3rd EUROPEAN DAYS OF ALBINISM

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PROCEEDINGS
of the

3RD EUROPEAN DAYS OF ALBINISM

Milan - Italy
7th and 8th April 2016

Azienda Ospedaliera
Ospedale Niguarda Ca' Granda

OSPEDALE SAN RAFFAELE

Sistema Sanitario Regione Lombardia

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Scientific and Medical abstracts

Session I: Clinical Definition of Albinism

Expanding the phenotype of albinism?

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Infantile strabismus syndrome

Presented are n=114 patients with infantile strabismus syndrome with no manifest nystagmus and good visual acuity (>0,6) of the dominant eye. We performed Albino-VEPs and found bilateral atypical chiasmal crossing in 22% of these patients, thus suggesting a diagnosis of albinism. Interestingly, in 66% of the patients there where "atypical atypical" chiasmal crossings: stimulation of one eye showed the physiological responses of more fibers remaining ipsilateral, and stimulation of the other eye showed a clear dominance of crossing fibers as opposed to non-crossing fibers. 12% had normal decussations.

In the course of evolution, the eyes have moved from a lateral to a frontal position, thus enabeling the monocular visual fields to overlap resulting in a binocular visual field. In binocular mammals, stereoscopic depth vision is thought to result from a combined effect of three signals emerging from 3 anatomical structures: the ipsilateral temporal hemiretina and the contralateral nasal hemiretina plus the foveal part which is transmitted via the contralateral uncrossed retinal ganglion cell pathway travelling through the corpus callosum. In the strabismic eye, the ipsilateral non-decussating projection from the temporal retina is suppressed, thus leading to hemiretinal suppression of only the temporal retina in viewing conditions with both eyes open.

It is well known that strabismus occurs in inborn diseases accompanied by pathway misroutings such as albinism and hypoplasia or agenesis of the corpus callosum. To our knowledge, unilateral atypical chiasmal crossing has not been associated with infantile strabismus syndrome up to now.

With our clinical and electrophysiological findings, we would like to discuss the possibilities of:

- Clinically very mild albinism showing infantile strabismus syndrome as the most prominent finding (22% of our patients)
- Unilateral atypic chiasmal decussation in one eye and typical chiasmal decussation of the other eye leading to infantile strabismus (66% of our patients).

o Futher studies will have to show whether "atypical atypical" chiasmatic crossing might be a sign of conductors for a gene for albinism

o Perhaps unilateral atypical chiasmal crossing is present much more often in infantile strabismus than previously thought.

o If an albinism conductor state could be demonstrated in strabismic patients with unilateral atypical chiasmal crossing, this could add to the knowledge of hereditary causes of infantile strabismus syndrome.

Patients with aniridia and atypical chiasmal crossing with or without hypopigmentation of the fundus

In a total of 181 patients with aniridia (sporadic / familiar; PAX6 gene related / related to other genes / moleculargenetic analysis not yet finished) we found 16 patients (8,8%) with bilateral atypical chiasmatic routings. Half of the patients show pale skin, blonde or light brown hair and a pale hypopigmented fundus plus small hypoplastic optic nerve heads. Another 4 patiens have normal cutaneous aspects, but a surprisingly hypopigmented fundus, as well accompanied by hypoplastig optic discs. The last group of 4 patients neither shows cutaneous manifestations nor ocular signs of hypopigmentation, in three of these 4 patients the optic nerve head size is normal.

Some of the patients have been examined for the molecular basis of aniridia, and 6 of them show PAX6 mutations. One patient has a defective ELP gene which leads to a dysfunction of PAX6. One patient presented with a CYP1B mutation (usually associated with Peters anomaly and / or congenital glaucoma) and complete aniridia. One patient hat a mutation of FOXC1. The remaining 7 patients did not show mutations in the three most frequent aniridia related genes. One of the patients with a mutation of PAX6 has two cousins with OCA1 (known and tested in our hospital).

Concerning the molecular genetic testing of albinism, three older patients had undergone one of the molecular genetic analyses initiated by us; two did not show any mutations in the genes OCA1 to 4; one patient has a mutation in the P gene associated with OCA2. Interestingly, one of the patients who did not show any mutations in OCA1 to 4 additionally has a complete agenesis of the corpus callosum without intellectual or motor deficits (he is just finishing high school).

With these patients I would like to start the discussion concerning the following questions:

- Might there be a common link between albinism and aniridia? 16 patients from a group of 181 is not a very high frequency, but definitely not just a coincidence.
- Hypopigmentation has sometimes been described in aniridia, but atypical chiasmal routing has not been described – should we add this to the standard evaluation of aniridia patients? Other signs the two inborn genetic diseases share are foveal hypoplasia and optic nerve head hypoplasia.

