

SUPPLEMENTARY TABLE S2. Reported cases of genetically diagnosed WS, TS, PCWH/PCH, and YDHS with hyperpigmentation of skin

Type of hyperpigmentation	Reference	Gene	Mutation	Disease subtype	Zygosity	Original description of hyperpigmentary symptoms	Origin of the patient	No. of affected members
Café-au-lait spots	Zazo Seco, <i>et al.</i> , 2015	<i>KITLG</i>	c.310C>G, p.Leu104Val	WS2	Hetero.	Nummular sharply demarcated hyperpigmented macule was seen on his back	Dutch origin	1
	Pingault, <i>et al.</i> , 2014	<i>SOX10</i>	c.336G>A, p.Met112Ile	WS4	Hetero.	Café au lait spots were also present on the lower extremities	Denmark	1
Café-au-lait spots and freckles	Leger, <i>et al.</i> , 2012	<i>MITF</i>	c.635T>G, p.Ile212Ser	WS2	Hetero.	Freckles in sun-exposed regions, lentigines and cafe-au-lait macules	Vietnam/Martinique	1
	Bondurand, <i>et al.</i> , 1999; Hennekam and Gorlin, 1996	<i>SOX10</i>	c.404G>C, p.S315T	YDHS	Hetero.	Multiple freckles on her trunk and limbs, and several larger cafe-au-lait spots on her trunk	Netherlands	1
Freckles	Shi, <i>et al.</i> , 2016	<i>MITF</i>	c.944_946delGAA, p.Δ315Arg	WS2	Hetero.	Pigmentation on the face (Clinical photo shows freckles on the face)	China	3
	Kim, <i>et al.</i> , 2015	<i>MITF</i>	c.763C>T (p.Arg255X)	WS2	Hetero.	Freckled face, Brown freckles ... characteristically started in their first decade, which differentiated this lesion from a simple dyschromia. The freckles were characteristically limited to the face and the extremities, not involving the trunk.	Korea	9 (out of 12 affected members)
	Yang, <i>et al.</i> , 2013a	<i>MITF</i>	c.647_649delGAA, p.Arg217del	WS2	Hetero.	Numerous brown freckles on the face, trunk, and limb extremities.	China	1
	Yang, <i>et al.</i> , 2013b	<i>MITF</i>	c.763C>T, p.Arg255X	WS2	Hetero.	Excessive facial brown freckles that frequently seen in Chinese WS2 patient	China	1
	Yang, <i>et al.</i> , 2013a	<i>MITF</i>	c.763C>T, p.Arg255X	WS2	Hetero.	Numerous brown freckles on the face, trunk, and limb extremities.	China	1 (out of 3 affected members)
	Yang, <i>et al.</i> , 2013a	<i>MITF</i>	c.20A>G, p.Tyr7Cys	WS2	Hetero.	Numerous brown freckles on the face, trunk, and limb extremities.	China	2 (out of 3 affected members)
	Leger, <i>et al.</i> , 2012	<i>MITF</i>	c.639A>C, p.Glu213Asp	WS2	Hetero.	Freckles in the pigmented areas	South African of European decent	1
	Yan, <i>et al.</i> , 2011	<i>MITF</i>	c.[742_743delAAinsT;746_747delCA]	WS2	Hetero.	Brown freckles on the skin	China	10 (out of 11 affected members)
	Chen, <i>et al.</i> , 2010 ¹	<i>MITF</i>	c.650G>T, p.Arg217Ile	WS2	Hetero.	Special brown freckles on the faces/Much brown freckles n the bodies extensively	China	1
	Chen, <i>et al.</i> , 2010 ¹	<i>MITF</i>	c.648_650delAAG, p.Arg217del	WS2	Hetero.	Special brown freckles on the faces/Much brown freckles n the bodies extensively	China	1
	Monma, <i>et al.</i> , 2008	<i>MITF</i>	IVS4-1G→C	WS2	Hetero.	Striking freckling on her allover pale face lacking obvious leukoderma	Japan	1 (out of 3 affected members)
	Smith, <i>et al.</i> , 2000	<i>MITF</i>	p.Asn210Lys	TS	Hetero.	affected family members may have reddish freckles	Caucasian, USA	Unknown number out of 15 affected members
	Tassabehji, <i>et al.</i> , 1995	<i>MITF</i>	p.del(R217)	WS2	Hetero.	Pale skin with numerous orange freckles	Europe?	1
	Amiel, <i>et al.</i> , 1998	<i>MITF</i>	3-bp deletion, del R217	TS	Hetero.	Numerous orange freckles	UK	1
