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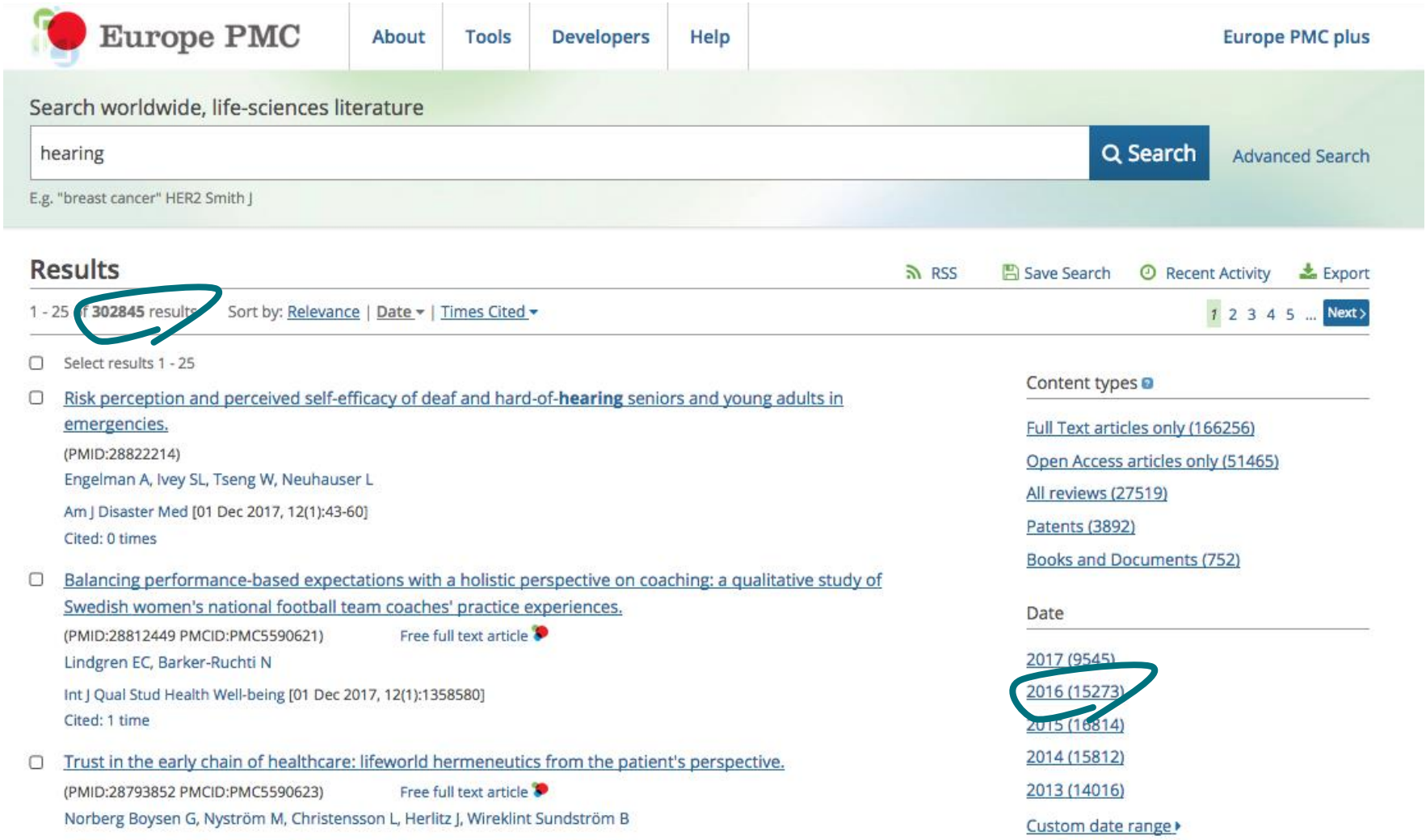

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☐ The CD2 isoform of protocadherin-15 is an essential component of the tip-link complex in mature auditory hair cells.
(PMID:24940003 PMCID:PMC4119359)

Abstract | Citations | BioEntities | Related Articles | External Links

Pepermans E[1], Michel V[1], Goodyear R[2], Bonnet C[3], Abdi S[4], Dupont T[1], Gherbi S[5], Holder M[6], Makrelouf M[7], Hardelin JP[1], Marlin S[5], Zenati A[7], Richardson G[2], Avan P[8], Bahloul A[1], Petit C[9]

Affiliations

EMBO Molecular Medicine [17 Jun 2014, 6(7):984-992]

Type: Research Support, Non-U.S. Gov't, research-article, Journal Article
DOI: 10.15252/emmm.201403976

Abstract

Protocadherin-15 (Pcdh15) is a component of the tip-links, the extracellular filaments that gate hair cell mechano-electrical transduction channels in the inner ear. There are three Pcdh15 splice isoforms (CD1, CD2 and CD3), which only differ by their cytoplasmic domains; they are thought to function redundantly in mechano-electrical transduction during hair-bundle development, but whether any of these isoforms composes the tip-link in mature hair cells remains unknown. By immunolabelling and both morphological and electrophysiological analyses of post-natal hair cell-specific conditional knockout mice (Pcdh15ex38-fl/ex38-fl Myo15-cre+/-) that lose only this isoform after normal hair-bundle development, we show that Pcdh15-CD2 is an essential component of tip-links in mature auditory hair cells. The finding, in the homozygous or compound heterozygous state, of a PCDH15 frameshift mutation (p.P1515Tfs*4) that affects only Pcdh15-CD2, in profoundly deaf children from two unrelated families, extends this conclusion to humans. These results provide key information for identification of new components of the mature auditory mechano-electrical transduction machinery. This will also serve as a basis for the development of gene therapy for deafness caused by PCDH15 defects.

