Revista de Psiquiatría
y Salud Mental

www.elsevier.es/saludmental

ORIGINAL ARTICLE

The Andalusian Bipolar Family (ABiF) Study: Protocol and sample description[☆]

Jose Guzman-Parra[a,*,◇], Fabio Rivas[a,◇], Jana Strohmaier[b,◇], Andreas Forstner[c,d],
Fabian Streit[b], Georg Auburger[e], Peter Propping[c,d], Guillermo Orozco-Diaz[f],
Maria José González[a], Susana Gil-Flores[g], Francisco Javier Cabaleiro-Fabeiro[h],
Francisco del Río-Noriega[i], Fermin Perez-Perez[j], Jesus Haro-González[k],
Yolanda de Diego-Otero[a], Pablo Romero-Sanchiz[a], Berta Moreno-Küstner[l],
Sven Cichon[m], Markus M. Nöthen[a,d,◇], Marcella Rietschel[b,◇], Fermin Mayoral[a,◇]

[a] Unidad de Salud Mental, Hospital Regional Universitario de Málaga, Instituto de Biomedicina de Málaga (IBIMA), Málaga, Spain
[b] Departamento de Epidemiología Genética en Psiquiatría, Instituto Central de Salud Mental, Facultad de Medicina de Mannheim, Universidad de Heidelberg, Mannheim, Germany
[c] Instituto de Genética Humana, Universidad de Bonn, Bonn, Germany
[d] Departamento de Genómica, Life & Brain Center, Universidad de Bonn, Bonn, Germany
[e] Clínica de Neurología, Universidad de Frankfurt, Frankfurt, Germany
[f] Unidad de Gestión Clínica del Dispositivo de Cuidados Críticos y Urgencias Coin-Gudalhorce, Málaga, Spain
[g] Departamento de Salud Mental, Universidad Hospital Reina Sofía, Córdoba, Spain
[h] Departamento de Salud Mental, Hospital de Jaén, Jaén, Spain
[i] Departamento de Salud Mental, Hospital de Jerez de la Frontera, Jerez de la Frontera, Cádiz, Spain
[j] Departamento de Salud Mental, Hospital de Puerto Real, Puerto Real, Cádiz, Spain
[k] Departamento de Salud Mental, Hospital Punta de Europa, Algeciras, Cádiz, Spain
[l] Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Universidad de Málaga, Málaga, Spain
[m] Departamento de Biomedicina, Universidad de Basel, Basel, Switzerland

Abstract
Introduction: Here, we present the first description of the Andalusian Bipolar Family (ABiF) Study. This longitudinal investigation of families from Andalusia, Spain commenced in 1997 with the aim of elucidating the molecular genetic causes of bipolar affective disorder. The cohort has since contributed to a number of key genetic findings, as reported in international journals.

However, insight into the genetic underpinnings of the disorder in these families remains limited.

Method: In the initial 1997–2003 study phase, 100 multiplex bipolar disorder and other mood disorder families were recruited. The ongoing second phase of the project commenced in 2013, and involves follow-up of a subgroup of the originally recruited families. The aim of the follow-up investigation is to generate: (i) longitudinal clinical data; (ii) results from detailed neuropsychological assessments; and (iii) a more extensive collection of biomaterials for future molecular biological studies.

Results: The ABiF Study will thus generate a valuable resource for future investigations into the etiology of bipolar affective disorder; in particular the causes of high disease loading within multiply affected families.

Discussion: We discuss the value of this approach in terms of new technologies for the identification of high-penetrance genetic factors. These new technologies include exome and whole genome sequencing, and the use of induced pluripotent stem cells or model organisms to determine functional consequences.