Phenotypic Spectrum in Fhonda and Albinism

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Albinism is a genetically determined disorder caused by defects in the melanin-biosynthesis pathway. Patients with albinism show a variety of visual defects, of which foveal hypoplasia and optic nerve misrouting have been considered pathognomonic for the disorder. However, these defects may also occur independently of albinism in a condition called FHONDA: Foveal Hypoplasia, Optic Nerve Decussation defects and Anterior segment dysgenesis. In 2013 mutations in SLC38A8 were identified as the cause of FHONDA. Furthermore, it was confirmed that this gene does not affect pigmentation.

To compare the phenotypic spectrum of FHONDA and albinism, we retrospectively investigated the clinical, genetic, and electrophysiological data of 19 patients with FHONDA and 489 patients with albinism. Albinism patients were collected from the databases of Bartiméus and Leiden University Medical Center from 1959 until 2016, FHONDA patients from the Bartiméus database and from the Leeds/Bartiméus study.[2-4]

Mutation analysis was done in 97/489 albinism patients. Diagnosis was genetically confirmed in 9 patients with OA1 (8%), 25 OCA1 (26%), 22 OCA2 (23%), 4 OCA4 (4%), and 1 HPS1 (1%) In 15 patients one mutation in OCA 1 or OCA2 was found and in 21 patients no mutations were found. Mutation analysis was done in 14/19 FHONDA patients, they all had mutations in SLC38A8. In 8 patients with albinism and 1 patient with FHONDA the diagnosis was confirmed by DNA-analysis in an affected family member.

Visual acuity (VA) in albinism ranged from 0.00 logMAR to 1.30 logMAR (mean 0.57). VA in FHONDA ranged from 0.60 logMAR to 1.30 logMAR (mean 0.83) No (0%) FHONDA patients had iris transillumination, compared to 78% of albinism patients. Foveal hypoplasia in FHONDA patients was on average much more severe than in albinism patients.

These observations suggest that FHONDA has a considerable smaller phenotypic spectrum than albinism with statistically significant poorer VA and more severe foveal hypoplasia. The group of FHONDA patients in this study was relatively small; when more patients are known to have the SLC38A8 mutation it will be possible to test this hypothesis. Since DNA-analysis for the SLC38A8 mutation is now available for standard testing, we expect more cases to be identified.

Scientific Session II: Clinical and Molecular Diagnosis of Albinism

Postnatal retinal development in albinism as compared to healthy controls

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Aim: To characterize postnatal retinal development in infants and young children with albinism using hand-held spectral domain optical coherence tomography (HH-SDOCT)

Methods: We obtained 181 mixed cross-sectional and longitudinal optical coherence tomograms from 44 children with a diagnosis of albinism and compared them with 297 tomograms obtained from 148 race-matched controls. The mean postnatal age at the time of examination was 37.8 months (range 0.9 - 83.6) for the albinism group and 37.7 months (range 0 - 83.3) for the control group.

Results: Normal retinal development is nonlinear, continues until adolescence and involves migration of the inner retinal layers (IRLs) away from the central fovea, migration of the cone photoreceptors into the central fovea and elongation of the outer retinal layers (ORLs) over time. In comparison to controls, IRL migration from the fovea is delayed and arrests prematurely in albinism, resulting in a significantly thicker central macular thickness. In contrast, the parafoveal and perifoveal retinal thicknesses were significantly decreased in albinism in comparison to controls. There is evidence of ongoing foveal ORL elongation in albinism, although reduced in amplitude in comparison to controls as a result of significant reductions in the degree of elongation of the photoreceptor inner (IS) and outer segments (OS). The retinal pigment epithelium (RPE) increases in thickness more slowly resulting in a uniform decrease in RPE thickness across all measured retinal locations in albinism.

Conclusion: We have demonstrated that retinal development is not arrested in children with albinism, but is ongoing albeit at a reduced rate and magnitude in comparison to controls. Potentially treatment during this crucial period of residual plasticity may promote normal retinal development and optimise visual function.

Visual cortex in human albinism - anatomy and function

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Human albinism is associated with a hypoplastic fovea and misrouting of the optic nerves [1], i.e. additional crossing of the fibres from the temporal retina at the optic chiasm. Further, the organisation of the visual cortex is significantly altered: (a) Cortex anatomy: A recent morphometric MRI study revealed for albinism (i) a negative correlation of primary visual cortex thickness with visual acuity, (ii) a reduced convolution of the ventral occipital cortex [2]. (b) Functional retinotopic organisation: In a series of studies we demonstrated that the abnormal representation of the temporal retina in albinism (i) is organised as a retinotopic map in the primary and higher visual cortex [3], (ii) is relevant for visual perception [4] (iii) does not interfere with perception in the contralateral visual hemifield [5], and (iv) leaves major lateralisation patterns in the primary motor and the somato-sensory cortex unaffected [6]. While these results demonstrate the impact of albinism on both visual cortex anatomy and functional organisation, they also highlight the potential of cortical plasticity to make abnormal representations available for visual perception [7].