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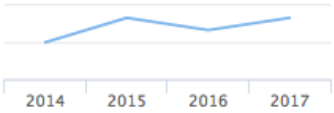

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Christine Petit

Unité de Génétique et Physiologie de l'Audition, Institut Pasteur, Paris, France UMRS 1120, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France Université Pierre et Marie Curie (Paris VI), Paris, France Syndrome de Usher et autres Atteintes Rétino-Cochléaires, Institut de la vision, Paris, France Collège de France, Paris, France cpetit@pasteur.fr.

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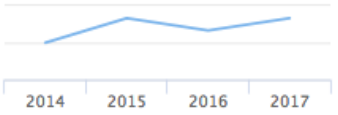

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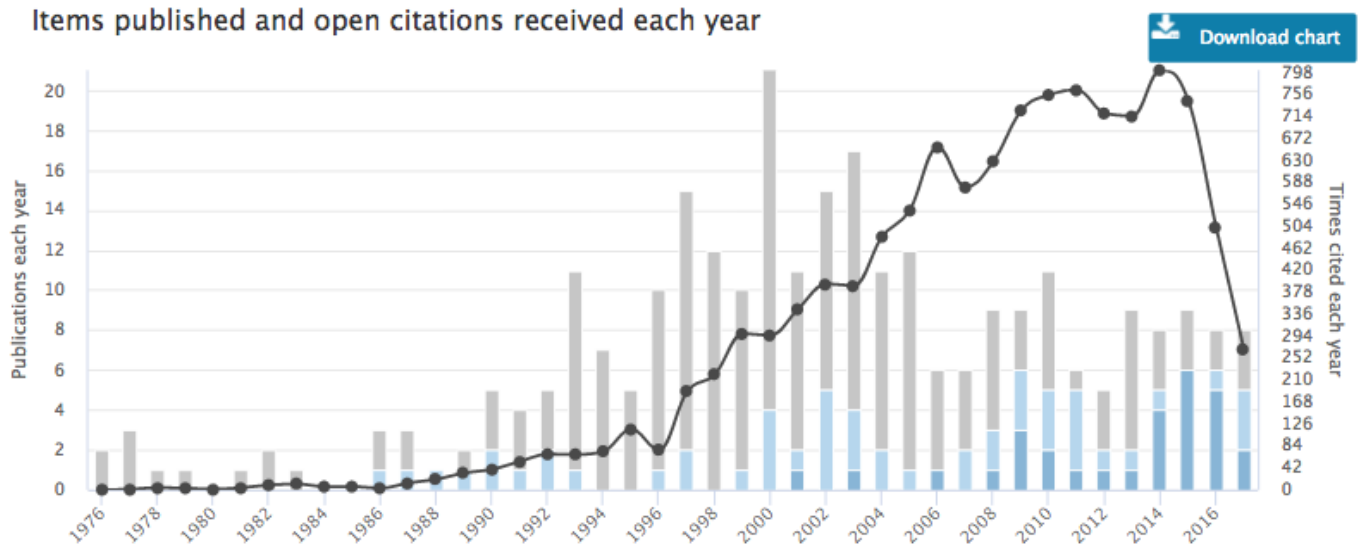

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Publications

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A novel mutation in the potassium channel gene KVLQT1 causes the Jervell and Lange-Nielsen cardioauditory syndrome.

Neyroud N, Tesson F, Denjoy I, Leibovici M, Donger C, Barhanin J, Fauré S, Gary F, Coumel P, Petit C, Schwartz K, Guicheney P

Nat Genet [01/02/1997, 15(2):186-189]

PMID:9020846

KCNQ4, a novel potassium channel expressed in sensory outer hair cells, is mutated in dominant deafness.

Kubisch C, Schroeder BC, Friedrich T, Lütjohann B, El-Amraoui A, Marlin S, Petit C, Jentsch TJ

Cell [01/02/1999, 96(3):437-446]

PMID:10025409

Loss-of-function mutations in FGFR1 cause autosomal dominant Kallmann syndrome.

Dodé C, Levilliers J, Dupont JM, De Paepe A, Le Dû N, Soussi-Yanicostas N, Coimbra RS, Delmaghani S, Compain-Nouaille S, Baverel F, Pêcheux C, Le Tessier D, Cruaud C, Delpech M, Speleman F, Vermeulen S, Amalfitano A, Bachelot Y, Bouchard P, Cabrol S, ...

