Oculocerebral Hypopigmentation Syndrome Maps to Chromosome 3q27.1q29

E. Chabchoub^{a,b} O. Cogulu^c B. Durmaz^c J.R. Vermeesch^a F. Ozkinay^c J.-P. Fryns^a

^aCentre for Human Genetics, University Hospital Gasthuisberg, Leuven, Belgium; ^bDepartment of Genetics and Immunology, Research Unit 04UR0805, Faculty of Medicine, University of Sousse, Sousse, Tunisia; ^cDepartment of Paediatrics, Ege University, Izmir, Turkey

Key Words

Oculocerebral hypopigmentation syndrome · Cross syndrome · Array comparative genomic hybridisation · Chromosome 3q · Deletion · Candidate gene · Genetic skin disease

Abstract

Background: In 1967, Cross et al. [J Pediatr 1967;70:398–406] reported four siblings with intellectual disability, microcephaly, neurologic and ocular disorders, and hypopigmentation involving skin and hair. This novel entity, known as oculocerebral hypopigmentation syndrome (OCHS) or Cross syndrome (OMIM 257800), is assumed to be autosomal recessive. However, its genetic cause is still unknown. **Case Report:** A 4-year-old girl is reported with OCHS, a history of recurrent infections and vertebral fusion of L4–L5. Central nervous system and cardiac imaging as well as metabolic screening were normal. Microscopic hair investigations did not show any melanin deposit defects. **Results:** Using molecular cytogenetics, we detected a de novo interstitial del(3)(q27.1q29) of the paternal chromosome. To our knowledge, this is the first molecular genetics finding in a patient with OCHS. Here we discuss the genotype-phenotype correlations and suggest candidate genes for this disorder. **Conclusion:** Investigating further patients would enable fine-mapping the OCHS locus and identifying its putative gene.

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Introduction

In 1967, Cross et al. [1] reported 4 siblings of a highly inbred Amish family with a combination of four major abnormalities: (i) cutaneous hypopigmentation, (ii) growth deficiency, (iii) severe ocular anomalies, and (iv) neurologic signs. The syndrome presents at birth with pigmentary and ocular anomalies including microphthalmia, exophthalmia, corneal and lens opacity, spastic ectropium, and nystagmus. The neurologic abnormalities are progressive and characterised by severe intellectual disability (ID), spastic diplegia, hyperreflexia, hyperirritability, and athetoid movements. These clinical features vary among affected individuals. This novel entity is known as oculocerebral hypopigmentation syndrome (OCHS) or Cross syndrome (OMIM 257800). A similar condition was described in 1983 by Preus et al. [2] in 2 sisters, born to consan-

guineous Italian parents, both presenting skin and hair hypopigmentation, dolichocephaly, cataracts, high arched palate, deafness, and severe ID. The older sister also had growth retardation, small widely spaced teeth, finger contractures, spasticity, hypochromic anaemia, myopia and moderate hydrocephalus of the lateral ventricles. This intrafamilial heterogeneity was also reported by Fryns et al. [3] with 3 siblings presenting pure cutaneous hypopigmentation for a 23-year-old otherwise normal male, while the two other siblings had severe ID and spastic tetraplegia with athetoid movements.

Up to date, 11 other patients have been reported [4–10]. The prevalence of OCHS in consanguineous families is in favour of an autosomal recessive inheritance, but no molecular or biochemical substratum is known so far.

Here, we report a 4-year-old girl born to normal consanguineous Turkish parents with OCHS and additional findings consisting of recurrent respiratory and urinary tract infections and vertebral fusion of L4–L5. We mapped this disorder to a 10 Mb region on chromosome 3(q27.1q29). We discuss the genotype-phenotype correlations and suggest candidate genes for this disorder.

