Patient-oriented definition of disease (PKB) according to ACHSE criteria

Hypotrichosis with juvenile macula dystrophy – (HJMD)

Target group	The current description was written for patients and parents of concerned children.
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Introduction	The subsequently very unusual disease, marked by sparsely growth of hair from birth and proceeding macular dystrophy, a degenerative disease with genetic origin. The disease is made up of two single symptoms that can also appear as separate diagnoses. Primarily visually remarkable is hypotrichosis (reduced body hair), not to be confused with hypertrichosis (increased body hair). The inherited macular dystrophy comes up with wispy granulated macula (macula: acutest point of vision), a so-called displacement of pigmented layer of retina. The disease is shortened also known as HJMD or CDH3, according to causing gene P-Cadherin Protein.
Frequency	The total frequency is roughly much less than 1 : 1.000.000. Medical literature recorded only few described cases. The prevalence (frequency of disease) since initial description rests with about 50 – 100 cases.
Cause	In order to an autosomal recessive inheritance, causes are mutations of CDH3 gene. CDH3 gene encodes the Cadherin-3 Protein, also called P-Cadherin; in different tissues it is a calcium-binding protein that is responsible for contact between cells. The so called cell-cell contact enables a variety of consecutive reactions and is thus very important for the organism. The descripted case deals with a compound-heterozygous mutation in CDH3 gene. Definition: “Compound-heterozygosity” means there are verifiably two different mutations on the same gene on both chromosome complements. “Autosomal-recessive”: inheritance pattern, where two mutated genes are passed on to the child. Father and mother will so pass on the mutated gene and the disease will break out.

	If only one parent passes on a mutated gene, the child will not fall ill; however, the child to pass on that gene as well. The chance of finding together of two carriers of that strain is to be rated as low.
Symptoms and differential diagnostics	Very moderate growth of hair (sparsely hair) with normal hair at the rest of the body. Main hair is not full as usual an with a very moderate growth. With beginning of school attendance, at least, the optic anomaly is also visible to outsiders. Furthermore, different hair shaft anomalies in the context of ectodermal dysplasia (deformity of ectoderm) can appear. Mutations in CDH3 gene may cause an HJMD in order to the autosomal recessive heritage, or also the so called EEM syndrome. A combination of deformities in the context of ectodermal dysplasia and electro dactyls and a macular degeneration. Strong anomalies like lobster-claw hand or foot, tooth anomalies and hair disorder like missing of eyebrows can also appear. In combination of macular change and of an existing hypotrichosis HJMD is symptomatically to be taken into account. In case of suspicion a diagnosis by human genetic examination is to be advised, otherwise a vague specific relation can only be made by the process itself and the hair anomaly.
Form of disease progress and prognosis	The degeneration of macula, the place of highest density of sensory cells in retina, is reflected in a slow and also progressive deterioration of central ability of seeing. Over the course a loss of reading ability is to be expectation; symptoms in terminal stage are similar to inheritable retinal degeneration. Apart from that, people concerned can develop in a completely healthy way and have a normal life expectancy. Impaired by low vision and hair phenotype the disease challenges people concerned and their relatives a lot.
Early diagnosis	Abnormality of hair anomaly should lead to an ocular fundus examination - at the latest with beginning of school attendance – since usual preventive check-ups do not have to expect visual impairment necessarily. It can also be noticeable and manifested in adolescent age. Diffused macular degeneration and not proper growing hair until age of beginning school attendance, may confirm suspicion of HJMD.
Therapy	A causative treatment is not jet given; however, a lot of studies about gene therapy, exon skipping and CRISPR/Cas9 give little hope. A specific classification of gene mutation, through solid diagnostics, also offers further potential approaches beyond gene replacements for a specific group of affected people – a diagnosed so called nonsense mutation, a mutation where a stop codon occurs by a change in one single base of a DNA sequence. Here it comes to an early chain break-off in protein biosynthesis. A shortened and functionless or low-function protein will be the result. Translational skipping of a stop codon; the so-called “Read-Through-Therapy”, can cause a skipping of a stop codon by administering particular substances and can so lead to suitable protein. This approach, however, is only conceivable at limited mutations that cause different diseases. There are already some promising clinical studies, like those of the muscular dystrophy of the Duchenne type. Definition: In genetics, a stop codon just describes the break of protein synthesis within a cell. In another process - the exon skipping - the damaged