El estudio *Andalusian Bipolar Family* (ABiF): protocolo y descripción de la muestra

Resumen

Introducción: Se presenta la primera descripción del estudio denominado *Andalusian Bipolar Family* (ABiF). Se trata de una investigación longitudinal con familias procedentes de Andalucía (España), que comenzó en 1997, con el objetivo de dilucidar las causas geneticomoleculares del trastorno afectivo bipolar. Desde entonces, esta cohorte ha contribuido a una serie de hallazgos clave, que han sido publicados en revistas internacionales. Sin embargo, el conocimiento sobre las bases genéticas del trastorno en estas familias sigue siendo limitado.

Método: El estudio consta de dos fases: en la fase inicial se reclutaron 100 familias con múltiples afectados de trastorno bipolar y otros trastornos del ánimo. La segunda fase del proyecto, actualmente en curso, comenzó en 2013 con el objetivo de realizar un seguimiento de la cohorte de familias reclutadas originalmente. Los objetivos del estudio de seguimiento son: i) recoger nuevos datos clínicos longitudinales; ii) realizar una evaluación neuropsicológica detallada, y iii) obtener una extensa colección de biomateriales para futuros estudios moleculares.

Resultados: El estudio ABiF, por tanto, generará unos recursos valiosos para futuras investigaciones sobre la etiología del trastorno afectivo bipolar; particularmente con respecto a las causas de la alta carga genética del trastorno en las familias con múltiples afectados.

Discusión: Se discute el valor de este enfoque en relación con las nuevas tecnologías para la identificación de factores genéticos de alta penetrancia. Estas nuevas tecnologías incluyen la secuenciación del exoma y del genoma completo, y el uso de células madre pluripotentes inducidas u organismos modelo para la determinación de consecuencias funcionales.

Introduction

Bipolar disorder (BD) is characterized by recurrent episodes of mania and depression,[1] and ranks among the major contributors to the global burden of disease.[2,3] BD has a lifetime prevalence of 0.5–1%,[4] and an estimated heritability of around 70%.[5–7] Molecular genetic candidate studies and recent genome wide association studies (GWAS), have identified the first BD susceptibility genes.[6,8–13] All genetic risk variants identified to date are common in the general population, and confer only a small individual risk. Although the identification of the first susceptibility genes is a major achievement, researchers assume that a larger disease risk

is conferred by, as yet unidentified rare variants.[6,14] Such variants may explain, at least in part, the high familial loading observed in some families. Detection of these variants may be of particular importance for investigations of the functional consequences of genetic variants. Such studies will in turn elucidate the biological pathways that are perturbed in BD. On the clinical level, families segregating high-risk variants are particularly suited for the study of pleiotropic effects, i.e., examination of the diversity of clinical symptoms and endophenotypes that are associated with a given variant, and analyses of gene–environment interactions. However, due to ever decreasing family sizes and the increasing mobility of family members, the recruitment of

multiplex families is problematic, particularly in Europe and North America.

In 1997, our group initiated a study of BD multiplex families from Andalusia, Spain, involving the collection of detailed phenotypic data and biomaterials. The present report describes the study, and how it has already contributed to key molecular genetic findings in the field. We discuss the potential value of this family cohort for future new technology studies of BD etiology.

Methods

Initiation of the study

The project was initiated by the identification of a BD inpatient of Andalusian origin at the Department of Psychiatry, University of Düsseldorf, Germany, who reported multiple affected family members. In view of the potential value of this pedigree to BD research, the responsible Spanish speaking neurologist (GA) confirmed the family history, and contacted psychiatric geneticists PP and MMN at the Institute of Human Genetics in Bonn, Germany. Together with Spanish speaking German psychiatrist MR from the Department of Psychiatry, University of Bonn (now at the Central Institute of Mental Health, University of Heidelberg, Germany), a collaboration was initiated with psychiatrists FR and FM from the Regional University Hospital of Malaga, Spain. To identify further multiplex BD families, this collaboration was subsequently extended to include the mental health departments of the following six centers in Andalusia: University Hospital Reina Sofia of Córdoba, Provincial Hospital of Jaen; Hospital of Jerez de la Frontera (Cádiz); Hospital of Puerto Real (Cádiz); Hospital Punta Europa of Algeciras (Cádiz); and Hospital Universitario San Cecilio (Granada).