Table 1. Overview of the clinical features of patients with OCHS

Clinical features	This report	Pollazzon et al. [19]	Cross et al. [1]	Elejalde et al. [30]	Preus et al. [2]	Patton et al. [8]	Fryns et al. [3]	De Jong and Fryns [5]	Tezcan et al. [9]
Skin hypopigmentation	+	–	+	+	+	+	+	+	+
Silver-grey/white hair	+	–	+	+	+	+	+	+	+
Ocular anomalies	+	–	+	+	+	+	+	+	+
Microcephaly	+	–	+	+	+	+	+	+	+
Hypotonia	+	–	NI	+	NI	+	+	+	+
Ataxia	–	–	+	+	+	+	+	+	+
Spasticity	–	+	+	+	NI	NI	+	+	+
Developmental delay/intellectual disability	+	+	+	+	+	+	+	+	+
Brain malformation	–	+ ^a	DWM	CAo	–	CAo	DWV	DWM	DWM
Growth retardation	+	–	+	NI	+	+	+	+	+
Consanguinity/autosomal recessive inheritance	+/+	–/–	+/+	+/+	+/+	–/+	+/+	+/+	+/+
Melanocytes (microscopy)	N	NI	↓	Ab	NI	↓	↓	NI	N
Melanosome maturation	NI	NI	NI	NI	NI	Ab	Ab	NI	Ab
Seizures	–	NI ^b	NI	+	NI	–	+ ^b	–	+ ^c
Recurrent urinary tract infections/malformations	+	–	NI	NI	NI	–	NI	–	+
Heart malformations	–	+	NI	NI	NI	–	–	–	+
Blood cells/lineage anomalies	–	NI	–	NI	anaemia	–	–	–	VMC
Vertebral anomalies	L4–L5 fusion	scoliosis	NI	NI	NI	–	–	–	–
Osteoporosis	–	NI	–	–	+	+	–	–	–
Acetabular hypoplasia	–	NI	–	–	+	+	–	–	–
Karyotype	46,XX	46,XX	NI	NI	NI	46,XY	46,XY	46,XX	NI

+ = Sign present; – = sign absent; ↓ = reduced; Ab = abnormal; CAo = cerebral atrophy (mainly the occipital lobes); DWM = Dandy-Walker malformation; DWV = Dandy-Walker variant; N = normal; NI = not indicated; VMC = vacuolated myeloid series cells.

^a Myoclonic epilepsy. ^b Nonspecific electroencephalographic signals without clinical manifestations. ^c Nonspecific white matter signals on magnetic resonance imaging.

Subject and Methods

Clinical Report

A 4-year-old girl was referred for developmental delay, multiple congenital anomalies with generalised hypopigmentation, and failure to thrive. She was born at 32 weeks of gestation by normal vaginal delivery to healthy consanguineous Turkish parents. She had a low birth weight (1,250 g) and suffered from recurrent respiratory and urinary tract infections. On physical evaluation, her weight (8 kg), height (80 cm) and head circumference (41 cm) were all below the 3rd centile. She showed dysmorphic features with microcephaly, sparse silver-grey hair, low frontal hairline, microphthalmia, telecanthus, blue sclera, broad nasal bridge, micrognathia, thin upper lip, joint laxity, broad hallux and partial syndactyly (fig. 1a–c). Her developmental milestones were delayed: she crawled on hands and knees at 12 months but could not walk without support. Generalised hypotonia was noticed at neurologic examination.

Skeleton X-rays showed a vertebral fusion of L4–L5 with a normal lumbosacral segment of spinal cord on magnetic resonance imaging that did not detect structural or migration anomalies of the brain apart from the microcephaly. Transthoracic echocardiography was normal. Urinary tract imaging showed nephrolithiasis with left ectopic kidney and vesicoureteral reflux grade III in the left kidney and grade II in the right one with a diverticulum of the bladder. Ureterolithotomy was successful.

Complete blood count, serum biochemistry profile and urine analyses were normal. Metabolic screening of urine and serum (urine organic acid analysis, mass spectrometry, dosage of biotinidase, phenylalanine, glucose-6-phosphate dehydrogenase, acylcarnitine) were within normal limits. Capillary zone electrophoresis of serum sialotransferrins was normal, thus excluding a congenital defect of glycosylation (CDG). Hair examination under light microscopy revealed no melanin deposit defect (table 1).

