HelmholtzZentrum münchen
German Research Center for Environmental Health

Scientific Highlight August 2010

Institute of Stem Cell Research

PSP-Element:
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Title of the Highlight:
New Method for Identifying the Cause of X-Linked Genetic Disorders

Keywords:
X-linked disease, phenotypic screen, completely ES cell-derived mouse embryos, functional genomics.

Central statement of the Highlight in one sentence:
We have added embryonic phenotypic and functional data to almost 10% of syntenic genes on the mouse X chromosome without generating individual mouse model, thus our method brings us much closer to understand the genetic cause of all X-linked disease.

Text of the Highlight:
Men have only one X chromosome, and therefore mutations on this chromosome disproportionately affect males, frequently leading to serious diseases such as hemophilia, muscular dystrophy, and mental retardation. The human X chromosome contains only 4% of all annotated genes (1098), but nearly 10% of all known Mendelian diseases are linked to the X chromosome (387/3983). Clearly, there is a need to better understand the function of genes on the X chromosome in order to link them to the causes of human X-linked disorders.

Using a straightforward approach of generating and directly analyzing mouse ES cell-derived embryos, without the need of generating chimeras and mouse lines using germ-line transmission, we have added embryonic phenotypic and functional data to almost 10% of syntenic genes on the mouse X chromosome.

To facilitate disease candidate data mining between human and mouse phenotypes, expression patterns, and genetic loci, we have compiled our data set into an online relational database (http://xlinkedgenes.ibme.utoronto.ca) along with human data from OMIM. This rapid and cost-effective screening method has identified 19 (13 novel to mouse and human) X-linked mutations

that cause developmental defects in the mouse and are therefore likely to cause human congenital disease.

Publication:
Cox, B., Vollmer, M., Tamplin, Lu, M., O., Biechele, S., Gertsenstein, M., Floss, T., Kuehn, R., Wurst, W., **Lickert, H.*** and Rossant, J.*(2010). Phenotypic annotation of the mouse X chromosome. Genome Research 20(8):1154-64.
(IF: 11.224)

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Taking account of the HMGU mission:
We aim to understand regeneration processes in the adult brain with the final goal to use them for repair. This is part of the HMGU mission to cure multifactorial disease as most neurological diseases are and the astrategic area of regenerative medicine.

The internal HMGU co-operation partners with whom the Highlight was compiled, if appropriate:
We closely collaborate with the IDG on the generation and use of mouse lines to examine adult neurogenesis and the mouse clinic (Dr. Hölter-Koch) to determine the behavioural consequences of adult neurogenesis for sensory discrimination. This is an important area of research as early olfactory discrimination deficits may be one of the earliest biomarkers for neurodegenerative disorders. Thus, this collaboration is essential for follow-up studies from this initial discovery. Moreover, mouse lines essential for this publication were generated together with the IDG.