	gene segment will be skipped during synthesis. A shortened but working protein could be built.
Prevention	Since appearing of HJMD is related genetically, preventive measures are unfortunately not known. No measures exist, which could prevent the disease. A molecular genetic examination of CDH3 gene of the parents or future partner, at further desire to have children, would be recommended. Further children of the original parents carry a 25 percent risk. Half of the children will be healthy carriers of the disease; another 25 percent won't inherit the disposition at all.
Genetic counseling/ molecular genetic diagnostics	A secure diagnosis of HJMD can only be made through molecular genetic diagnostics. It should be made by a genetic counseling. The human genetic counseling shall help concerned persons and their relatives to answer questions that go with that inheritable disease. The wish to find the cause, naming the inheritance and the mutation, is presuming for a prospective therapy option.
Recommended examination methods	Besides the examination of the ocular fundus the pigment examination of retina and retina scan, with an optic coherence tomography (OCT) are approved methods to make statements on the intensity of retinal damage. Over time the results of an electrophysiological examination with the Electroretinography (ERG) or the multifocal Electroretinography can give more information about the damage. An annual examination interval is enough for an not acute progressive behavior.
Help for coping and life planning	A disease, which threatens eyesight and further shows a noticeable hair anomaly to strangers, harms people not only physically, but always generally. It is not surprising that disclosing diagnosis to affected people is like a shock. This goes for affected children as well as for their parents and relatives. They'll be confronted with the statement that there will be no treatment option yet. They would never have felt more left alone in their lives than now – and the question comes up: "Why me or why my child?" Nevertheless, there will always be hope. Especially for concerned children, a lucky childhood should be in the foreground. Too many examinations and visits to the doctor are very time intensive and do not solve the problem of gene mutation within a few months. Therefore it is advisable that parents are sensitive with their children, but educate them to mature independently and self-confidently in their teenage years. Open handling of the disease and exchange of experiences can help coping with life, although it is unlikely to meet someone with the same seldom disease personally. There's a variety of concerned people with similar diseases, who can give advice. There are different self-help association united in the "ACHSE" association – an alliance of chronically seldom disorders (web: http://www.achse-online.de). It also offers the European counterpart "EURORDIS" – the voice of people with seldom diseases in Europe. Contact and support can be found here. Especially the internet offers immense help of getting into contact with people from outsides. Even social networking has found its way into seldom diseases, and a lot of specific groups can be found there. Beyond there are networks specially made for people with seldom diseases, e. g. "RareConnect". The website http://www.rareconnect.org by "EURORDIS" is a platform where patients with seldom diseases can build up online communities

and can exchange their experiences beyond boarders and language barriers. The website of “My Retina Tracker” http://www.myretinatracker.org offers detailed possibilities to create your own disease profile, e. g. to find concerned people more easily. It also offers a possibility to doctors to search for patients for their research.
For concerned patients and their relatives, who have been confronted by childhood, there is still hope to wait for results in research and clinical studies and to find a doctor who can interpret them related to his patients.

Contact

PRO RETINA Deutschland e. V.
Self-help organization of people with macular degeneration

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with auto-didactical acquired knowledge about the disease
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Landhausweg 3
72631 Aichtal / Germany
Phone: +49 7127 96 96 91
Web: http://www.ektodermale-dysplasie.de

Hints on special consultation-hours, Special ambulances or other diagnostic

Patients with that disease presented at the following hospital / medical centers - as far as known to the author.
Furthermore the project <se-atlas> offers a treatment atlas for regional search for people with seldom diseases.
Web: http://www.se-atlas.de/

Specific centers

Universitäts-Augenklinik Tübingen
(University Hospital for Ocular Diseases)
Dr.med. Tonagel
Schleichstraße 12
72076 Tübingen / Germany

Universitäts-Augenklinik Heidelberg
Prof. Dr. Rohrschneider
Im Neuenheimer Feld 400
69120 Heidelberg / Germany

Clinic for Skin Diseases
University Hospital Erlangen
Prof. Dr. med. Kiesewetter

Augenzentrum Siegburg
(Medical Center for Ocular Diseases)
Prof. Dr. U. Keller

Ulmenweg 18
91054 Erlangen / Germany

Europaplatz 3
53721 Siegburg / Germany

Genetic consulting with molecular genetic diagnostics – personally known to the author.

CeGaT GmbH
Paul-Ehrlich-Str. 23
72076 Tübingen / Germany
Phone: +49 7071 565 44 00

There is a huge number of further labs for diagnostic, which can be found with the search form of the <orphanet> portal nationally.
Web: http://www.orpha.net/consor/cgi-bin/ClinicalLabs_Search.php

Information for patients, doctors and other professionals

• Publications on HJMD Syndrome
Investigative Ophthalmology & Visual Science 04/2014 in English
A rare Syndrome: Hypotrichosis with Juvenile Macular Dystrophy (HJMD)
Web: http://iovs.arvojournals.org/article.aspx?articleid=2272128

Orphanet –Portal for seldom diseases and Orphan Drugs 08/2011
Hypotrichosis - juvenile Makular degeneration
Web: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=de&Expert=1573