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Contribution of Electrofunctional Examinations in Albinism's Diagnostics

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The genetic inability to melanin synthesis, peculiarity of albinos subjects, produces, in the eye's neurostructures, sensory abnormalities related to the absence of the pigment but also anatomical and functional characteristic alterations.

The Electrofunctional Exams: Electroretinogram (ERG), ERG Pattern (PERG), Multifocal ERG (mfERG) and Visual Evoked Potential (VEP), document the formation and transmission along the visual pathways of the electrical activity generated by neurotransmitters.

The report presents the characteristics of the electrofunctional tests consequent to macular hypoplasia and misrouting of the retino-cortical fibers typical of albinism.

Molecular diagnostic approaches: Targeted sequencing, exome, array-CGH?

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Albinism is a clinically and genetically heterogeneous disorder characterized by nystagmus, hypoplasia of the fovea, and decreased visual acuity, associated with a variable degree of skin, hair and eye hypopigmentation. 19 genes are involved in the various forms of the disease, including oculocutaneous (OCA), ocular (OA, FHONDA) and syndromic (Hermansky-Pudlak, Chediak-Higashi) albinism. Our molecular diagnostic strategy nowadays includes investigations by next generation sequencing (NGS) with an AmpliSeq panel (Life Technologies) covering the exons of 18 genes (the recently identified HPS10/AP3D1 gene is not analyzed as yet). Gross genomic rearrangements are analyzed by high resolution array-CGH. We have analyzed 640 patients. A molecular diagnosis was obtained for 479 (74.8%): 31.8% OCA1; 22.5% OCA2; 2% OCA3; 8.6% OCA4; 2% OCA6; 0.3% OCA7; 5.5% OA1; 0.15% FHONDA; 1.5% HPS1; 0.15% HPS4; 0.75% HPS5; 0.3% HPS6. 10% of patients carried heterozygous mutations and 14.45% had no mutation in any of the known genes. Why 24.45% of patients remain without molecular diagnosis remains unclear. Whereas albinism is considered to be monogenic, our evidence for digenism (*TYR/OCA2*) in one family suggests that oligogenism may account for more cases. Some mutations may be missed by NGS either because they are located deep into introns or distant regulatory elements, or because they are in poorly covered amplicons, as exemplified by a HPS8 homozygous mutation that was only identified after bioinformatics quality filters were alleviated and the sequence was scrutinized closely. It is also likely that more albinism genes remain to be identified. The use of the NGS panel is a very efficient for the diagnosis of albinism since it allows the identification of both point mutations and, at least to some extent, of gene rearrangements. Our experience with exome sequencing to look for new genes will be reported.

Scientific Session III: European Diagnostic Experiences

Clinical and Molecular Diagnostics in Denmark

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In Denmark the clinical diagnosis of albinism is mainly made by the ophthalmologist based on low vision/nystagmus (referral reason), reduced retinal pigment, iris translucency and misrouting of optic nerve fibers. Because of the general light complexion in the Danish population, the skin and hair color often do not differ markedly from the rest of the population. This makes it difficult to distinguish between oculocutaneous albinism (OCA) and ocular albinism (OA). Only individuals with OCA1A might be detected at birth based on lack of skin pigmentation.

Optical aids are offered by the local communities, which also provide an educational consultant for the children during kindergarten and school. Children with albinism are offered regular ophthalmological checkup according to need. The families are also seen by pediatricians at centers for rare diseases. There are two such centers in Denmark.

There is a Danish patient association DFFA (Danish Society for Albinism) funded in 1996 with 130 members. DFFA gives information and arrange two yearly 3-days meetings for members.

Ophthalmological or clinical genetic departments refer for molecular genetic testing. Clinical genetic departments undertake the genetic counseling. The analysis is performed by targeted Next Generation Sequencing. Three gene panels are offered:

- OCA panel: including *TYR*, *OCA2*, *TYRP1*, *SLC45A2*, *SLC24A5*, *C10orf11* and *GPR143*,
- Hermansky-Pudlak, Griscelli and Chediak Higashi syndromes including *AP3B1* , *BLOC1S3, BLOC1S6, DTNBP1, HPS1, HPS3, HPS4, HPS5, HPS6, LYST, MITF, MLPH, MYO5A, RAB27A*
- Nystagmus and fovea hypoplasia with *NYX*, *CACNA1F* and *SLC38A8*

All findings by NGS are verified by Sanger sequencing. MLPA analysis for deletions and duplications is offered for *TYR*, *OCA2, SLC45A2* and *GPR143*. Furthermore, *TYR*, *OCA2*, *TYRP1*, *SLC45A2* and C10orf11 are offered as single gene analysis using Sanger sequencing. Prenatal analysis can be performed although this is rarely requested by individuals of Danish origin (one case).

