ACDA NOTES

From The Alveolar Capillary Dysplasia Association

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Dear Friends and Family,

We have so much news to share! Progress is being made in the ACD research arena as you will read in this newsletter, but additional funding is required to find the answers. We hope you will be inspired to do your own fundraising after reading about our ACDA families in the United Kingdom that continue to be so successful at fundraising.

Finally, we have many new families that have joined the ACDA in the last three months. Please reach out and introduce yourselves.

Fondly,

Steve and Donna Hanson
Executive Directors, ACDA
Parents of Eric – June 7-17, 1997

INSIDE

Fundraising Soars at Thomson Airways

By [redacted], Mom to [redacted]

As you all know, I work for a UK airline and they have decided to have The David Ashwell Foundation as the charity that we collect for on each flight into London's Gatwick Airport from May 2012 until October 2013.

As of November 2012, my colleagues have collected £19964.65 which is roughly the equivalent of $30,000 (US)! Amazing amounts!

I am currently working in the Recruitment Department and the Training team has asked all of the charity's that the bases collect for, to send in brochures and pamphlets about their charity so that they can educate the new recruits for the summer season.

As the David Ashwell Foundation is very tiny in comparison to some of the charities that the other bases collect for, we do not have this information. So, I have volunteered to go and talk about where the money raised goes and that it is in aid of our ACD Angels.

I have five talks planned up to the end of May so hopefully I can educate the new crew on what to convey to the passengers! I know it's not the happiest talk that I will have to give, but I am proud that our little Angels are being remembered each day, and we are doing good for research into such a cruel condition that has affected all of us.

I will let you all know in the next edition how it all goes and hopefully, there will be no tears!

See page 5 for more fundraising news!

RESEARCH NEWS

By Diana Locke
ACDA Research Committee Chairperson

Recent Research Publications

Novel FOXF1 mutations in sporadic and familial cases of Alveolar Capillary Dysplasia with Misaligned of Pulmonary Veins imply a role for its DNA binding domain - Partha Sen PhD, Assistant Professor; Director, Molecular Core lab, Department of Pediatrics at the Baylor College of Medicine has informed us that this paper has been accepted as a mutation update in the journal "Human Mutation." This was a global collaboration as the article discusses patients from four continents, eleven countries and thirteen U.S. states. There are more than fifty co-authors. They report a total of 38 mutations including four that were published in 2009 (Stankiewicz et al). Most of these mutations are sporadic with approximately 10% being familial. They are currently pursuing five new cases and two of them already have been identified with mutations. One of these cases is also familial. The authors are trying to include these cases in the manuscript as well. (A copy of this article is not yet available.)

A novel mutation in FOXF1 gene associated with Alveolar Capillary Dysplasia with Misalignment of Pulmonary Veins, Intestinal malrotation and annular pancreas – Dr. Sen co-authored another paper that was published in February 2013. This is a collaboration with doctors from Portugal. The patient described in this article is one of the patients described in Dr. Sen's paper above. This is a case report and provides more information about this particular patient. It is published in the medical journal "Neonatology 2013;103:241–245 ."

Abstract from the Paper: Alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) is a rare, fatal, neonatal developmental lung disorder, which usually presents as persistent pulmonary hypertension unresponsive to treatment. The authors report: the case of a neonate with persistent pulmonary hypertension, associated with duodenal stenosis secondary to annular pancreas and intestinal malrotation. Support treatment, inhaled nitric oxide, oral sildenafil and nebulized iloprost were used with no clinical improvement. The neonate presented an overwhelming course, with hypoxemia refractory to treatment. At autopsy lung histology showed the characteristic features of ACD/MPV. DNA sequence analysis revealed a heterozygous nonsense mutation c.539C>A;p.S180X, in the first exon of *FOXF1* . *FOXF1* has been identified as one of the genes responsible for ACD/MPV associated with multiple congenital malformations. This clinical case is the first report of a heterozygous nonsense mutation c.539C>A;p.S180X in the first exon of *FOXF1* , in a patient with ACD/MPV associated with annular pancreas and intestinal malrotation.

Radio Interviews for ACD Help Raise Awareness

Ft. Worth/Dallas radio newsman Gordon Griffin interviewed Dr. Becky Sharp and nurse (and ACDA Mom) Diana Locke about Alveolar Capillary Dysplasia. It aired on two AM stations & one FM station in the Dallas/Ft. Worth metroplex recently. The interview aired on the following stations:

1160 AM KVCE - http://www.kvceradio.com/
660 AM The Answer KSKY - http://www.660amtheanswer.com/
The Word 100.7 KWRD - http://www.thewordfm.com/

The interviews were aired in the middle of the night so if anyone happened to catch one or better yet, recorded one of the interviews, please share them! Thanks to Cami McCraw (aunt to Bella) who coordinated the interview and Diana for their continued efforts to raise awareness of ACD.