Original cohort (initial study phase, 1997–2003)

Assessment
Recruitment commenced with in- and outpatient index cases, and was then extended to family members. Diagnostic assessment was performed using the Schedule for Affective Disorders and Schizophrenia (SADS)[15]; the Operational Criteria Checklist for Psychotic Illness (OPCRIT)[16]; a review of medical records; and interviews with first and/or second degree family members using the Family Informant Schedule and Criteria (FISC).[17] Consensus best estimate diagnoses were assigned by two or more independent senior psychiatrists and/or psychologists, and according to the Research Diagnostic Criteria,[18] and the Diagnostic and Statistical Manual of Mental Disorders IV.[19] Both affected individuals and healthy relatives were evaluated. Over the initial six year study period, recruitment was carried out by the same neurologist (GOD) from the Regional University Hospital of Malaga. GOD was trained and supervised by three senior psychiatrists (MR, FR, and FM), and a human geneticist (MMN). Blood samples were collected from all participants and sent to the Institute of Human Genetics in Bonn for whole blood DNA extraction.

The study protocols for clinical assessment and genetic investigation were approved by the local ethics committees of all participating centers.

Between 1997 and 2003, a total of 1174 individuals from 100 multiplex families were recruited. Face-to-face SADS interviews were conducted with 758 individuals. For 655 of these 758 individuals, information was also obtained from up to seven best informants using the FISC. For 14 individuals only OPCRIT data were available based on different sources of information. For 402 additional individuals, information was obtained from best informants only: from 320 individuals with the FISC and from 76 individuals the obtained information was so sparse that no valid FISC could be completed. From six further family members, no information could be obtained except for sex, relationship to the family, and disease status. Thus valid FISC information was available for 975 individuals. Blood samples were collected from a total of 732 individuals. Supplementary Figure 1 displays the multiplex family recruitment procedure in flow-chart form.

Follow-up study (2013–ongoing)

For the follow-up investigations, the study protocol has been extended to include neuropsychological phenotypes and the collection of additional biomaterials.

Sample re-assessment
Families who had previously given their written informed consent to being re-contacted are now being asked whether they are willing to participate in a follow-up assessment. Written informed consent to the extended study protocol is then obtained. At the time of writing, four families (4–28 family members) have already been re-contacted, and are now undergoing assessment.

Clinical re-assessment
Detailed phenotype characterization is performed for each family member. This involves: (i) the Interview for Psychiatric Genetic Studies (IPGS; Fangerau et al., 2004); (ii) a comprehensive inventory for phenotype characterization, including the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I),[20] and the OPCRIT; (iii) a review of all medical records; and (iv) interviews with family members. Clinical diagnoses are assigned by two trained clinicians using a best estimate approach. The IPGS enables a highly structured and reproducible assessment of the DSM-IV diagnoses; sociodemographic characteristics; life-time psychopathological symptoms; current depressivity; level of functioning prior to disease onset, in the life-time worst disease episode, and after remission from the last disease episode; alcohol and nicotine abuse and dependence; premorbid adjustment; history of medical and obstetric complications; medical treatment and side effects; personality; and environmental factors, such as parental bonding, trauma and stressful life-events. The phenotypes of interest and the clinical assessment instruments are shown in Table 1.

Neuropsychological assessment
The neuropsychological assessment comprises tests selected from the Cambridge Neuropsychological Test Automated Battery (CANTAB),[21] as well as paper and pencil tests. The neuropsychological tests are listed in Table 2.

Table 1 Phenotypes and clinical assessment instruments used in the follow-up study.