Freckles and other undetermined hyperpigmentation	Kim, <i>et al.</i> , 2015	<i>PAX3</i>	c.668G>A, p.Arg223Gln	WS1	Hetero.	Freckled face, Brown freckles ... characteristically started in their first decade, which differentiated this lesion from a simple dyschromia. The freckles were characteristically limited to the face and the extremities, not involving the trunk.	Korea	3 (Out of 3 affected members)
	Yang, <i>et al.</i> , 2007	<i>PAX3</i>	c.626_627delCT, p.Ser209Ter	WS1	Hetero.	Brown freckles on the face	China	1
	Yang, <i>et al.</i> , 2007	<i>PAX3</i>	c.667C>T, p.Arg233Ter	WS1	Hetero.	Brown freckles on the face	China	1
	Pingault, <i>et al.</i> , 2014	<i>SOX10</i>	c.336G>C, p.Met112Ile	WS2	Hetero.	In adulthood, she developed some freckles on the face	France	1 (out of 2 affected members)
	Chen, <i>et al.</i> , 2016	<i>MITF</i>	c.649_651delAGA	WS2	Hetero.	Pigmentation and freckles on the skin	China	3 (out of 5 affected members)
	Hyperpigmented macules within hypomelanotic areas	Qin, <i>et al.</i> , 2006	<i>PAX3</i>	c.701T>C, p.Leu233Pro	WS1	Hetero.	Within the areas of hypomelanosis, there were normally pigmented and hyperpigmented macules of various sizes.	China
Shamseldin, <i>et al.</i> , 2010		<i>EDN3</i>	c.277C>G, p.Arg93Gly	WS4	Homo.	(Clinical picture shows small hyperpigmented spots within the hypopigmented maules on the face)	Egypt	1
Fernandez, <i>et al.</i> , 2014		<i>SOX10</i>	c.1107ins19, p.Thr370Serfs038	WS4	Homo.	Hyperpigmented spots can be observed on the hypopigmented skin	Portuguese origin	1
Other hyperpigmentary anomalies	Elmaleh-Berges, <i>et al.</i> , 2013	<i>SOX10</i>	c.1401A>C, p.467TyrextX86	PCWH	Hetero.	A light prototype of hyperpigmented macules on her lower limbs, and hypopigmented patches that appeared progressively	Nigeria/France	1
	Inoue, <i>et al.</i> , 2002	<i>SOX10</i>	c.748C>T, p.Gln250Ter	WS4	Hetero.	Hyperpigmented and hypopigmented patches on the face, body, and extremities	USA	1
	Wildhardt, <i>et al.</i> , 2013	<i>PAX3</i>	c.111dupC, p.Val38Argfs*76	WS1	Hetero.	Skin hyperpigmentation anomalies	Caucasian	1
	Tassabehji, <i>et al.</i> , 1994a	<i>PAX3</i>	deletion	WS1 or WS3	Hetero.	Several naevi on his back but no leukoderma	Unknown (Europe)	1
	Zlotogora, <i>et al.</i> , 1995	<i>PAX3</i>	c.251C>T, p.Ser84Phe	WS3	Homo.	Spots of hyperpigmentation were present on the scrotum	Palestinaian kindlet	1
No clear indication if cutaneous hyperpigmentation exists (hypo- or hyperpigmentation)	Wu, <i>et al.</i> , 2016	<i>PAX3</i>	c.238C>G, p.His80Asp	WS1	Hetero.	Pigmentary disturbance	China	1
	Wu, <i>et al.</i> , 2016	<i>PAX3</i>	c.808C>T, p.Arg270Cys	WS1	Hetero.	Pigmentary disturbance	China	1
	Wildhardt, <i>et al.</i> , 2013	<i>PAX3</i>	c.958+?_1174-3del	WS1	Hetero.	Pigmentation anomalies	Caucasian	1
	Tassabehji, <i>et al.</i> , 1992; Foy, <i>et al.</i> , 1990	<i>PAX3</i>	exon 4 18-bp deletion	WS1	Hetero.	Hypo- or hyperpigmented skin patches	England	2 (out of 6 affected members)
	Morell, <i>et al.</i> , 1992	<i>PAX3</i>	exon 4 14-bp deletion	WS1	Hetero.	Hypo- or hyperpigmentation	Indonesia	7 (Out of 11 affected members)
	Tassabehji, <i>et al.</i> , 1993; Foy, <i>et al.</i> , 1990	<i>PAX3</i>	exon 2 1-bp deletion	WS1	Hetero.	Hypo- or hyperpigmented skin patches	England	2 (out of 6 affected members)
	Wu, <i>et al.</i> , 2016	<i>EDN3</i>	c.293C>A, p.Thr98Lys	WS1	Hetero.	Pigmentary disturbance	China	1
	Hofstra, <i>et al.</i> , 1996	<i>EDN3</i>	c.476G>T, p.Cys159Phe	WS4	Homo.	Pigmentary defects	USA	5 (out of 7 affected members)
	Wu, <i>et al.</i> , 2016	<i>MITF</i>	c.650G>T, p.Arg217Ile	WS2	Hetero.	Pigmentary disturbance	China	1

¹This paper also reports that 4 other patients from 3 families (out of 13 patients from 11 families) with mutation of either PAX3, MITF, or SOX10 showed the similar freckles.