Status of Research Funded by the ACDA via NORD

Your contributions and fundraising have resulted in two grants to be awarded for ACD research through the National Organization for Rare Disorders (NORD).

NORD Grant #1
Partha Sen PhD, Assistant Professor;
Director, Molecular Core lab,
Department of Pediatrics at the Baylor College of Medicine

Dr. Sen has started working on his project funded through NORD. The title of the project is "To investigate the role of FOXF1 in lung development, particularly with respect to Alveolar Capillary Dysplasia with Misalignment of Pulmonary Veins." This work is in the early stages of a two year grant funded by our restricted research grant at NORD.

NORD Grant #2
Przemyslaw Szafranski PhD
Department of Molecular and Human Genetics
Baylor College of Medicine

From Dr. Szafranski: Mutations and deletions of the *FOXF1* gene have been found in ACD/MPV patients (Stankiewicz et al. *American Journal of Human Genetics* 2009; Sen et al. *Human Mutation* 2013), and studies using mouse as a model organism showed that *Foxf1* haploinsufficiency can result in ACD/MPV-like phenotype (Kaliniczenko et al. *Developmental Biology* 2001). These findings laid foundation for research leading to development of prenatal diagnostic tests and therapeutic applications for ACD/MPV. However, equally important remains identification of (1) the regulators of the *FOXF1* expression, (2) its downstream targets in the lungs, and (3) other ACD/MPV genes functioning in signaling pathways other than that of *FOXF1*.

Towards this goal, we identified deletions on chromosome 16q24.1 overlapping 250 kb upstream of *FOXF1* in several ACD/MPV patients with *FOXF1* gene intact. These deletions define a protein-gene desert that remotely regulates *FOXF1* expression (Szafranski et al. *Genome Research* 2013). We also found that this genomic region contains three *loci* for long non-coding RNAs (lncRNAs) that are expressed at higher levels in the lungs than in majority of other organs. This finding opens new direction in research on the etiology of ACD/MPV and brings us to one of the fastest developing and most exciting fields of contemporary biology dealing with structure and function of non-coding RNAs. LncRNAs (RNA molecules longer than 200 nt with little or no protein-coding potential) are the most enigmatic of all non-coding RNAs, and are often referred to as the Dark Matter of the genome. The portion of the genome responsible for protein coding constitutes only about 1.5%. Surprisingly, the majority of the remaining portion, mapping to the intra- and intergenic regions, is still transcribed producing RNAs which are, in general, not translated into proteins, but play important regulatory functions. In contrast to the small non-coding RNAs, lncRNAs are poorly conserved and regulate chromatin structure and gene expression by diverse mechanisms that are not yet fully understood. The emerging picture shows them as *cis*- and *trans*-regulators of gene activity that function as scaffolds for chromatin-modifying complexes and other regulatory factors, as enhancers and as mediators of long-range chromatin interactions. We are working on deciphering the role of the lncRNAs transcribed from loci 250 kb upstream of *FOXF1* in early lung development and how their loss can lead to ACD/MPV. In particular, we are asking whether and if so how they regulate expression of *FOXF1*.

Most recently, we identified a deletion in the intron of *FOXF1* in a patient with fully developed ACD/MPV. An intron is a part of a gene that does not code for any part of the protein product of the particular gene and is removed from mRNA following gene transcription in the process of RNA splicing. The identified ACD/MPV intronic deletion did not affect the splicing pattern of *FOXF1* to the point that would explain extend of the observed decrease of *FOXF1* expression in this ACD/MPV case. This suggests that the intron plays regulatory role in *FOXF1* expression. We are currently elucidating the nature of this regulation. It is possible that the intron harbors an enhancer sequence, or miRNA gene that suppresses the expression of a *FOXF1* suppressor, or, following its splicing, functions as a regulatory lncRNA needed for *FOXF1* expression. Of note, according to other studies (Nakaya et al. *Genome Biology* 2007), as much as 74% of protein-coding genes generate intragenic lncRNAs that map to intronic regions.