Nat Genet [10/03/2003, 33(4):463-465]

PMID:12627230

Prelingual deafness: high prevalence of a 30delG mutation in the connexin 26 gene.

Denoyelle F, Weil D, Maw MA, Wilcox SA, Lench NJ, Allen-Powell DR, Osborn AH, Dahl HH, Middleton A, Houseman MJ, Dodé C, Marlin S, Boulila-ElGaïed A, Grati M, Ayadi H, BenArab S, Bitoun P, Lina-Granade G, Godet J, Mustapha M, ...

Hum Mol Genet [01/11/1997, 6(12):2173-2177]

PMID:9336442

Is it an important paper?

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(PMID:24940003 PMCID:PMC4119359)

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☐ TMIE is an essential component of the mechanotransduction machinery of cochlear hair cells.
(PMID:25467981)
Zhao B, Wu Z, Grillet N, Yan L, Xiong W, Harkins-Perry S, Muller U.
Neuron [2014]

☐ A precisely defined role for the tip link-associated protein TMIE in the mechanoelectrical transduction channel complex of inner ear hair cells.
(PMID:25475183)
Liedtke W.
Neuron [2014]

☐ Subunit determination of the conductance of hair-cell mechanotransducer channels.
(PMID:25550511)

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(PMID:24940003 PMCID:PMC4119359)

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Funding

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- Diseases
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- Organisms

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What is it about?

Protocadherin-15 (Pcdh15) is a component of the tip-links, the extracellular filaments that gate hair cell mechano-electrical transduction channels in the inner ear. There are three Pcdh15 splice isoforms (CD1, CD2 and CD3), which only differ by their cytoplasmic domains; they are thought to function redundantly in mechano-electrical transduction during hair-bundle development, but whether any of these isoforms composes the tip-link in mature hair cells remains unknown. By immunolabelling and both morphological and electrophysiological analyses of post-natal hair cell-specific conditional knockout mice (*Pcdh15*$^{ex38\text{-}fl/ex38\text{-}fl}$ *Myo15-cre*$^{+/-}$) that lose only this isoform after normal hair-bundle development, we show that Pcdh15-CD2 is an essential component of tip-links in mature auditory hair cells. The finding, in the homozygous or compound heterozygous state, of a *PCDH15* frameshift mutation (p.P1515Tfs*4) that affects only Pcdh15-CD2, in profoundly deaf children from two unrelated families, extends this conclusion to humans. These results provide key information for identification of new components of the mature auditory mechano-electrical transduction machinery. This will also serve as a basis for the development of gene therapy for deafness caused by *PCDH15* defects.

To probe the role of Pcdh15-CD2 in mature hair bundles, a post-natal hair cell-specific conditional knockout mouse model, *Pcdh15*$^{ex38\text{-}fl/ex38\text{-}fl}$*Myo15-cre*$^{+/-}$ mice, was generated. Conditional post-natal deletion of exon 38, specific to the Pcdh15-CD2 isoform, circumvented the early morphogenetic defects caused by the absence of this isoform during hair-bundle development (Webb *et al*, 2011; see Methods and Supplementary Fig S4). The auditory function of these mutant mice was probed by *in vivo* audiometric tests, which explore the activities of IHCs and OHCs. At the onset of hearing, on P15, auditory function, measured as auditory brainstem responses (ABRs), was identical in *Pcdh15*$^{ex38\text{-}fl/ex38\text{-}fl}$*Myo15-cre*$^{+/-}$mice (referred to as conditional Pcdh15Δ'CD2 mice) and their *Pcdh15*$^{ex38\text{-}fl/ex38\text{-}fl}$ littermate controls. By P17, ABR thresholds in the mutants started to increase, and by P30, they were above 90 dB SPL across the frequency spectrum tested (5–40 kHz). By P45, the conditional Pcdh15Δ'CD2 mice lacked any identifiable ABR response to loud sound stimulation (115 dB SPL), indicating complete hearing loss and fully defective IHCs. Distortion-product otoacoustic emissions (DPOAEs), which involve OHC MET channel function (Avan *et al*, 2013),

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- [ ] Diseases
- [x] Gene Function (3)
- [ ] Gene Ontology
- [x] Gene-Disease OpenTargets (11) ›
- [x] Genes/Proteins (107) ›
- [x] Organisms (34) ›

‹ Genes/Proteins (107)

- Pcdh15 (43) ...
- CD2 (36) ...
- PCDH15 (12) ...
- CD1 (4) ...
- protocadherin-15 (2) ...
- cadherin-23 (2) ...
- Protocadherin-15 (1) ...
- P15 (1) ...
- P21 (1) ...
- actin (1) ...
- GJB2 (1) ...
- MYO15A (1) ...

Where is the primary data?

