that genetics play a role in WS phenotype, but any divergence in effects produced by different *PAX3* variants are largely overshadowed by multifactorial elements in the patient's genetic background.

3.2 | Frequency of neural tube defects

Other reports can provide some insight into the frequency of this presentation. One cohort study performed in South Africa examined 52 individuals with WS and found spina bifida in two unrelated patients (de Saxe, Kromberg, & Jenkins, 1984). Another study reported 28 new cases of WS across seven families; three of these patients had spina bifida (Baldwin et al., 1995). Both of these reports are included in Table 1. Lastly, an unpublished review of the Waardenburg Consortium database in 1999 found 6 out of 617 cases had reported neural tube defects (Nye, McLone, Charrow, & Hayes, 1999). This last number may be an underestimate, as for much of the 1990s the link between spina bifida and Waardenburg syndrome was much less clear, and concomitant spina bifida may have been underreported in WS cases. In our review of the literature, we found no other study that examined a large cohort of unrelated WS patients and recorded the incidence of neural tube defects.

4 | CONCLUSION

This is the largest published collection of neural tube defects in Waardenburg syndrome to date. *PAX3* variants carry increased risk for spina bifida, and it may increase the risk of myelomeningocele in particular. Myelomeningocele is a serious presentation of Waardenburg syndrome, arguably causing a larger reduction to quality of life than any other symptom. Our patient lacked the audio-pigmentary abnormalities, and the facial features had only a minor impact on his life, but the sequelae of his myelomeningocele caused him significant disability. Physician awareness of this association will allow for better genetic counseling, and will better prepare families for a complicated pregnancy should one occur. It is unknown if folate affects the odds and severity of spina bifida in these patients, but it would be prudent to

proactively educate WS carriers on the importance of folate during and before pregnancy. In instances when the presence of neural tube defects will affect decisions to continue the pregnancy, we recommend offering prenatal screening via transvaginal ultrasound at both 12–14 weeks as well as 18–20 weeks, following the American College of Obstetricians and Gynecologists' guidelines for pregnancies at high risk for neural tube defects (American College of Obstetricians and Gynecologists, 2009). Though spina bifida remains an uncommon manifestation of WS, its severity makes it an important element of the disease.

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REFERENCES

Adzhubei, I. A., Schmidt, S., Peshkin, L., Ramensky, V. E., Gerasimova, A., Bork, P., … Sunyaev, S. R. (2010). A method and server for predicting damaging missense mutations. *Nature Methods*, *7*(4), 248–249.

Agopian, A. J., Bhalla, A. D., Boerwinkle, E., Finnell, R. H., Grove, M. L., Hixson, J. E., … Mitchell, L. E. (2013). Exon sequencing of PAX3 and T (brachyury) in cases with spina bifida. *Birth Defects Research Part A, Clinical and Molecular Teratology*, *97*(9), 597–601.

American College of Obstetricians and Gynecologists. (2009). ACOG practice nulletin no. 101: Ultrasonography in pregnancy. *Obstetrics and Gynecology*, *113*, 451–461.

Aymé, S., & Philip, N. (1995). Possible homozygous Waardenburg syndrome in a fetus with exencephaly. *American Journal of Medical Genetics*, *59*(2), 263–265.

Baldwin, C. T., Hoth, C. F., Macina, R. A., & Milunsky, A. (1995). Mutations in PAX3 that cause Waardenburg syndrome type I: Ten new mutations and review of the literature. *American Journal of Medical Genetics*, *58*(2), 115–122.

Begleiter, M. L., & Harris, D. J. (1992). Waardenburg syndrome and meningocele. *American Journal of Medical Genetics*, *44*(4), 541.

Carezani-Gavin, M., Clarren, S. K., & Steege, T. (1992). Waardenburg syndrome associated with meningomyelocele. *American Journal of Medical Genetics*, *42*(1), 135–136.

Chatkupt, S., Chatkupt, S., & Johnson, W. G. (1993). Waardenburg syndrome and myelomeningocele in a family. *Journal of Medical Genetics*, *30*(1), 83–84.

Copp, A. J. (1994). Genetic models of mammalian neural tube defects. *Ciba Foundation Symposium*, *181*, 118–134.

da-Silva, E. O. (1991). Waardenburg I syndrome: A clinical and genetic study of two large Brazilian kindreds, and literature review. *American Journal of Medical Genetics*, *40*(1), 65–74.

de Saxe, M., Kromberg, J. G., & Jenkins, T. (1984). Waardenburg syndrome in South Africa. Part I. An evaluation of the clinical findings in 11 families. *South African Medical Journal*, *66*(7), 256–261.

Firth, H. V., Richards, S. M., Paul Bevan, A., Clayton, S., Corpas, M., Rajan, D., … Carter, N. P. (2009). DECIPHER: Database of chromosomal imbalance and phenotype in humans using ensembl resources. *American Journal of Human Genetics*, *84*, 524–533. https://doi.org/10/1016/j.ajhg.2009.03.010

Hol, F. A., Geurds, M. P., Chatkupt, S., Shugart, Y. Y., Balling, R., Schrander-Stumpel, C. T., … Mariman, E. C. (1996). PAX genes and human neural tube defects: An amino acid substitution in PAX1 in a patient with spina bifida. *Journal of Medical Genetics*, *33*(8), 655–660.

Hol, F. A., Hamel, B. C., Geurds, M. P., Mullaart, R. A., Barr, F. G., Macina, R. A., & Mariman, E. C. (1995). A frameshift mutation in the gene for PAX3 in a girl with spina bifida and mild signs of Waardenburg syndrome. *Journal of Medical Genetics*, *32*(1), 52–56.