Genetic Investigations

Conventional standard G-banded karyotype at a resolution of 450 bands was performed on peripheral blood lymphocytes according to standard procedures. BAC array comparative genomic hybridisation (aCGH) at a mean resolution of 1 Mb was performed as previously described [11]. Since only the patient's DNA was still available, fluorescence in situ hybridisation could not be performed and the aCGH data were confirmed by real-time quantitative PCR (qPCR) and completed by genotyping using (CA)_n repeat polymorphic marker analysis mapping to 3q27.1 (D3S1571, D3S3609, D3S3578) and to 3q29 (D3S3669, D3S3562) which, in addition, enabled to determine the parental origin of the abnormality. We further fine-mapped the breakpoints using a dye-swap labelling of the patient's DNA, hybridised to a ten-fold higher resolution OGTTM CytoSure ISCA 180k DNA oligoarray[®] (Oxford Gene Technology, Oxford, UK, based on a technology from AgilentTM, USA) following the manufacturer's protocol [12].

Bioinformatic Analyses and Candidate Gene Prioritisation

The genes in the rearranged region were mapped in silico using the BIOMART tool of the Ensembl genome browser (annotation NCBI 36 from http://may2009.archive.ensembl.org/Homo_sapiens). To look for the candidate gene(s) for OCHS, we selected, in a first step, 11 known genes for hypopigmentation diseases (*EDNRB*, *MITF*, *PAX3*, *EDN3*, *HPS1*, *AP3B1*, *HPS3*, *OCA2*, *GPR143*, *MYO5A* and *RAB27A*), then we applied a gene prioritisation strategy using the software String v8.3 [13, 14] (available online from <http://string-db.org>) for an overview of the possible in silico interactions between these disease genes and the candidate genes within the rearranged region and their statistical significance. We also used the software Endeavour [14] (from <http://homes.esat.kuleuven.be/~bioiuser/endeavour/index.php>) to rank the candidate genes within the rearranged region using the above-mentioned 11 disease genes as a training set. The model was set after internally validating the data sources as recommended by the authors [14]. In a third step, we manually investigated the genes within the candidate region using the OMIM database (from <http://www.ncbi.nlm.nih.gov/omim>), the expression data resources from the BioGPS database [15] (from <http://biogps.gnf.org/#goto=welcome>) and by checking the existence of mice models from the Jackson Laboratory mouse genome database MGI (from <http://www.informatics.jax.org>).

Results and Discussion

By aCGH we detected an interstitial deletion of 3q27.1q29 with a maximal size of 10.094 Mb. The flanking clones are RP11-14I2 and RP11-279P10. The proximal breakpoint maps between the oligoprobes A_16_P00886023 (185,168,209 bp) and A_14_P113421 (185,203,917 bp) disrupting the *ABCC5* gene (OMIM 605251). The distal breakpoint maps between the probes A_14_P113559 (195,212,832 bp) and A_16_P00900866 (195,262,297 bp) (annotation NCBI 36) (fig. 1d, e). With qPCR, we confirmed the deletion and showed that it was de novo (data not shown). Using the microsatellite markers mapping to 3q we confirmed the deletion and showed that the derivative chromosome 3 is paternal (data not shown). We

Fig. 1. a–c The patient aged 4 years showing dysmorphic features with skin and hair hypopigmentation. d Partial 1 Mb resolution BAC aCGH data from chromosome 3 of the child displaying the log₂ ratio plot with the deleted clones encircled in red. On the x axis the relative distance of the BAC clones from the 2p telomere is indicated in Mb with the chromosome 3 ideogram. e Partial data of chromosome 3 from the 100 kb resolution OGTTM CytoSure ISCA 180k DNA oligoarray displaying the dye-swap hybridisations (the Cy-5-labelled patient's DNA is represented by the red plot for the first hybridisation and the Cy-3-labelled patient's DNA by the blue plot representing the data from the dye-swap hybridisation with every coloured spot representing an oligoprobe from the arrays). f A screen capture from the Ensembl database (annotation NCBI 36) showing the physical map of the deleted BAC clones and the Ensembl genes. The deletion in the present patient is delineated by the red lines and the patient reported by Pollazzon et al. [19] is represented by the blue line. The thin arrows delineate the maximum size of the deletions at the flanking probes. The del/dup 3q29 syndromes map to the black line.

mapped 107 Ensembl-annotated genes to this region (fig. 1f), with 82 protein-coding genes encompassing 61 OMIM genes, 18 genes were expressed in melanocytes and 12 genes were identified as disease-associated genes.