Table 2

LPS biosynthesis loci obtained from sequenced genomes of *L. pneumophila* Sg1 strains

Strain	mAb subgroup	Accession no.	Reference
Alcoy 2300/99	Knoxville	GenBank: NC_014125.1	28]
Corby	Knoxville	GenBank: NC_009494.2	29]
L10/23 (Ulm)*	Knoxville	EMBL: HF545881	his study
Uppsala 3*	Knoxville	EMBL: HE980445	his study
Paris	Philadelphia	GenBank: NC_006368.1	30]

Where do I find these?

Supplementary Data

Supplementary Data

Which is what?

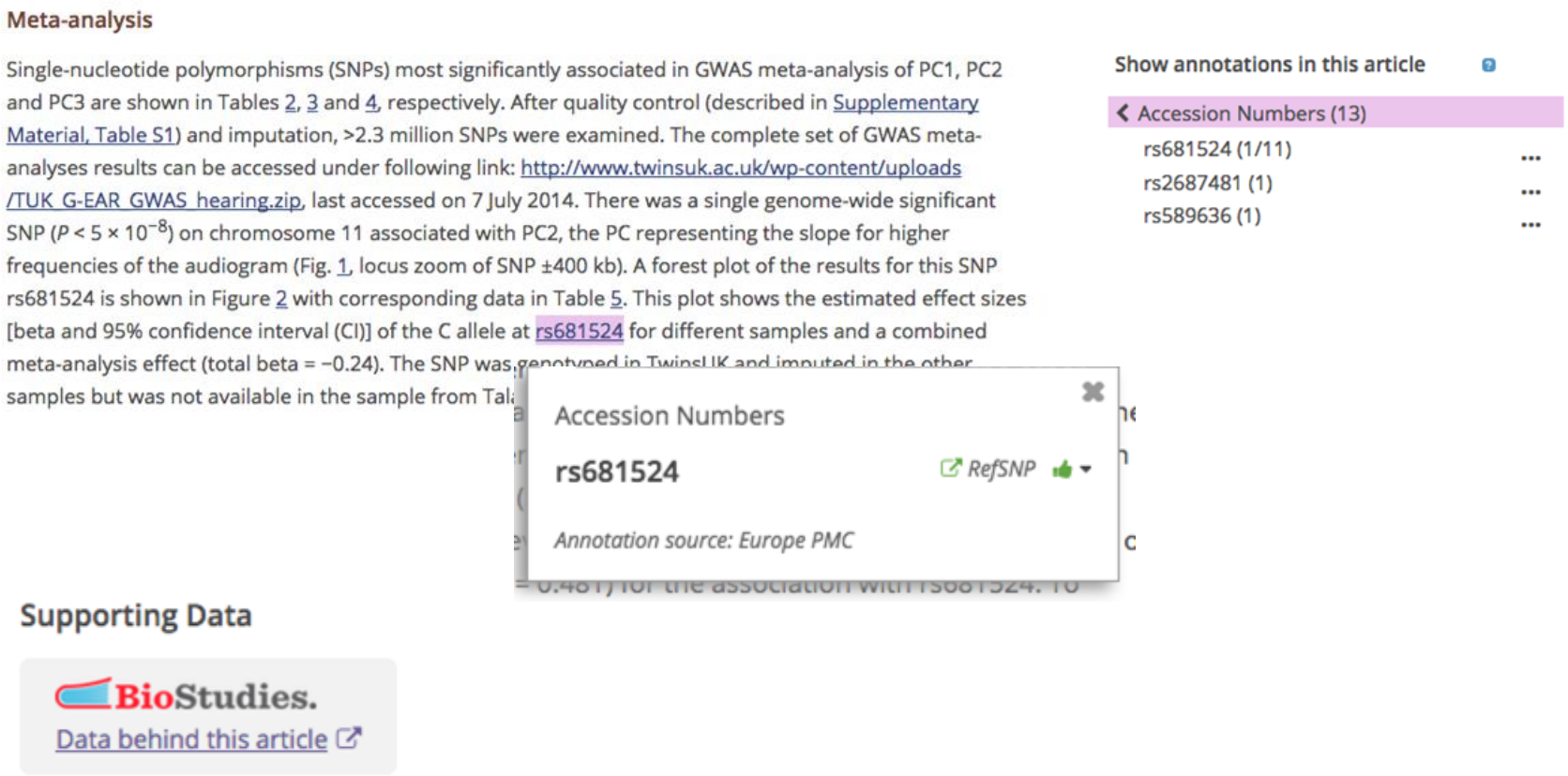
Files in this Data Supplement:

- Supplementary Data - Supplementary Data
- Supplementary Data - Supplementary Data
- Supplementary Data - Supplementary Data

So many links!

Single-nucleotide polymorphisms (SNPs) most significantly associated in GWAS meta-analysis of PC1, PC2 and PC3 are shown in Tables 2, 3 and 4, respectively. After quality control (described in Supplementary Material, Table S1) and imputation, >2.3 million SNPs were examined. The complete set of GWAS meta-analyses results can be accessed under following link: http://www.twinsuk.ac.uk/wp-content/uploads/TUK_G-EAR_GWAS_hearing.zip, last accessed on 7 July 2014. There was a single genome-wide significant SNP ($P < 5 \times 10^{-8}$) on chromosome 11 associated with PC2, the PC representing the slope for higher

Where is the primary data?