Clinical and Molecular Experience in Italy

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Oculocutaneous albinism (OCA) is characterized by hypopigmentation of the skin, hair and eye, and by ophthalmologic abnormalities caused by a deficiency in melanin biosynthesis. OCA is commonly subdivided into main four types (OCA1–4) due to mutations in the *TYR, OCA2, TYRP1*, and *SLC45A2* genes, respectively. Recently we introduced OCA6 (*SLC24A5*) mutational screening to implement OCA molecular diagnosis. Ocular albinism type 1 (OA1) is an X-linked form whose phenotype is mainly restricted to eyes and optic system, caused by *GPR143* gene mutations.

A total of 200 OCA or OA affected patients were recruited from the Medical Genetic Unit and the Department of Pediatric Ophthalmology of the Niguarda Ca' Granda Hospital of Milan (Italy) through a multidisciplinary diagnostic workup that included ophthalmologic exams, dermatological and ENT (Ears, Nose and Throat) visits and genetic counselling. Furthermore different Genetic Units and Ophthalmology Centres in Italy contributed to our cohort of albino patients, reaching a total of 321 patients genetically tested. Ophthalmological and instrumental evaluations include: motor and sensory status, visual acuity, refraction, iris transillumination with slitlamp biomicroscope, and macular translucency with indirect ophthalmoscope. Visual acuity assessment for distance and near was evaluated in monocular and binocular vision with appropriate tests (Pigassou figures, Teller acuity cards, E test and Snellen charts).

The following instrumental examinations were performed: optical coherence tomography (OCT), visual evoked potential (VEP) and electroretinogram (ERG). Through Spectral Domain OCT were evaluated the macular morphological characteristics with attention to the presence or absence of foveal depression. Electrophysiological tests were performed to evaluate the optic nerve fibers decussation.

The coding regions and adjacent flanking regions of TYR, OCA2, TYRP1, SLC45A2, SLC24A5 and GPR143 genes, associated to the different phenotypes OCA1, OCA2, OCA3, OCA4, OCA6 and OA1, have been analyzed by sequencing analysis. In order to detect the presence of TYR and OCA2 exons rearrangements (deletion/duplication), MLPA (Multiplex Ligation-dependent Probe Amplification) assay was performed.

We report the frequencies of the major causative OCA genes as follows: *TYR* (44%), *OCA2* (17%), *TYRP1* (1%), *SLC45A2* (7%) and *SLC24A5* (<05%). An additional 5% of patients had *GPR143* mutations (OA1). In 19% of cases a reliable second mutation was not detected, while 7% of our patients remain still molecularly undiagnosed. This study of a consecutive series of OCA/OA1 patients allowed us to perform a clinical evaluation of different OCA forms.

Albino Day in Madrid

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Albinism is a group of rare inherited disorders genetically and phenotypically heterogeneous. Classically albinism was understood as hypopigmentation but nowadays visual impairment defines the condition, together or not with hypopigmentation of skin, hair and/or eyes. Therefore, it is now recommended to carry out a clinical multidisciplinary evaluation of albinism.

In order to promote these multidisciplinary approach in Spain, the first clinical day on albinism was held in Spain in October 2015, being a similar initiative to that are periodically developing in Bordeaux and Milan. The Albino Day in Madrid was organized in the Jimenez Diaz Foundation Hospital (FJD) by the Spanish Centre for Biomedical Network Research on Rare Diseases (CIBERER) and the Spanish National Center for Biotechnology (CNB-CSIC), in collaboration with the Spanish Association in Support of People with Albinism (ALBA). The main aim of this event was to meet and train health professionals to advance in the clinical diagnosis of this rare genetic condition.

Four people suffered from different types of albinism (suspicion of OCA1, OCA2, OCA4 and OA, respectively) had the opportunity to be visited in one day by dermatologists, ophthalmologists, geneticists and hematologists. This talk will focus on our Albino Day experience and the integrated findings from the interdisciplinary clinical assessment and the subsequent genetic studies of these patients.

A closer collaboration between all the parties (patients, clinicians, researchers, associations, ...) involved in the process is allowing the development of more accurate protocols and a clinical guide in Spanish to manage diagnosis of albinism. We expect that together these initiatives transcend in better overall care of these patients. An early diagnosis and an appropriate genetic counseling, providing not only a better individualized treatment and monitoring of people with albinism, but also access to the benefits of an accurate diagnosis.

Albino day hospital: a multidisciplinary approach helping for diagnosis and management of the patients

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Oculocutaneous albinism (OCA) is a rare autosomal recessive disorder characterized by diffuse hypopigmentation associated with ophthalmological abnormalities including retinal hypopigmentation, foveal hypoplasia and misrouting of optic nerves. Syndromic forms include Hermansky-Pudlak (HPS) and Chediak-Higashi syndrome.