Phenotype	Clinical assessment instrument	Details of assessment instruments
Interview		
Clinical DSM-IV diagnosis	Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[20]	Research version 2.0
Family interview	Family Informant Schedule and Criteria (FISC)[17]	Interview with best informants from the family
Impairment in social, occupational, or other important areas of functioning	Global Assessment of Functioning Scale (GAF)[45]	Overall rating of functioning between 0 and 100%
	Functioning Assessment Short Test (FAST)[46]	24 items (3-point rating scale) to assess functioning in the worst, best, and current period
Affective and/or psychotic symptoms	Operational Criteria in Psychotic Illness OPCRIT[16]	90-Item scale assessing affective and psychotic core psychopathology
Circadian rhythms	Reduced Horne and Ostberg Questionnaire[47]	5-Item scale to assess morningness and eveningness
History of somatic illnesses and obstetric complications	Interview for Psychiatric Genetic Studies (IPGS)[48]	
Past/current treatment with psychotropic medication	Interview for Psychiatric Genetic Studies (IPGS)[48]	Assessment of dosage, treatment response, and side effects
Lithium response	Alda lithium response scale[49]	Brief 11-item scale
Aggressiveness	Life history of aggression[50]	11 items with a 6-point scale assessing aggression during, and independently of, disease episodes
Parental bonding	Parental bonding instrument[51]	Fundamental parental dimensions of care and protection
Premorbid adjustment	Premorbid Adjustment Scale (PAS)[52]	Degree of achievement of developmental goals at several periods of life before the onset of schizophrenia
Life-events	List of life-events based on various life-event scales[53–56]	79 life-events (LE) to assess if LE occurred 6 months prior to onset of illness, and is perceived as having caused the disorder and as pleasant, neutral or unpleasant
Self-rating		
Psychological symptoms	Brief Symptom Inventory (BSI)[57]	53 items (5-point rating scale) to assess the burden of mental symptoms
Depressivity within previous week	The Center for Epidemiologic Studies Depression Scale (CES-D)[58]	20 items (4-point rating scale)
Childhood trauma	Childhood Trauma Screener (CTS)[59]	5-Item brief screening version of the Childhood Trauma Questionnaire (CTQ)
Personality	Short version of the Big Five Inventory (BFI-10)[60];	10 items (5-point rating scale) to assess the Big Five personality dimensions;
	Neuroticism scale of the NEO Five-Factor Inventory (NEO-FFI)[61]	12 items (5-point rating scale)
Impulsiveness	Barratt Impulsiveness Scale (BIS)[62]	34 items (4-point rating scale)
Alcohol consumption and dependence	Alcohol Use Disorders Identification Test (AUDIT)[63]	10-Item questionnaire developed by the WHO
Nicotine consumption and dependence	Fagerström Test of Nicotine Dependence (FTND)[64]	10-Item questionnaire to assess the intensity of physical addiction to nicotine
Self-efficacy	General Self-Efficacy Scale (GSE)[65]	10 items (4-point rating scale) to assess perceived self-efficacy

Collection and storage of biomaterial

A 32.5 ml blood sample is collected for DNA extraction (20 ml); permanent cell lines as a basis for induced Pluripotent Stem Cells (iPSCs; 8 ml); mRNA (2.5 ml); and protein expression and metabolomics (2 ml). Hair samples are collected for measurement of hair cortisol and the hormones testosterone, progesterone, and dehydroepiandrosteron. The blood and hair samples are sent to the laboratory of the

Table 2 Neuropsychological assessment at follow-up.

Test	Neuropsychological domain	Behavioral measure
CANTAB		
Simple reaction time	Reaction time	Reaction time to a stimulus
Choice reaction time		Reaction time to two possible stimuli
Stop signal task	Response inhibition	Response inhibition in a reaction time test with answer choice
Cambridge gambling task	Impulsivity, decision, and risk behavior	Impulsivity control and risk behavior in situations of choice
Information sampling task		Impulsivity and decision making behavior
Stockings of Cambridge	Executive and planning functions	Spatial planning skills and motor skills
Intra/Extradimensional shift	Cognitive flexibility	Identification of patterns and cognitive and attentional flexibility
Paper and pencil tests		
Trail making test[66,67]	Cognitive processing speed and cognitive flexibility	Visual attention and task switching
Digit Span Forwards and Backwards of the (HAWIE-R)[68]	Working memory	Numeric learning
Hopkins Verbal Learning Test-Revised[69]	Declarative memory	Verbal learning
Word Accentuation Test of the TAP[70]	Premorbid intelligence	Read infrequent, irregularly stressed Spanish words

Regional University Hospital of Málaga where the samples are processed and stored according to biobank guidelines. Depending on the planned experiments, samples are sent to collaborating laboratories such as the laboratories of the Central Institute of Mental Health in Mannheim, and the Institute of Human Genetics in Bonn.