Hoth, C. F., Milunsky, A., Lipsky, N., Sheffer, R., Clarren, S. K., & Baldwin, C. T. (1993). Mutations in the paired domain of the human PAX3 gene cause Klein-Waardenburg syndrome (WS-III) as well as Waardenburg syndrome type I (WS-I). *American Journal of Human Genetics*, *52*(3), 455–462.

Kfoury, T., Staiti, G., Baujard, C., & Benhamou, D. (2008). Pudendal nerve block by nerve stimulation in a child with Waardenburg disease. *Paediatric Anaesthesia*, *18*(12), 1267–1268.

Kujat, A., Veith, V. P., Faber, R., & Froster, U. G. (2007). Prenatal diagnosis and genetic counseling in a case of spina bifida in a family with Waardenburg syndrome type I. *Fetal Diagnosis and Therapy*, *22*(2), 155–158.

Kumar, P., Henikoff, S., & Ng, P. C. (2009). Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nature Protocols*, *4*(7), 1073–1081.

Kromberg, J. G., & Krause, A. (1993). Waardenburg syndrome and spina bifida. *American Journal of Medical Genetics*, *45*(4), 536–537.

Laurence, K. M., & Tew, B. J. (1971). Natural history of spina bifida cystica and cranium bifidum cysticum. Major central nervous system malformations in South Wales. IV. *Archives of Disease in Childhood*, *46*(246), 127–138.

Martin, L. J., Machado, A. F., Loza, M. A., Mao, G. E., Lee, G. S., Hovland, D. N., Jr., … Collins, M. D. (2003). Effect of arsenite, maternal age, and embryonic sex on spina bifida, exencephaly, and resorption rates in the splotch mouse. *Birth Defects Research Part A, Clinical and Molecular Teratology*, *67*(4), 231–239.

Moline, M. L., & Sandlin, C. (1993). Waardenburg syndrome and meningomyelocele. *American Journal of Medical Genetics*, *47*(1), 126.

Mousty, E., Issa, S., Grosjean, F., Col, J. Y., Khau Van Kien, P., Perez, M. J., & Pingault, V. (2015). A homozygous PAX3 mutation leading to severe presentation of Waardenburg syndrome with a prenatal diagnosis. *Prenatal Diagnosis*, *35*(13), 1379–1381.

Narod, S. A., Siegel-Bartelt, J., & Hoffman, H. J. (1988). Cerebellar infarction in a patient with Waardenburg syndrome. *American Journal of Medical Genetics*, *31*(4), 903–907.

National Center for Biotechnology Information. (2016). Database resources of the national center for biotechnology information. *Nucleic Acids Research*, *44*(D1), D7–19.

Nye, J. S., Balkin, N., Lucas, H., Knepper, P. A., McLone, D. G., & Charrow, J. (1998). Myelomeningocele and Waardenburg syndrome (type 3) in patients with interstitial deletions of 2q35 and the PAX3 gene: Possible digenic inheritance of a neural tube defect. *American Journal of Medical Genetics*, *75*(4), 401–408.

Nye, J. S., McLone, D. G., Charrow, J., & Hayes, E. A. (1999). Neural crest anomaly syndromes in children with spina bifida. *Teratology*, *60*(4), 179–189.

Pandya, A., Xia, X. J., Landa, B. L., Arnos, K. S., Israel, J., Lloyd, J., James, A. L., … Nance, W. E. (1996). Phenotypic variation in Waardenburg syndrome: Mutational heterogeneity, modifier genes or polygenic background?. *Human Molecular Genetics*, *5*(4), 497–502.

Persad, V. L., Van den Hof, M. C., Dube, J. M., & Zimmer, P. (2002). Incidence of open neural tube defects in Nova Scotia after folic acid fortification. *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne*, *167*(3), 241–245.

Pingault, V., Ente, D., Dastot-Le Moal, F., Goossens, M., Marlin, S., & Bondurand, N. (2010). Review and update of mutations causing Waardenburg syndrome. *Human Mutation*, *31*(4), 391–406.

Schwarz, J. M., Cooper, D. N., Schuelke, M., & Seelow, D. (2014). MutationTaster2: Mutation prediction for the deep-sequencing age. *Nature Methods*, *11*(4), 361–362.

Seidahmed, M. Z., Abdelbasit, O. B., Shaheed, M. M., Alhussein, K. A., Miqdad, A. M., Samadi, A. S., … Salih, M. A. (2014). Genetic, chromosomal, and syndromic causes of neural tube defects. *Saudi Medical Journal*, *35*(Suppl 1), S49–S56.

Shim, S. H., Wyandt, H. E., McDonald-McGinn, D. M., Zackai, E. Z., & Milunsky, A. (2004). Molecular cytogenetic characterization of multiple intrachromosomal rearrangements of chromosome 2q in a patient with Waardenburg's syndrome and other congenital defects. *Clinical Genetics*, *66*(1), 46–52.

Tassabehji, M., Newton, V. E., Leverton, K., Turnbull, K., Seemanova, E., Kunze, J., … Read, A. P. (1994). PAX3 gene structure and mutations: Close analogies between Waardenburg syndrome and the Splotch mouse. *Human Molecular Genetics*, *3*(7), 1069–1074.

Wollnik, B., Tukel, T., Uyguner, O., Ghanbari, A., Kayserili, H., Emiroglu, M., & Yuksel-Apak, M. (2003). Homozygous and heterozygous inheritance of PAX3 mutations causes different types of Waardenburg syndrome. *American Journal of Medical Genetics Part A*, *122A*(1), 42–45.

Zlotogora, J., Lerer, I., Bar-David, S., Ergaz, Z., & Abeliovich, D. (1995). Homozygosity for waardenburg syndrome. *American Journal of Human Genetics*, *56*(5), 1173–1178.

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