Where is the primary data?

BioStudies.

Time-course global proteome analyses reveal an inverse correlation between Aβ burden and immunoglobulin M levels in the APPNL-F mouse model of Alzheimer disease

Wang H[1], Williams D[1], Griffin J[1], Saito T[2], Saido TC[2], Fraser PE[3], Rogaeva E[4], Schmitt-Ulms G[5]

[1]Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada. [2]Laboratory for Proteolytic Neuroscience, RIKEN Brain Science Institute, Hirosawa, Wako-shi, Saitama, Japan. [3]Department of Medical Biophysics, University of Toronto, Toronto, Canada. [4]Department of Medicine (Neurology), University of Toronto, Toronto, Canada. [5]Department of Laboratory Medicine & Pathobiology, University of Toronto, Toronto, Canada.

Accession Number

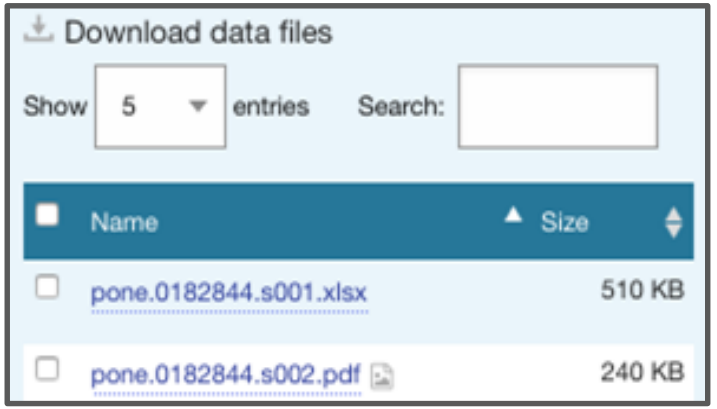
S-EPMC5568403

Title

Time-course global proteome analyses reveal an inverse correlation between Aβ burden and immunoglobulin M levels in the APPNL-F mouse model of Alzheimer disease.

Abstract

Alzheimer disease (AD) stands out amongst highly prevalent diseases because there is no effective treatment nor can the disease be reliably diagnosed at an early stage. A hallmark of AD is the accumulation of aggregation-prone amyloid β peptides (Aβ), the main constituent of amyloid plaques. To identify Aβ-dependent changes to the global proteome we used the recently introduced APPNL-F mouse model of AD, which faithfully recapitulates the Aβ pathology of the disease, and a workflow that interrogated the brain proteome of these mice by quantitative mass spectrometry at three different ages. The elevated Aβ burden in these mice was observed to cause almost no changes to steady-state protein levels of the most abundant >2,500 brain proteins, including 12 proteins encoded by well-confirmed AD risk loci. The notable exception was a striking reduction in immunoglobulin heavy mu chain (IGHM) protein levels in homozygote APPNL-F/NL-F mice, relative to APPNL-F/wt littermates. Follow-up experiments revealed that IGHM levels generally increase with



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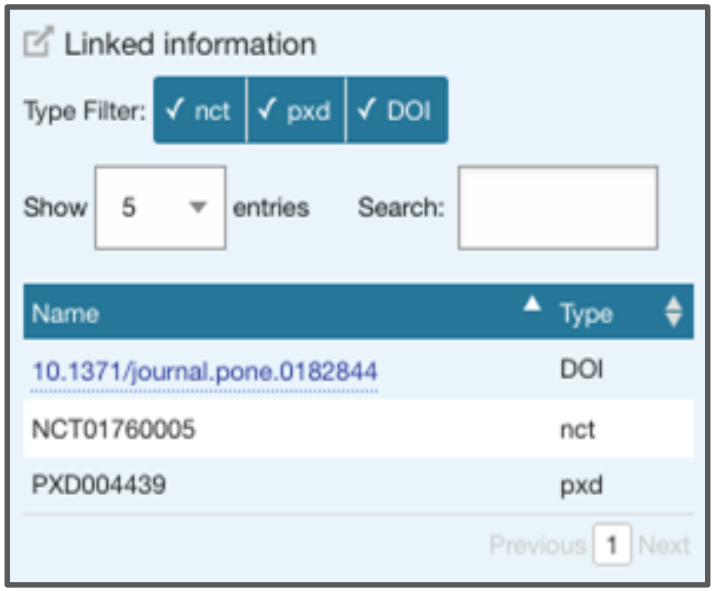

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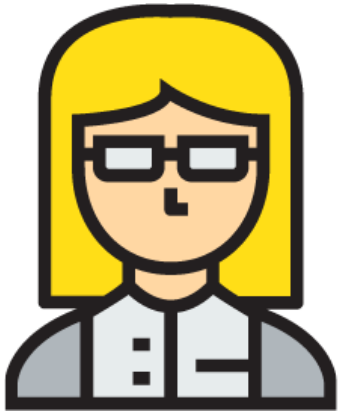