• Publications about function of CDH3 gene

OMIM - Database of human genes and genetic diseases 09/2015 in English
CADHERIN 3; CDH3
Web: http://omim.org/entry/114021

Journal of Investigative Dermatology 06/2012 in English
P-Cadherin Regulates Human Hair Growth and Cycling via Canonical Wnt Signaling and Transforming Growth Factor-β2
Web: http://www.nature.com/jid/journal/v132/n10/full/jid2012171a.html

• Publications on “Read-Through Therapy“

Non-technical explanation by
Gesellschaft für Mukopolysaccharidosen e.V.
further therapy approaches:
Web: http://www.mps-ev.de/mps/mukopolysaccharidosen/kausale-therapien-23831/weitere-therapieansaetze

Cambridge University Press 09/2014 in English
Translational read-through as an alternative approach for ocular gene therapy of retinal dystrophies caused by in-frame nonsense mutations.
Web: http://dx.doi.org/10.1017/S0952523814000194

Journal of Clinical & Experimental Ophthalmology 07/15 in English
No STOPS: Translational read-through of nonsense mutations for the treatment of hereditary retinal disorders 07/15
Web: http://www.omicsonline.org/proceedings/no-stops-translational-readthrough-of-nonsense-mutations-for-the-treatment-of-hereditary-

retinal-disorders-27919.html

Johannes Gutenberg-Universität 10/2012
Silver linings for therapy of human Usher-Syndrome
Web: http://www.uni-mainz.de/presse/53509.php

PTC Therapeutics, South Plainfield (New Jersey, USA)
Producer of experimental agent “Ataluren”
Web: http://www.ptcbio.com

The Journal of Clinical Investigation 12/2013 in English
Postnatal manipulation of Pax6 dosage reverses congenital tissue malformation defects
Web: http://www.jci.org/articles/view/70462

Oxford University Press 10/2014 in English
Translational read-through of the RP2 Arg120stop mutation in patient iPSC-derived retinal pigment epithelial cells
Web: http://hmg.oxfordjournals.org/content/early/2014/10/06/hmg.ddu509

Information for doctors and other professionals

Pictures and data provided here for doctors and professionals are related to a young boy, born in 2009 in Southern Germany.
At the time of presenting, aged 5, at the hospitals of Tübingen and Heidelberg in 2014, he already had thin hair, which he had from birth on. For the first time noticeable, he was at a school fitness assessment, where no defective vision was found.
The ocular intensity was within a tolerance range which surely was not applicable. However, a few weeks later an oculist examination showed there was no normal range at all.
Diagnosis: R/L Amblyopia at Ametropia, R/L intense hyperopia, R/L astigmatism, R/L central shift of pigmented layer of retina
An implemented ERG was ordinary, as far as noticeable.
Funduscopic there were intense shifts of pigmented layer of retina in macula. The OCT examination showed a not remarkable fovea configuration.

Picture credits:
Autofluorescence
Web: http://hjmd.de/pkb/Autofluoreszenz_5Jahre.jpg
Fundus copy left eye
Web: http://hjmd.de/pkb/Funduskopie_Links_5Jahre.jpg
Fundus copy right eye
Web: http://hjmd.de/pkb/Funduskopie_Rechts_5Jahre.jpg
OCT pic. Left / right
Web: http://hjmd.de/pkb/OCT_5Jahre.jpg
main hair pic.1
Web: http://hjmd.de/pkb/Haupthaar1.jpg
main hair pic.2
Web: http://hjmd.de/pkb/Haupthaar2.jpg

The suspected diagnosis has been confirmed after recent panel diagnostics CeGaT Eye12-panel at the affected person and appropriate segration analysis of the parents.

Genetic results:
CDH3 gene: 1.) c.316_317delAA; p.Lys106Glufs*12 (heterozygous)

2.) c.1086>A; p.Trp362* (heterozygous)

To 1.) The mutation leads on DNA level to loss of two adenine at position 316 and 317, resulting in shifting the open reading frame. An in that way premature stop codon causes a truncated protein or a “nonsense mediated mRNA-decay”.

To 2.) The mutation also leads to a stop codon and thus to truncated protein or a “nonsense mediated mRNA-decay”.

An exchange at position 1086 from G to A takes place here, TGG in normal sequence becomes TGA and so a stop codon arises.

Normal sequence of CDH-3 gene in >Ensembl Project<
Web:
http://www.ensembl.org/Homo_sapiens/Transcript/Sequence_cDNA?db=core;g=ENSG00000062038;r=16:68670092-68756519;t=ENST00000264012

On website >Ge(h)n mit HSP< another disease that can be caused by nonsense mutation - mechanisms for arising of stop codons - is clearly described.
Web: http://hsp-hilfe.de/medikament-bei-nonsensemutation-entwicklung