Methods: The patients are evaluated at Bordeaux University Hospital, based on a multidisciplinary day hospital programme which has been approved by the institution in 2013 and implemented in 2014. Dermatological, genetic and ophthalmological assessments are scheduled over one day. Skin photographs are systematically taken, and blood is taken for molecular and hematological testing when necessary. All the data (dermatology, ophthalmology, genetics) are collected in a standardized form filled by the physicians. A summary is made at the end of the day and shared with the patient.

Results: We have evaluated 34 patients (12 boys and 23 girls): 25 Europeans, 3 originating from Cameroun, 1 from Turkey, 1 from Morocco, and 1 from Iran. The mean age of the patients ranged from 3 months to 74 years (mean age: 25 years). 29 patients were characterized at the molecular level: 10 patients were found to be *OCA1*, 9 *OCA2*, 7 *OCA4*, 1 *HPS1*, 1 *HPS5* and 1 *OA1*. A large *OCA2* deletion, *HPS1* and *HPS5* mutations had never been described. White hair was observed in 12 patients including 4 *OCA1* and 5 *OCA4*. Skin cancer complications were observed in 2 *OCA1* patients, 1 *OCA2* and 1 *OCA4*. Foveal hypoplasia was absent in 3 patients for which molecular analysis was negative. Regarding *HPS* patients, the only associated finding noted was easy bruising.

Discussion: In this OCA population, the degree of hypopigmentation ranges from a total lack of pigment to a moderate pigmentary dilution. In our series, *OCA4* patients are presenting with a marked hypopigmentation as initially described in *OCA1* patients. The degree of pigmentary dilution could be related to the mutated gene but also to the type of mutation as shown by clinical heterogeneity among *OCA1* patients. The absence of foveal hypoplasia seems to decrease the probability to find a mutation in a known OCA gene. Further studies are required in order to establish a link between the level of photoprotection and early appearance of actinic damage and skin cancer. In this mostly European fair skinned population, the number of pigmentary nevi seems to be an independent inherited trait that could modulate the risk of malignancy.

Conclusion: OCA is a clinically and genetically heterogeneous disorder. An accurate clinical delineation of the phenotype is essential to improve our knowledge of the disorder. Molecular data will help to establish phenotype-genotype correlation and guide the follow-up especially for syndromic OCAs such as HPS.

Scientific Session IV: Pathogenesis of Albinism

Understanding visual defects in albinism using mouse and cellular models

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Several visual defects associated with albinism, such as poor visual acuity or altered depth perception, are consequences of abnormal retinal development. We have shown using a mouse model of albinism, the C57BL/6 *Tyr* $^{c\text{-}2J/c\text{-}2J}$ strain, that fewer retinal ganglion cells (RGCs) projecting to the same side of the brain (ipsilateral) and more RGCs projecting to the opposite side of the brain (contralateral) are generated. This results in modified and unbalanced projections to the brain that could explain the altered depth perception found in patients with albinism. More recent results suggest that RGC neurogenesis is delayed in albino mice and could explain why fewer ipsilateral RGCs are produced at a given time during development. Using both in vivo and in vitro models, we now aim to understand the cellular mechanisms of retinal development altered in albinism.

Syndromic albinism disorders affecting membrane trafficking during melanosome formation

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Melanin is synthesized and stored in skin and eye pigment cells within membrane-bound organelles called melanosomes. Many albinism patients have mutations in the genes encoding enzymes, transporters, or structural components that facilitate melanin synthesis within melanosomes. However, several diseases – including the 10 known variants of the Hermansky-Pudlak syndrome (HPS) – result from gene mutations that impact the delivery of these and other tissue-specific proteins to newly forming melanosomes or additional "lysosome-related" organelles in other cell types. The genes that are targeted in HPS encode subunits of four distinct multi-subunit protein complexes called AP-3 and BLOC-1, BLOC-2 and BLOC-3. I will present data identifying the sites of action of each of these complexes in the transport of melanogenic proteins to maturing melanosomes. In particular, BLOC-1 promotes the generation of tubular membrane transport carriers that emerge from endosomes, are targeted specifically to maturing melanosomes through the action of BLOC-2, and ferry newly synthesized melanogenic cargoes to the maturing melanosomes. By studying a factor that is required for fusion of these carriers with melanosomes, VAMP7, we have found that BLOC-3 regulates a pathway required for the recycling of membranes from melanosomes back to the endosomes. This pathway is required in some pigment cells to promote new rounds of forward trafficking, resulting in secondary forward trafficking defects in those pigment cell types; in other pigment cell types, however, forward trafficking continues normally, resulting in enlarged melanosomes. Since VAMP7 is likely shared among lysosome-related organelles in multiple cell-types, our findings not only explain albinism in HPS patients, but likely also apply to the formation of other lysosome-related organelles that are affected in the disorder.