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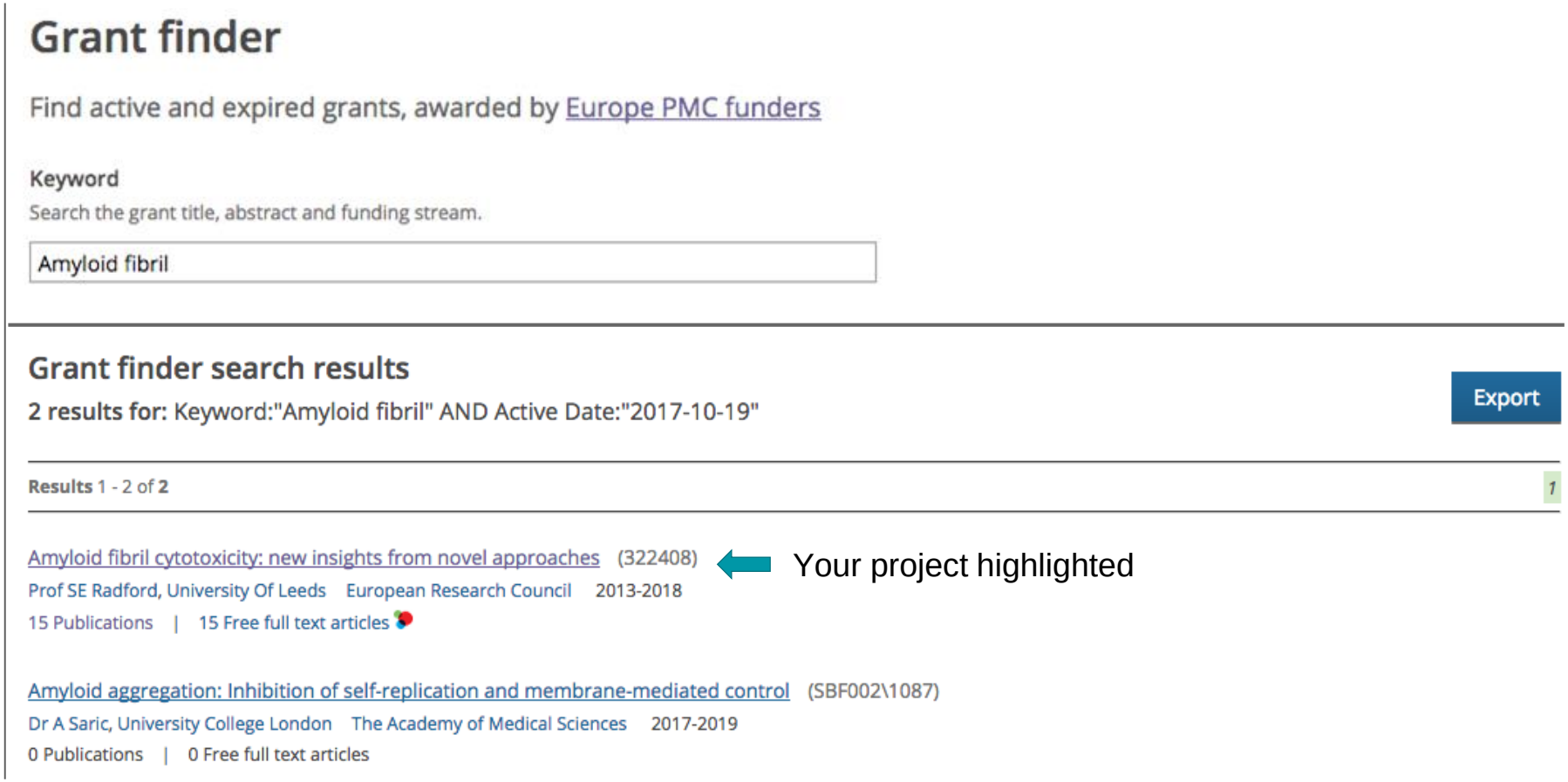

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Dr A Saric, University College London The Academy of Medical Sciences 2017-2019

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Visualization of transient protein-protein interactions that promote or inhibit amyloid assembly.
(PMID:24981172 PMCID:PMC4104025)

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Karamanos TK[1], Kalverda AP[1], Thompson GS[1], Radford SE[2]

Abstract

In the early stages of amyloid formation, heterogeneous populations of oligomeric species are generated, the affinity, specificity, and nature of which may promote, inhibit, or define the course of assembly. Despite the importance of the intermolecular interactions that initiate amyloid assembly, our understanding of these events remains poor. Here, using amyloidogenic and nonamyloidogenic variants of β2-microglobulin, we identify the interactions that inhibit or promote fibril formation in atomic detail. The results reveal that different outcomes of assembly result from biomolecular interactions involving similar surfaces. Specifically, inhibition occurs via rigid body docking of monomers in a head-to-head orientation to form kinetically trapped dimers. By contrast, the promotion of fibrillation involves relatively weak protein association in a similar orientation, which results in conformational changes in the initially nonfibrillogenic partner. The results highlight the complexity of interactions early in amyloid assembly and reveal atomic-level information about species barriers in amyloid formation.