Our studies linking lncRNAs to ACD/MPV and the finding that *FOXF1* intron regulates *FOXF1* expression, although still in their early stages, have already important implication for prenatal diagnosis of ACD/MPV and other congenital diseases in general. Diagnostic procedures currently in use almost exclusively focus on protein-coding genes whereas point mutations or genomic copy number variation occur not only within coding sequences (exons), but also in non-coding genomic regions including regulatory sequences such as promoters, enhancers, insulators, and in non-protein coding *loci* including lncRNA genes. Finding these genomic regions is of primary importance for early ACD/MPV diagnosis and development of effective therapies.

FAMILY SUPPORT NEWS

By Kim Anderson Bush
ACDA Family Support Committee Chairperson

Coping with infant loss is a life-long journey that changes you forever. Your perspective on life and the world around you is different, as if you look suddenly see the world through differently-colored glasses. Seeking comfort, a way to ease this journey, a way to honor your child, is one of the ways to process the loss. There are many charitable organizations whose mission is to comfort families who have lost children, and many were started by families who have experienced child loss and want to provide some comfort, knowing how difficult a journey this is. Here are just a few:

Molly's Bears - Molly's Bears was started by a family after the loss of their daughter, Molly. They make a bear the exact birth weight of your child as a way of comforting the family after their loss. Be aware, there is a waiting list for the bears. Their website is: www.mollybears.com. They can also be found on facebook: www.facebook.com/mollybearsorg.

Seashore of Remembrance - In honor of her son Christian, Carly Marie does incredible photography of the seashore at sunset and will write your child's name in the sand. There is no charge for the picture, but there is a small fee if you want to buy the digital rights to it to be able to use it. She also produces calendars, cards and other items specifically dealing with the loss of a child. There is often a waiting list for the sunset names, so watch for her to open up the waiting list (facebook seems like the best way to find out when the waiting list is open) Websites are as follows:
http://carlymarieprojectheal.com
http://theseashoreofremembrance.blogspot.com.au
www.facebook.com/CarlyMarieProjectHeal.com

FUNDRAISING NEWS

By Emily & Tim Eschweiler
ACDA Fundraising Committee Chairpersons

Many of you have posted on the ACD Parent Group page on Facebook that you would like additional information about Alveolar Capillary Dysplasia. There is exciting ongoing research. However, medical research requires funds. Let's show the medical community that we care about this issue. Here are some ways (small and large) that you can help:

- Include the link to the NORD online donation site (https://www.rarediseases.org/about/support/research-donations/fq_base_view_p3) on your Facebook page or another website. Make sure that you ask your friends and family to select "alveolar capillary dysplasia" from the restricted fund drop down.
- Sell an item on eBay that you no longer need and send the proceeds of the auction to NORD.
- If you know someone who sells a product that offers opportunity for fundraisers, book a show, or an eshow. (If the organization needs to be a 501(c)(3) organization to be a recipient of the funds, contact me and I can put you in touch with someone at NORD who should be able to help you get the money directed to the correct research fund balance.)
- Start collecting things now for a summer garage sale.
- Visit the CafePress site (http://www.cafepress.com/acdawareness) - Also, if you have an upcoming walk and would like to design a t-shirt or buttons to the site, please let me know (emily_eschweiler@comcast.net). I would be happy to work with you on that. The price is likely to be slightly lower than purchasing directly without setting up a shop, and the 10% commission goes to support research. Win-win!

As always, please feel free to contact me if you have any fundraising ideas! - Emily

Report from The David Ashwell Foundation

Amelia Ashwell Lake and Simon Ashwell, Parents of David

Donations to ACD Research via The David Ashwell Foundation have been continuing. Since March 2011, we have raised £89,712 ($136,730) for ACD Research. £33,118.00 ($52,053) was transferred in February to NORD and over £56,593 ($86,253) has been raised **since** the NORD transfer in February 2012. To have raised this amount in memory of David and other babies is phenomenal and goes towards helping heal my loss (Amelia).

This phenomenal amount is in part due to the amazing efforts of [redacted] and [redacted] who nominated The David Ashwell Foundation as Thomson Airline's local charity in memory of their son [redacted] (see lead article on front page). [redacted] and [redacted] have also raised money in memory of their son, [redacted] (please see their article). Also, in Scotland [redacted] and [redacted] are raising money in memory of their son [redacted].

Over Christmas, a number of individuals selected to donate to the charity rather than send Christmas cards. This included Simon's hospital department who rather than send cards at work raised over £200.00 for ACD research. Stamp donations continue to come through! Thank you all for your contributions. In April there will be a coffee morning in aid of the charity in our area. A church whose hall we use for our Woman's Institute (WI) meetings heard about David and our charity and have

contacted us. It's simply lovely to have this happen.