Melanosomal ion channels critical for pigmentation

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Pigment cells contain melanosomes, unique lysosome-related organelles that produce and store melanin, the major pigment in animals. The oculocutaneous albinism II gene (OCA2) encodes a melanosome-specific transmembrane protein critical for pigmentation. We characterize the physiological properties of OCA2 in skin and eye melanosomes and found that OCA2 functions as an anion channel that affects melanin synthesis by regulating melanosomal pH. We also identified two-pore channel 2 (TPC2), previously implicated in human pigmentation and melanoma via an unknown mechanism, as the first reported melanosomal cation channel. We demonstrate that the vesicular signaling lipid phosphatidylinositol bisphosphate PI (3,5) P_2 modulates TPC2 activity to control melanosomal pH, and increase pigmentation. Our studies suggest that melanosomal pH is a key regulator of melanogenesis controlled by a complex mechanism that might be deficient in different forms of oculocutaneous albinism.

Scientific Session V: Beyond Eyes

Oculocutaneous albinism in East and Southern Africa

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The frequency of oculocutaneous albinism type 2 (OCA2) is relatively high in populations throughout sub-Saharan Africa. The hypopigmentory phenotype makes them visibly different from their dark-skinned peers. People with albinism in Africa are triply vulnerable: their pale skin makes them highly susceptible to sun induced skin damage, they are visually impaired, and often marginalised in their communities. The prevalence of OCA varies between and within countries. An epidemiological study of 1.3 million schoolchildren in Zimbabwe gave an overall frequency of 1 in 4000 for this central African country, with a carrier frequency of 1 in 33; the values varied between different regions of the country, with hotpots in the capital city (1 in 2660) and in geographically isolated groups such as a group of Tonga people in the Zambezi River Valley (1 in 1000, with a carrier rate of 1 in 16). The male to female ratio at primary school was 1.04, as predicted, but at secondary school the value was 1.25, significantly different from the expected ratio. Across the southern border from Zimbabwe, in northern South Africa, a retrospective study of birth records gave an incidence of OCA2 at birth of 1 in 1970 amongst the rural Venda people.

A current study to analyse the data on albinism from the 2012 census in Tanzania will be reported. In this and other parts of east and central Africa those with albinism have been targeted for their body parts for use in rituals and charms erroneously believed to bring wealth and good fortune, making albinism a topical political issue in the region.

Examples of using evidence from research studies to inform advocacy efforts will be considered, including the development of posters, information booklets and radio dramas to inform and educate communities about albinism.

The importance of obtaining information on the number, age, gender and distribution of those with albinism will be discussed, as it impacts directly on governmental and non-governmental educational, health and welfare policies.

Skin photoprotection issues in albinism

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The severity of skin pigment dilution is a good starting point to assess clinically skin photoprotection issues. The spectrum of skin hypopigmentation is quite large with in general patients with OCA1 and 4 with the most severe hypopigmentation. The other important risk factor especially in European populations is the number of nevi, which is not clearly related to the albino trait, but may constitute an independent risk factor. A family history of nevi, freckling and melanoma should be taken into account in an albino patient, and molecular markers of risk such as CDKN2A mutations as well as germline "red" variants in MC1R could be assessed in case of positive family history. The need to perform cutaneous phototesting to assess more precisely responses to UV is discussed. In cases with mild cutaneous albinism, performing a minimal erythemal dose finding may reassure the patient and help to adapt adequately photoprotective measures.
The environment of the patient is another key issue. The risk of actinic keratosis and basal or spinous cell carcinoma (BCC/SSC) is well established in OCA2 sub-saharan populations. In general, this risk is limited in Caucasian populations whatever the genotype. Assessment of photoprotection in sun exposed countries is important. History taking assesses usually easily number of severe sunburns. Skin palpation in addition to inspection allows to detect actinic keratoses. Dermoscopic evaluation is of limited interest in case of high pigment dilution. Clinically some areas appear as good markers of photoprotective habits such as the nape of the neck, which shows premature photoaging when photoprotection is limited. The optimal skin photoprotection required in countries with moderate sun exposure needs clearly more research, including vitamin D status. Limited biological data exists on the presence of non functional melanocytes in the epidermis versus the risk of cutaneous cancer. In contrast with vitiligo, where depigmentation results from a loss of melanocytes and is associated with a raised level of immune surveillance against melanocytic antigens, the risk of skin cancer seems clearly increased in albinism. The role of melanocytic membranes as providers of prooxidant molecules under UV exposure is considered. Compared to SSC/BCC, melanoma risk seems low based on epidemiologic studies in OCA2 in Africa, suggesting that melanin is by itself an important risk factor for melanoma, as also demonstrated in mouse models. As a general recommendation, sunburn needs to be strictly avoided, but non erythemogenic exposure of skin is probably not conveying at very high risk, as compared with that noted in DNA deficient patients xeroderma pigmentosum.