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Amyloid fibril cytotoxicity: new insights from novel approaches (322408)
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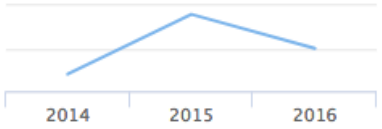

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Amyloid fibril cytotoxicity: new insights from novel approaches

Prof SE Radford, University Of Leeds
View author profile ORCID: 0000-0002-3079-8039

Abstract

Despite the discovery of amyloidosis more than a century ago, the molecular and cellular mechanisms of these devastating human disorders remain obscure. In addition to their involvement in disease, amyloid fibrils perform physiological functions, whilst others have potentials as biomaterials. To realise their use in nanotechnology and to enable the development of amyloid therapies, there is an urgent need to understand the molecular pathways of amyloid assembly and to determine how amyloid fibrils interact with cells and cellular components. The challenges lie in the transient nature and low population of aggregating species and the panoply of amyloid fibril structures. This molecular complexity renders identification of the culprits of amyloid disease impossible to achieve using traditional methods. Here I propose a series of exciting experiments that aim to cast new light on the molecular and cellular mechanisms of amyloidosis by exploiting approaches capable of imaging individual protein molecules or single protein fibrils in vitro and in living cells. The proposal builds on new data from our laboratory that have shown that amyloid fibrils (disease-associated, functional and created from de novo designed sequences) kill cells by a mechanism that depends on fibril length and on cellular uptake. Specifically, I will (i) use single molecule fluorescence and non-covalent mass spectrometry and to determine why short fibril samples disrupt biological membranes more than their longer counterparts and electron tomography to determine, for the first time, the structural properties of cytotoxic fibril ends; (ii) develop single molecule force spectroscopy to probe the interactions between amyloid precursors, fibrils and cellular membranes; and (iii) develop cell biological assays to discover the biological mechanism(s) of amyloid-induced cell death and high resolution imaging and electron tomography to visualise amyloid fibrils in the act of killing living cells.

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Duration
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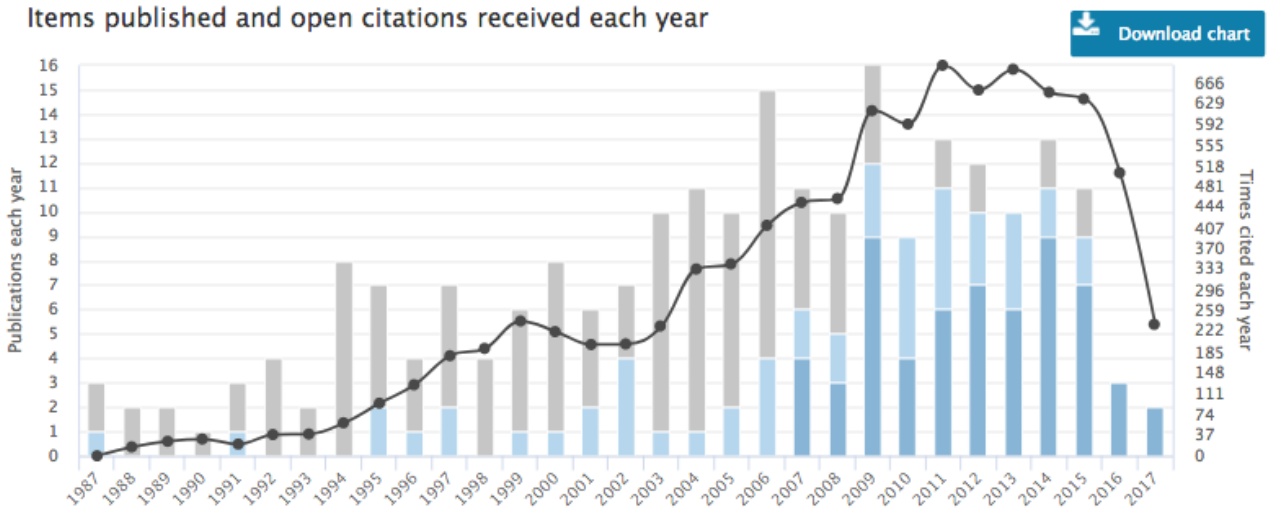

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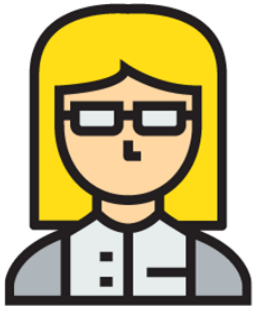