Our present patient has no structural brain malformations, but microcephaly and thus the clinical picture is most compatible with the Cross type of OCHS. This shows a clear overlap of the clinical features in these OCHS subtypes as illustrated in table 1.

Few reports of microscopically visible 3qter deletion patients have been published with growth retardation, hypotonia, ear abnormalities, and cognitive delay. 3 out of the 5 reported patients died at a

young age [16]. In 2001, the first submicroscopic microdeletion of 3qter was reported in 3q29 [17]. Willatt et al. [18] described 6 more cases. Characteristic features were a long and narrow face, high nasal bridge, short philtrum, a tight upper lip, and mild to moderate ID. Less frequent features were ataxic and unsteady gait, autism, microcephaly, long fingers, and chest wall deformity. This clinical description fits with the dysmorphic features of our patient. Pollazzon et al. [19] reported a 9.3 Mb deletion of 3q27.3q29 overlapping distally with the deletion in our patient but not resembling the spectrum of Cross syndrome. Moreover, unlike the deletion in our patient, the one reported by Pollazzon et al. [19] extends further distally to overlap

with the critical region of the 3q29 deletion/duplication syndrome (fig. 1f). Interestingly, several reports were published with dup3q27q29 in patients presenting hypotonia, dysmorphic features, increased head circumference (p75) and skin hyperpigmentation [20–22]. To our knowledge, this is the first molecular genetics finding in a patient with OCHS. We assume that haploinsufficiency in chromosome 3q could have unravelled a mutation in a gene located in the homologous region in the ‘cytogenetically normal’ maternal chromosome in our patient, leading to the phenotypic manifestations of OCHS.

Neurons and melanocytes are neuroectodermal derivatives. This can explain the occurrence of brain and sensorineural anomalies and skin and hair hypopigmentation as suggested earlier [9]. When analysing in silico the genes in the deleted 3q region, we identified some valuable candidates for OCHS. Heterozygous mutations in the *OPA1* gene induce abnormal apoptosis and cause autosomal dominant optic atrophy, sensorineural deafness and myopathy [23]. *PARL* interacts with *OPA1* and is also involved in the regulation of apoptosis [24], so the loss of both alleles can be causal for the brain malformations and ectodermal depigmentation reported in OCHS. Furthermore, *DVL3* encodes a cytoplasmic phosphoprotein regulating cell proliferation and acts as a transducer molecule for developmental processes such as segmentation and neuroblast specification [25]. Thus *DVL3* can be a good

candidate. On the other hand, mutations in *EDN3* cause Waardenburg syndrome type IV_B. Mice deficient in *ECE1* have reduced levels of Edn3 [26]. We think that *ECE2* on 3q, a close homologue of *ECE1*, can also play a similar role in explaining the ectodermal hypopigmentation and cognitive disorders described in OCHS. Besides *ETV5*-deficient mice showed hypoplastic or missing kidneys, suggesting that *ETV5* plays a role in branching morphogenesis in the developing kidney [27]. Similarly, several families with nephrolithiasis and recurrent urinary tract infections have been reported with homozygous mutations in the *CLDN16* gene [28]. This may explain the urologic manifestations in OCHS. Besides, the deletion of *FGF12* might be the cause of microcephaly, which is a common sign for the clinical spectrum of OCHS manifestations. A special note is to be addressed to the *ALG3* gene were patients harbouring homozygous mutations had failure to thrive, epilepsy, hypotonia, marked ID, microcephaly, ocular anomalies, facial dysmorphism and reduced mannosyltransferase activity corresponding to a CDG type Id [29]. The clinical spectrum of OCHS overlaps with CDG Id, nevertheless this diagnosis was excluded by the capillary zone electrophoresis of serum sialotransferrins.

In conclusion, we report a new patient with OCHS and peculiar manifestations consisting of recurrent respiratory and urinary tract infections and vertebral fusion of L4–L5. We mapped for the first

time this syndrome to 3q27q29. Investigating further patients with this condition would enable fine-mapping of the locus and identification of the putative gene for OCHS.

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Ethics Approval

The authors declare that informed, written consent was obtained and that the experiments comply with the current laws of Belgium and with the ethical principles of the WMA Declaration of Helsinki.

Disclosure Statement

The authors declare that they have no conflict of interest.

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