Dermatological characterization in Italian albinos

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Oculocutaneous albinism (OCA) is characterized by hypopigmentation of the skin, hair and eye, and by ophthalmologic abnormalities caused by a deficiency in melanin biosynthesis. OCA is commonly subdivided into main four types (OCA1–4) due to mutations in the TYR, OCA2, TYRP1, and SLC45A2 genes, respectively. Recently we introduced OCA6 (SLC24A5) mutational screening to implement OCA molecular diagnosis.

In OCA patients skin hypopigmentation causes severe photosensitivity and increase risk of developing sun-induced skin cancer. This implies the need for albino patients of accurate dermatological controls during the lifetime.

A total of 200 unrelated albino subjects were recruited from the Medical Genetics Unit and the Department of Pediatric Ophthalmology of the ASST Niguarda Hospital of Milan through a multidisciplinary diagnostic workup including ophthalmologic exams, dermatological and ENT (Ears, Nose and Throat) visits and genetic counselling. Albino patients were carefully examined by well-trained dermatologists. Besides traditional dermatological examination by epiluminescence light microscopy (ELM), digital epiluminescence was employed in order to evaluate lesions at higher definition and magnification with a better diagnostic accuracy. At dermatological examination actinic keratosis were detected in sun-exposed areas of three adult patients (from 30 to 50 years old). They were topically treated by specific drugs. A case of malignant cutaneous melanoma was identified on the right leg of a 40 years old male histologically classified as superficial spreading, Clark level 4, Breslow 0.8. Promptly sent to the surgical department he underwent specific treatment protocol. The same patient had multiple actinic keratosis on the face and also on the back of the hands. In spite of the lack of melanin, skin pigmented lesions were present in most of the adult patients, the majority of which were benign (common naevi and angiomas), without submicroscopic and vascular atypias. The aim of the dermatological examination was to detect pigmented skin lesions and sunlight damages in albinos and to give them correct information about sun exposure in current life. Thanks to these dermatological controls three cases of actinic keratosis and one case of melanoma were identified and treated in four adult patients. Adequate photo protection by sunscreens and dietary supplements were recommended to all patients together with periodic dermatological checks.

Audiological deficits in albinos: correlation with genetic/clinical phenotype

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As well as in the eye the mechanism by which the melanin may have a role as protective function on the light absorption and dissipation, so in the inner ear it seems related to the possibility to interact with the sound waves in a protective way. In this study we have performed the ENT evaluation and the audiometric test to a group of albino patients. In the ENT we look for the presence of nystagmus and facial district malformations. By audiological tests it was investigated the presence of neurosensory hearing loss, looking for the threshold at different frequencies from 250 Hz up to 8000 Hz. In the younger group up to 5 years old we used behavioural audiometry and conditioned play audiometry that don't require a active collaboration of the child. Between all the 147 patients investigated we have found in 15 adult's patients over 37 year old a neurosensory deficit on frequencies between 2000 and 8000Hz. This patients, selected by genetic phenotype, were 8 OCA1 (out of 25), 2 OCA2 (out of 8), 1 OCA3(out of 1), 2 OCA4(out of 5) and 2HPS (out of 3) of 42 patient aged more than 37 years old. In the younger patients we have found only few hearing loss caused by catharral inflammation. They were investigated after on their personal history of working and hobby noise exposure, finding this in 3 patients as working related and in 2 other as a hobby related. The normal population, not noise exposed, has a physiological decrease of hearing over 65 year (presbycusis) and the mean age of our albino with hearing loss (46) was much lower than this. It would appear from our study confirmed that in the albino there is a defect of hearing protection probably linked to the lack of melanin in the inner ear, which shows itself with a neurosensory hearing loss on high frequencies in adulthood. From our point of view, this study is also an opportunity to inform patients about the prevention of hearing damage that could occur, and following up this patients with constant audiometric tests to better determine the age of onset of the first signs and eventually the worsening with the progress of the age.

Scientific Session VI: Technical Support and Therapeutic Frontiers

Visual management training in low vision patients

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Albinism does not alterate life expectancy and the disease does not worsen during growth, but it could have implications on the learning, emotional and social development.

An early abilitative-rehabilitative course, along with a moral and psychological support to the family and a collaboration with the school, can help the child better compete with his/her peers, by developing an "archive of images" related to the visual experiences; the motivated adult uses his/her visive residue at its maximum to engage autonomously into social, cultural and professional life.

Pharmacological therapy

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Patients with oculocutaneous albinism (OCA) have decreased best-corrected visual acuity due, at least in part, to hypoplasia of the fovea, a highly specialized region of the neurosensory retina. Because foveal development continues after birth, we posit that children identified as having albinism at birth could benefit from interventions that promote foveal development. At present, we do not understand how mutations in various melanin-pigment-related genes expressed in the retinal pigment epithelium and the choroid of the eye lead to non-cell-autonomous effects on retinal development. However, we hypothesize that improving the process of melanin deposition in melanosomes during development may aid in the formation of the fovea.