All UK families are welcome to use The David Ashwell Foundation as a means of fundraising for ACD Research. If you live in the UK (and elsewhere), there are a number of options available for funding ACD research through The David Ashwell Foundation.

1. You can make a donation directly, using the Virgin Money giving website to gather donations for your fundraiser. http://David Ashwell Foundation
2. Fundraise while you shop (The Giving Machine) (a percentage of what you spend is donated)
3. Fundraise when you ebay (ebay for Charity).
4. Collect postage stamps http://David Ashwell Foundation

For additional information, please contact Simon and Amelia. http://David Ashwell Foundation
davidashwellfoundation@yahoo.co.uk
Amelia's mobile: 07855473686

We are more than happy to hear from other families who would like to use the charity to raise money for ACD Research. All money raised will be transferred to NORD.

I didn't want to kiss you goodbye - that was the trouble - I wanted to kiss you goodnight. And there's a lot of difference.
~Ernest Hemmingway

Fundraising In Memory of Alan

From [redacted] and [redacted]
Parents of [redacted]

On the 8 July 2012 our beautiful baby boy, [redacted], was born. Sadly, only 11 days later Baby [redacted] was taken away from us, due to Alveolar Capillary Dysplasia. In memory of Baby [redacted], [redacted], Baby [redacted]'s dad and 14 of his friends - [redacted] - are walking the West Highland Way, a 96 mile hike over 5 days from Milngavie to Fort William in Scotland. All funds raised will be donated to the David Ashwell Foundation. The current sponsorship raised with a month to go is at £1,300.00 ($1,950 US).

Thanks [redacted] and [redacted]!

Fundraising in Memory of [redacted]

From [redacted] and [redacted] [redacted]
Parents of [redacted]

Both [redacted] and I have been overwhelmed by the generosity of people when they hear [redacted]'s story and when they hear about ACD. Since we first found out that [redacted] was ill, we have had a lot of support from our family and local community. While we spent three weeks in hospital with [redacted], our local convenience store started a collection for [redacted]. Over the two weeks that they did the collection, they raised £436 ($660 US). Once we found out that [redacted] had ACD, we decided that this money should be donated to help find out the answers that we all want and need.

When we had [redacted]'s memorial service, we decided that rather than family and friends bring flowers with them, we would ask for donations towards The David Ashwell Foundation. We collected £806 ($1,220 US) and we continue to receive donations when people hear [redacted]'s story.

In addition, [redacted] works for our local water company and they hold an annual raffle at Christmas time. Each year the reception team chooses a different charity for the raffle to be in aid of and they chose The David Ashwell Foundation. The raffle raised £436 ($660 US).

[redacted] has always been into cars and one of his aunties, [redacted], regularly attends car meets where she has a huge number of friends who have all heard [redacted]'s story. While at the car meet, [redacted] walks around with a bucket asking for 'Nuggets for [redacted]'. So far, [redacted] has raised £150 ($227) and is continuing to collect throughout the year.

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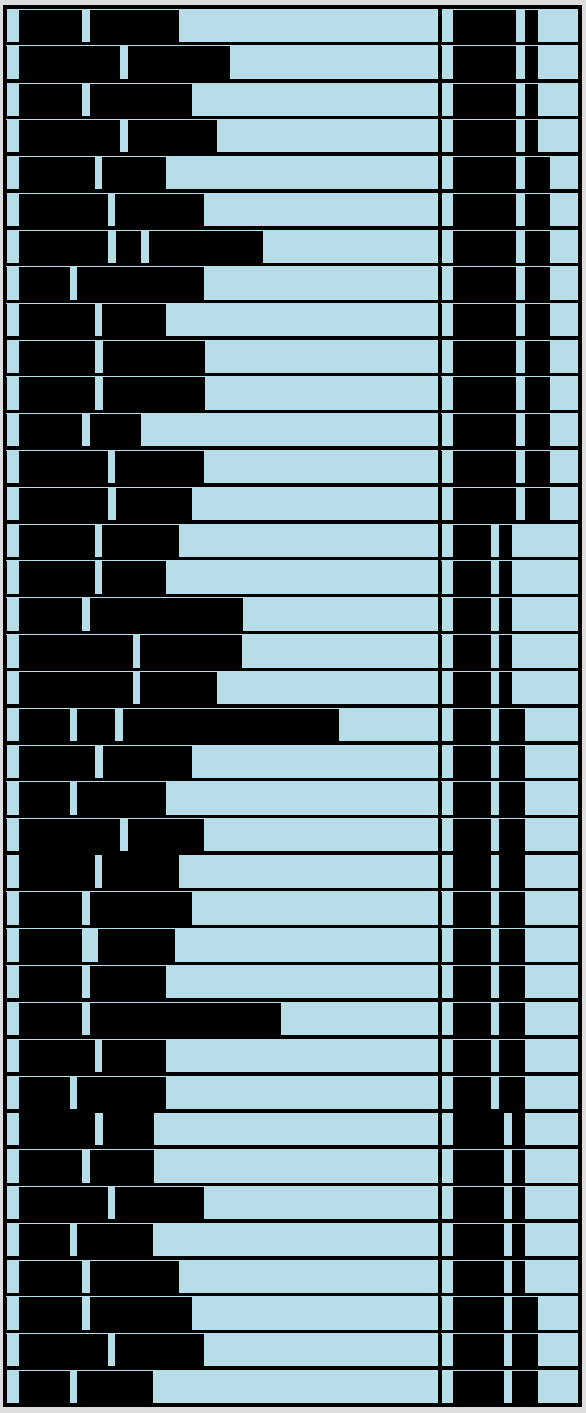
Many thanks to the [redacted], [redacted] and their friends and family who have raised $2,767!