New Method for Identifying the Causes of X-Linked Genetic Disorders

Institute for Stem Cell Research, Lickert

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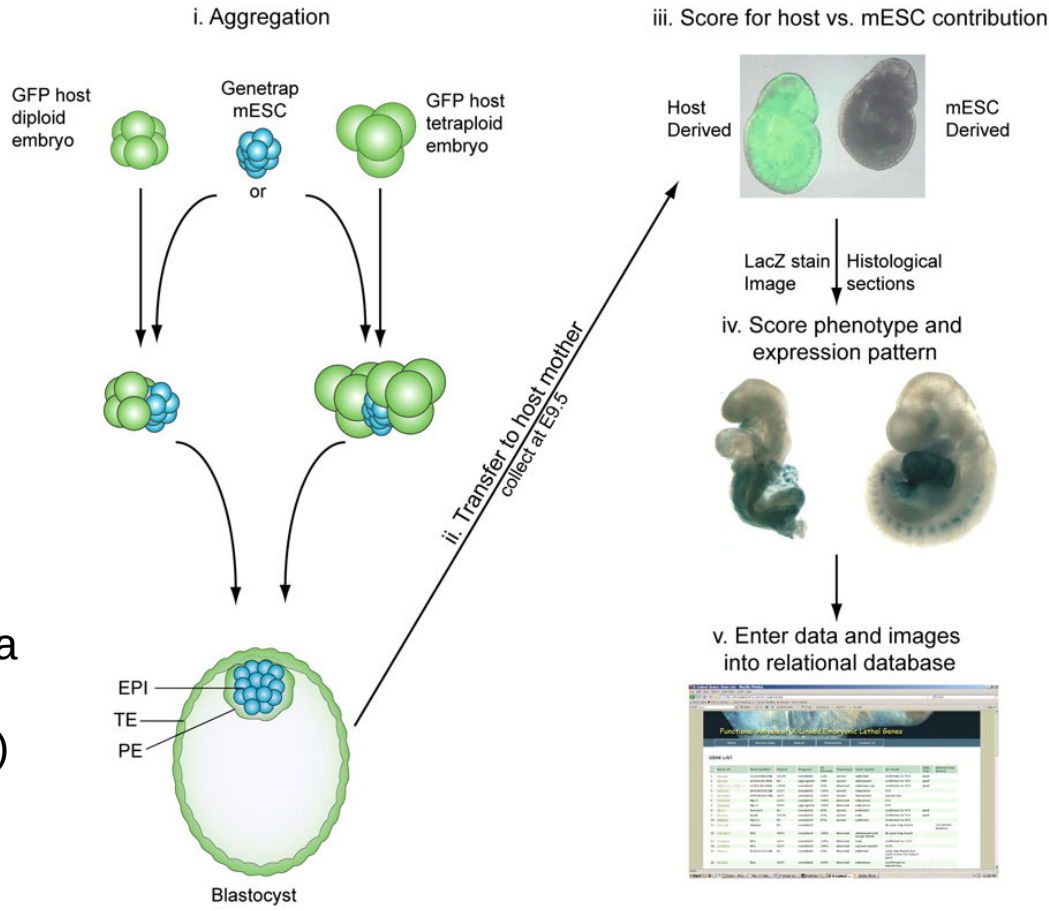
An overview of the screening method



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Cox B J et al. Genome Res. 2010;20:1154-1164

HELMHOLTZ ASSOCIATION

New Method for Identifying the Causes of X-Linked Genetic Disorders

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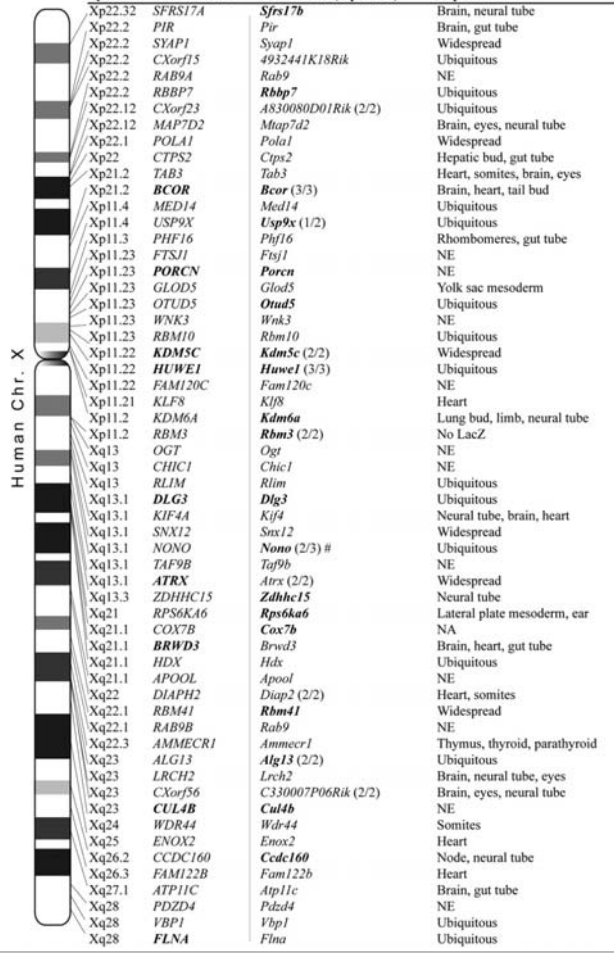
This rapid and cost-effective screening method has identified 19 (13 novel to mouse and human) X-linked mutations that cause developmental defects in the mouse and are therefore likely to cause human congenital disease.

For the first time, the effect of the respective mutation on embryonic development could be shown without generating individual mouse models. This brings us much closer to the understanding of the genetic causes of all X-linked disease.