We have previously shown that oral administration of an FDA-approved drug, nitisinone, is capable of improving the melanin pigment in the fur and eyes of a mouse model of one form of albinism, OCA1b, caused by hypomorphic alleles of the tyrosinase gene. We are currently conducting a one year pilot clinical trial of 2mg/day oral nitisinone in five adults (ages, 24-52; 3 female, 2 males) with molecularly-proven OCA1b. Visual acuity, contrast sensitivity, iris transillumination, fundus pigmentation, electroretinograms, and foveal morphology have been documented at baseline and are being documented at pre-specified intervals (3, 6, 9, and 12 months). Skin melanin content is similarly quantified using skin reflectometry, hair is collected for biochemical analysis of melanin, and qualitative changes in hair and skin are photographed. The last patient to complete the year of treatment will be complete in September 2016. To avoid bias, data will be analyzed after all data are collected. In parallel, we have ascertained if nitisinone improves the melanin pigment in a mouse model of OCA3 (*Tyrp1* mutation) and OCA4 (*Slc45a2* mutation). Preliminary data indicate that nitisinone does not have a clinically-significant effect in our model of OCA3, but does improve melanin content in melanosomes of our OCA4 mouse model. Lastly, in an effort to find compounds that may stabilize tyrosinase (and therefore improve its folding) and/or activate its enzymatic activity, we have purified the intramelanosomal portion of human wild-type and mutant forms of tyrosinase and performed enzymology. In collaboration with the National Center for Advancing Therapeutics, we have screened 10,770 compounds at a single dose (115μM) wild-type enzyme. Nine compounds have potential activator activity, while 115 are potential inhibitors. These compounds are currently undergoing more detailed enzymatic screening and confirmation in tertiary model systems.

Defining safety and efficacy end-points for OCAI gene therapy-based clinical studies

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Recently, we and others have demonstrated that gene therapy with Adeno-associated virus (AAV) vectors is safe and effective in patients affected with the blindness retinal disease, Leber congenital amaurosis (LCA) type 2. LCA2 is caused by mutations in the RPE65 gene, which is expressed in the retinal pigment epithelium (RPE). In addition, the availability of AAV vector serotypes such as AAV2/4, which efficiently targets the RPE, further supports the use of AAV-based gene therapy for the treatment of RPE-specific ocular disorders . Oculo-cutaneous albinism type 1 (OCA1) is characterized by congenital hypopigmentation and is due to mutations in the *TYROSINASE* gene (*TYR*). We characterized the ocular morpho-functional consequences of the lack of tyrosinase activity in the spontaneous null mouse model of OCA1 (*Tyrc-2j*) and showed that adult *OCA1* mice have several postnatal retinal functional anomalies. AAV vector delivery of the *TYR* gene to the RPE resulted in melanosome biogenesis and *ex novo* synthesis of melanin. Furthermore, ocular melanin accumulation rescued postnatal retinal function defects. Considering the low risk showed by the AAV-based LCA2 trials, retinal gene therapy clinical studies may be envisaged also for ocular diseases whose clinical severity is reasonably low, such as OCA1. These aspects together with the AAV-based proof-of-concept on OCA1 model enable to propose critical issues for a potential gene therapy-based OCA1 clinical translational study, including pre-clinical testing (toxicological studies), vector production (Good-Manufactory-Production; GMP) clinical protocol (safety and efficacy end-points) and costs. OCA1 patient will be engaged in the discussion of these issues.

New animal models of albinism generated with CRISPR tools

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Animal models have been generated and used since many years for the study of numerous human diseases, including human rare diseases such as albinism. Our laboratory has been contributing to this field with diverse transgenic mice that have been instrumental for our current understanding of some types of albinism, like oculocutaneous albinism type I (OCA1), associated with mutations in the TYR locus. We have used transgenic animals, mainly mice, to define the entire TYR expression domain, its borders, its crucial DNA regulatory elements responsible for the faithful expression of the gene and, also, to investigate the visual abnormalities that are diagnostic and hence characteristic of all types of albinism. However, traditional animal transgenesis has been often suboptimal, providing mutations that were easy to generate in the mouse genome however uncommon in the human population. This situation has entirely changed with the appearance of the CRISPR-Cas tools, derived from an immune system in bacteria and archaea. These innovative tools drive double strand breaks into specific genomic locations, thus triggering the corresponding cellular endogenous repair. Thereafter, depending on the presence of exogenous DNA template or not, the result of the repair mechanisms will lead to the correction or establishment of mutations, to the edition of the genome or the generation of targeted alterations, respectively. We have applied successfully CRISPR-Cas strategies for preparing new and informative mouse models of different types of albinism. Particularly, we have used CRISPR-Cas approaches to inactivate and functionally assess the relevance of non-coding genomic sequences in albinism-related loci, directly on their corresponding endogenous loci, for the first time. This presentation will review our efforts and ongoing experiments using CRISPR-Cas genome-edited mice aiming to further progress into our understanding of albinism.