Informed consent and ethical approval

The follow-up study protocol was approved by the ethics committee of the University Regional Hospital of Malaga (*Málaga Nordeste*) as re-assessment commenced at this institution. When ready to commence re-assessment, the other centers will obtain ethical approval from their local ethics committees. The updated informed consent addresses ethical issues that have arisen through new developments and advances in technology in more detail than was the case in the original informed consent procedure. Among others, these developments enable genome-wide sequencing to be performed in a research context. Important issues in terms of informed consent are data protection, the disclosure of incidental and secondary findings, and confidentiality. Confidentiality and the sharing of genetic information with relatives can become particularly problematic in cases where large-scale sequencing generates secondary findings.[22] For example, if a dominantly inherited cancer-causing mutation is identified as a secondary finding in one family member, the mutation carrier may not wish to share this information with his children, even though the cancer is preventable. We therefore follow up-to-date guidelines and recommendations for informed consent, such as those from EURAT (Ethical and Legal Aspects of Whole Genome Sequencing), and engage in regular discussions of ethical issues with representatives from European ethics commissions, as well as international philosophers and legal experts. During the informed consent procedure and thus prior to inclusion, ABiF participants must indicate whether or not they wish to be informed of potential incidental and secondary findings. Participants must also indicate whether they are willing to be re-contacted for further research investigations, e.g., neuro-imaging or more extensive neuropsychological assessment.

Results

Sociodemographic and clinical characteristics

Analysis of sociodemographic and clinical characteristics was performed for all multiplex family members using: (i) both SADS and OPCRIT data, $n = 426$; (ii) SADS data only, $n = 332$; (iii) OPCRIT data only, $n = 14$; (iv) or best informant information only, $n = 402$. Supplementary Table 1 provides an overview of the total number of family members and affected family members per multiplex family and per assessment center. Table 3 shows the sociodemographic and clinical characteristics of the family members, as well as for the diagnostic groups MDD rec (Major Depressive Disorder recurrent, $n = 169$); and BD (Bipolar Disorder I, $n = 258$; Bipolar Disorder II, $n = 78$; Bipolar Disorder not otherwise specified, $n = 18$; Schizoaffective Disorder Bipolar Type; $n = 1$).

The multiplex family cohort collected between 1997 and 2003 comprised 355 BD cases, 169 MDD rec cases, and 650 individuals in the category *others* (Major Depressive Disorder single episode, $n = 35$; Depressive Disorder not otherwise specified, $n = 12$; Drug or Alcohol Abuse or Dependence, $n = 31$; Schizophrenia, $n = 2$; Agoraphobia, $n = 1$; and Healthy, $n = 569$). Compared to MDD rec patients, BD patients showed: a significantly higher duration of continuous outpatient treatment; a lower age at onset of the psychiatric

Table 3 Sociodemographic characteristics of individuals from the 100 multiplex families of the original cohort (1997–2003) presenting with BD (BD-I, BD-II, BP-NOS, SCA-B) and MDD rec.