Linkage to human homologs and summary of expression and phenotype



Cytoband	Human Gene	Mouse Gene (replicates)	Expression
Xp22.32	*SFRS17A*	***Sfrs17b***	Brain, neural tube
Xp22.2	*PIR*	*Pir*	Brain, gut tube
Xp22.2	*SYAP1*	*Syap1*	Widespread
Xp22.2	*CXorf15*	*4932441K18Rik*	Ubiquitous
Xp22.2	*RAB9A*	*Rab9*	NE
Xp22.2	*RBBP7*	***Rbbp7***	Ubiquitous
Xp22.12	*CXorf23*	*A830080D01Rik* (2/2)	Ubiquitous
Xp22.12	*MAP7D2*	*Mtap7d2*	Brain, eyes, neural tube
Xp22.1	*POLA1*	*Pola1*	Widespread
Xp22	*CTPS2*	*Ctps2*	Hepatic bud, gut tube
Xp21.2	*TAB3*	*Tab3*	Heart, somites, brain, eyes
Xp21.2	***BCOR***	***Bcor*** (3/3)	Brain, heart, tail bud
Xp11.4	*MED14*	*Med14*	Ubiquitous
Xp11.4	*USP9X*	***Usp9x*** (1/2)	Ubiquitous
Xp11.3	*PHF16*	*Phf16*	Rhombomeres, gut tube
Xp11.23	*FTSJ1*	*Ftsj1*	NE
Xp11.23	***PORCN***	***Porcn***	NE
Xp11.23	*GLOD5*	*Glod5*	Yolk sac mesoderm
Xp11.23	*OTUD5*	***Otud5***	Ubiquitous
Xp11.23	*WNK3*	*Wnk3*	NE
Xp11.23	*RBM10*	*Rbm10*	Ubiquitous
Xp11.22	***KDM5C***	***Kdm5c*** (2/2)	Widespread
Xp11.22	***HUWE1***	***Huwe1*** (3/3)	Ubiquitous
Xp11.22	*FAM120C*	*Fam120c*	NE
Xp11.21	*KLF8*	*Klf8*	Heart
Xp11.2	*KDM6A*	***Kdm6a***	Lung bud, limb, neural tube
Xp11.2	*RBM3*	***Rbm3*** (2/2)	No LacZ
Xq13	*OGT*	*Ogt*	NE
Xq13	*CHIC1*	*Chic1*	NE
Xq13	*RLIM*	*Rlim*	Ubiquitous
Xq13.1	***DLG3***	***Dlg3***	Ubiquitous
Xq13.1	*KIF4A*	*Kif4*	Neural tube, brain, heart
Xq13.1	*SNX12*	*Snx12*	Widespread
Xq13.1	*NONO*	***Nono*** (2/3) #	Ubiquitous
Xq13.1	*TAF9B*	*Taf9b*	NE
Xq13.1	***ATRX***	*Atrx* (2/2)	Widespread
Xq13.3	*ZDHHC15*	***Zdhhc15***	Neural tube
Xq21	*RPS6KA6*	***Rps6ka6***	Lateral plate mesoderm, ear
Xq21.1	*COX7B*	***Cox7b***	NA
Xq21.1	***BRWD3***	*Brwd3*	Brain, heart, gut tube
Xq21.1	*HDX*	*Hdx*	Ubiquitous
Xq21.1	*APOOL*	*Apool*	NE
Xq22	*DIAPH2*	*Diap2* (2/2)	Heart, somites
Xq22.1	*RBM41*	***Rbm41***	Widespread
Xq22.1	*RAB9B*	*Rab9*	NE
Xq22.3	*AMMECR1*	*Ammecr1*	Thymus, thyroid, parathyroid
Xq23	*ALG13*	***Alg13*** (2/2)	Ubiquitous
Xq23	*LRCH2*	*Lrch2*	Brain, neural tube, eyes
Xq23	*CXorf56*	*C330007P06Rik* (2/2)	Brain, eyes, neural tube
Xq23	***CUL4B***	***Cul4b***	NE
Xq24	*WDR44*	*Wdr44*	Somites
Xq25	*ENOX2*	*Enox2*	Heart
Xq26.2	*CCDC160*	***Ccdc160***	Node, neural tube
Xq26.3	*FAM122B*	*Fam122b*	Heart
Xq27.1	*ATP11C*	*Atp11c*	Brain, gut tube
Xq28	*PDZD4*	*Pdzd4*	NE
Xq28	*VBP1*	*Vbp1*	Ubiquitous
Xq28	***FLNA***	*Flna*	Ubiquitous

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