These Are My Footprints

These are my footprints, so perfect and so small.
These tiny footprints never touched the ground at all.
Not one tiny footprint, for now I have my wings
These tiny footprints were meant for other things.
You will hear my tiny footprints, in the patter of the rain
Gentle drops like angel tears, of joy and not from pain.
You will see my tiny footprints, in each butterflies lazy dance
I'll let you know I'm with you, if you give me just a chance.
You will hear my tiny footprints, in the rustle of the leaves
I will whisper names into the wind and call each one that grieves.
Most of all these tiny footprints are found in mummy's heart
Cause even though I'm gone now, we'll never truly part.

- **As of February 19, 2013, our ACD restricted research account balance was $1,270.**
- **Copies of our new ACDA brochure have been sent to Partha Sen at Baylor College of Medicine. If you would like to have some for your fundraiser or to share with your local hospitals, contact us. To see the new tri-fold brochure, visit**
  http://www.acd-association.com/documents/ACDA%20Brochure.pdf

Remembering Our Babies



New Families

[redacted]

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[redacted]

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[redacted]

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[redacted]

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[redacted]

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[redacted]

- …to an anonymous ACDA member who donated $250 to the ACDA. We used part of the donation to move the ACDA website to another website hosting service and paid for three years of web hosting for the site.
- …to [redacted], mom to [redacted], who researched and found 23 articles on ACD in medical journals from 2011 - 2013! References and links to these new articles can be found at on our website at http://www.acd-association.com/journal_articles.php.

Make a Tax-deductible Contribution for ACD Research

In the spring of 2002, the ACDA established an ACD Research Account at NORD. This means that your contribution to NORD can be earmarked specifically for ACD research. As stated below in *NORD's Rare Disease Clinical Research Program Policy*, NORD requires that a research account reach $33,500 before it will initiate the grant process to award research money to the medical community. Therefore, the goal of the ACDA is to raise more than $33,500 for research.

To make a tax-deductible contribution to NORD for ACD research either by mail or on the NORD website, please use one of the instructions:

***** Make a Donation by Mailing a Check *****

- **Please make your check payable to "NORD - Alveolar Capillary Dysplasia Restricted Research Fund" to earmark your donation for ACD research.**
- **In the memo section of the check or on a separate note attached to the check, state that the donation is "in memory of (name of child)."**
- **Your family and friends can attach a note to their check with your name and address and NORD with promptly notify you of their gift.**
- **Send your check to the following address:**

National Organization for Rare Disorders, Inc.
P.O. Box 1968
Danbury, CT 06813-1968 USA

The most critical part of this process is ensuring that your check is made out to "NORD - Alveolar Capillary Dysplasia Restricted Research Fund" to ensure that your donation is earmarked for our ACD Research Account.

***** Make a Donation on the NORD Website *****

Go to https://www.rarediseases.org/about/support/research-donations. Select "Alveolar Capillary Dysplasia" in the research fund pull-down menu and complete the rest of the form. In the "Additional Comments" box, type "Alveolar Capillary Dysplasia Restricted Research Account."

Special Information for Families Living Outside of the United States

NORD recommends that families living outside of the United States use a credit card to make a donation since it costs less to convert international currency when using a credit card. Use the NORD website at https://www.rarediseases.org/about/support/research-donations.

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