	BD (N_{total} = 355) M (SD)	MDD rec (N_{total} = 169) M (SD)
Age at interview	46.40 (16.3)	52.54 (17.5)[*]
	Bipolar N (%)	MDD N (%)
Gender (female)	205 (57.7)	127 (72.2)[*]
Marital status		
Married	242 (68.9)	121 (72.5)
Separated, divorced	8 (2.3)	0
Widowed	16 (4.6)	17 (10.2)[*]
Single	85 (24.2)	29 (17.4)
Educational level		
Primary school or less	252 (72.2)	127 (76.5)
Secondary school	73 (20.9)	28 (16.9)
University degree	24 (6.9)	11 (6.6)

Note. BD: bipolar disorder; MDD rec: Major Depressive Disorder recurrent; M: mean; SD: standard deviation.
Note. In *Marital status* the category of reference for comparisons is *Married* and in *Educational level* is *Primary School or Less*.
[*] Denotes significant difference of $p < 0.05$ (Mann Whitney test for continuous variables and Chi Square for categorical variables).

disorder, first treatment, and first depressive episode; more hospitalizations over their lifetime and during depressive episodes; more suicide attempts over their lifetime and during depressive episodes; and more delusions during depressive episodes (for details see Supplementary Table 2). BD patients were also more likely to have been unable to work within the preceding five years due to psychological problems as compared to MDD rec patients.

Analysis of the clinical symptom dimensions *Mania/Excitement*, *Depression*, *Disorganization*, *Positive Symptoms*, and *Negative Symptoms* showed that BD patients scored higher than MDD rec patients on the dimensions *Mania/Excitement*, *Depression*, and *Positive and Negative Symptoms* (for details see Supplementary Table 3). For the depression-dimensions *Suicidal Ideation*, and *Early Morning Wakening* were more frequent in BD than in MDD rec patients, while *Loss of Energy* and *Slowed Activity* were more frequent in MDD rec than in BD.

Molecular genetic findings

For the investigation of risk genes for BD, a plausible hypothesis is that multiplex families carry high penetrance genetic variants, and that these are shared across affected family members. To investigate this, we initially performed linkage analyses of the most promising Andalusian families. These linkage data were then analyzed in combination with data collected from non-Andalusian multiplex families.

For the Andalusian families, linkage analysis generated evidence for a new susceptibility locus on chromosome 1p35–p36, and provided support for an established locus on chromosome 6q21–q24.[23] In pooled analyses with family samples from other countries, evidence for linkage was obtained for the pseudoautosomal region 1 Xp22.3/Yp11.3.[24] Using a covariate approach, suggestive evidence was generated for linkage of mood incongruent psychotic symptoms

in BD to 1q32.3, 7p13, and 20q13.31.[25] In the first genome-wide linkage study of BD, testing for interaction between genomic loci in families from different countries – including pedigrees from the Andalusian Bipolar Family Study – generated evidence of genetic epistasis between regions of chromosomes 6q and 2q.[26] Unfortunately, the linkage paradigm has not led to the unequivocal identification of chromosomal loci for BD. Even if a high penetrance gene effect does exist in individual families, the sharing of such loci across families is probably too low to allow consistent replication of linkage findings across samples.

The first consistent molecular genetic findings for BD were generated by GWAS. Index patients from the Andalusian families underwent genome-wide genotyping of single-nucleotide polymorphisms and these data were subsequently included in larger, international analyses. These GWAS generated evidence for the involvement of chromosomal regions harboring genes such as *NCAN*, *ANK3*, *ODZ4*, *TRANK1*, *ADCY2*, and a region between *MIR2113* and *POU3F2*.[9,11]

Discussion

In this work, we present the first description of the Andalusian Bipolar Family (ABiF) Study which provides a sociodemographic and clinical analysis of the original cohort of multiplex families, a summary of genetic studies and relevant findings to which the cohort has contributed, and a new extensive protocol for the re-assessment of the multiplex families.