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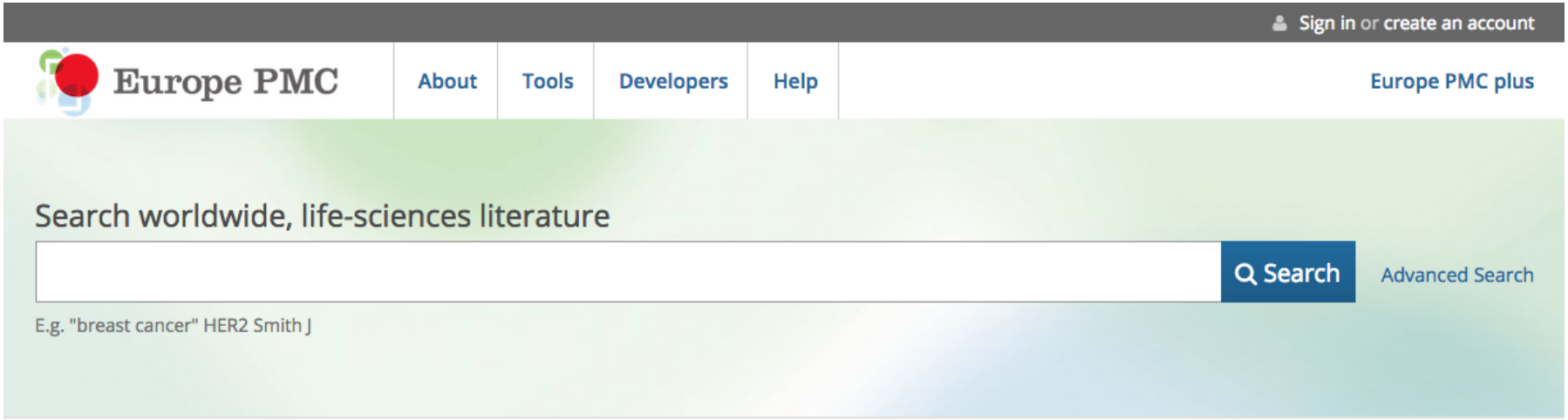

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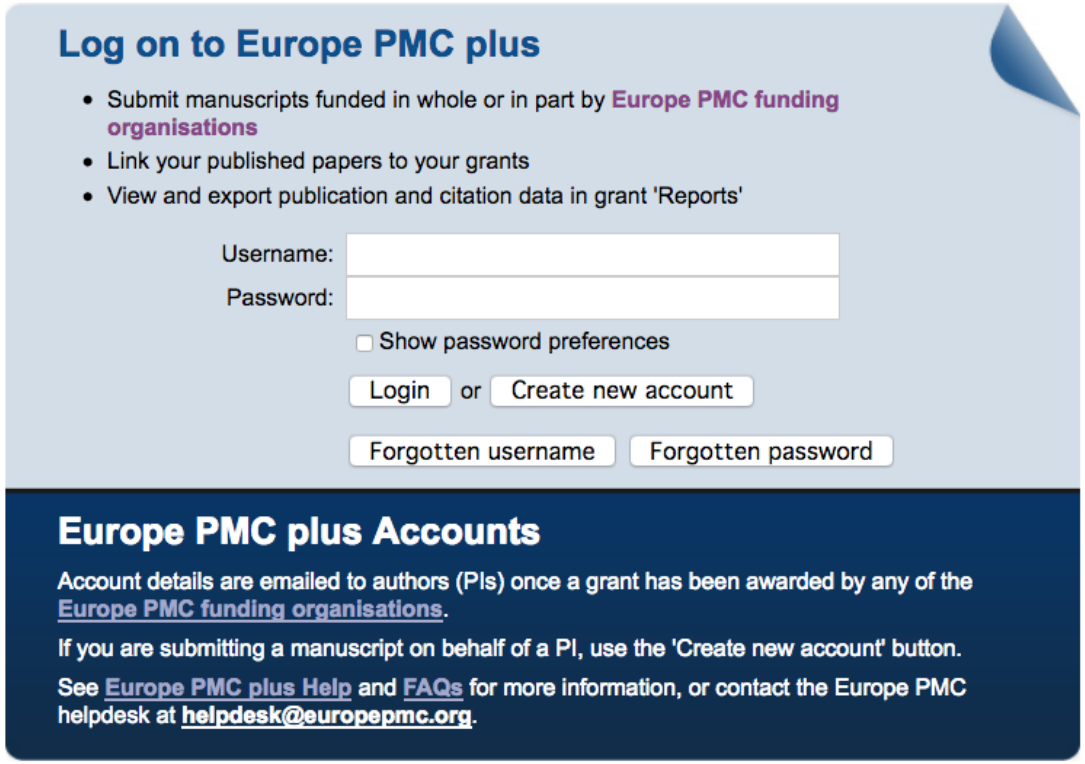

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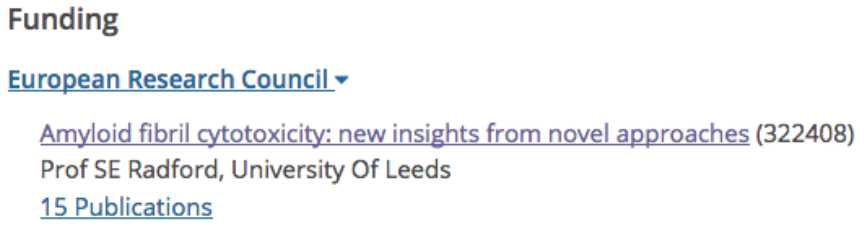

Funding

European Research Council

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15 Publications

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