Regarding sociodemographic and clinical differences between BD and MDD rec, previous authors have also reported similar results. The respective studies found that the following features were more frequent in BD compared to MDD: (i) lower age of onset[27–32]; (ii) suicidal behavior[31,33]; (iii) psychotic symptoms[30,32,34,35]; (iii)

hospitalization[27,28,30,35]; (iv) impaired social functioning[28]; (v) alcohol abuse[27,28,31]; and (vi) depressive symptoms.[28] The present findings are therefore in line with data reported from investigations of non-familial BD and MDD cases. However, the present analyses could not replicate the following differences observed in previous studies: (i) more depressive episodes in BD[27,30–32,34,36]; (ii) shorter depressive episodes in BD,[27,29,34] and (iii) more cyclothymia in BD.[31]

With respect of genetic findings, despite the success of GWAS, the majority of BD genetic variants still await identification, and the investigation of extended pedigrees with multiple affected family members is experiencing a true Renaissance in research into rare mutations.[37–40] Sequencing efforts are currently underway to identify such rare high penetrance variants, and these efforts are being facilitated by the use of new DNA sequencing technologies. Since the completion of the human genome project in 2003, extraordinary progress in developing new sequencing technologies has been made and the availability of so-called next generation sequencing (NGS) technologies render large-scale exome (containing all protein coding sequences) or genome-wide sequencing more efficient and affordable.[41] However, due to the rarity of individual mutations and the overall abundance of neutral rare variation in the genome,[42] confirming a definite association with the illness is a challenging task. Besides the identification of several mutations in the same gene, the investigation of familial segregation will be an important aspect of such research attempts, and the ABiF sample will provide a highly valuable resource for this. The observation of implicated mutations in a number of relatives also opens the possibility to explore the phenotypic spectrum associated with a particular mutation. The assessment of neuropsychological functions may allow insights into underlying functional processes, such as those conceptualized in the Research Domain Criteria (RDoC),[43] and may, therefore, generate hypotheses for future functional studies.

Once promising rare variants have been identified, their function can be tested in various ways, including bioinformatic analyses and the use of animal model systems such as the mouse. However, complete replication in the mouse of the complex genetic make-up of a particular patient is impossible. Here, iPSCs from these patients offer great potential.[44] In a recent study, iPSCs were generated from family members of an Old Order Amish pedigree with- and without BD, and functional effects and expression changes were demonstrated.[39] The acquisition of blood cells, which may later be transformed in iPSCs, is therefore an important aspect of the ABiF follow-up study. Moreover, the broad collection of biomaterials, including mRNA, proteins, and hairs will allow the investigation of functional changes at various biological levels in vivo and the exploration of such changes as potential biomarkers.

In summary, the phenotype data and the biomaterials obtained within the ABiF study represent a promising resource for future investigations into the etiology of BD.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Confidentiality of data. The authors declare that they have adhered to the protocols of their centre of work on patient data publication.

Right to privacy and informed consent. The authors must have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence must be in possession of this document.

Conflict of interests

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rpsmen.2017.03.003.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5(TM)). Arlington, VA: American Psychiatric Publishing; 2013.
2. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2197–223.
3. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet. 2013;382:1575–86.
4. Kessler RC, Berglund P, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of-onset distributions' of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry. 2005;62:593–602.
5. Craddock N, Sklar P. Genetics of bipolar disorder. Lancet. 2013;381:1654–62.
6. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. Nat Rev Genet. 2012;13:537–51.
7. Wray NR, Gottesman II. Using summary data from the Danish national registers to estimate heritabilities for schizophrenia, bipolar disorder, and major depressive disorder. Front Genet. 2012;3:118.
8. Baum AE, Akula N, Cabanero M, Cardona I, Corona W, Klemens B, et al. A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. Mol Psychiatry. 2008;13:197–207.
9. Cichon S, Mühleisen TW, Degenhardt FA, Mattheisen M, Miró X, Strohmaier J, et al. Genome-wide association study identifies genetic variation in neurocan as a susceptibility factor for bipolar disorder. Am J Hum Genet. 2011;88: 372–81.
10. Ferreira MAR, O'Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet. 2008;40:1056–8.

11. Mühleisen TW, Leber M, Schulze TG, Strohmaier J, Degenhardt F, Treutlein J, et al. Genome-wide association study reveals two new risk loci for bipolar disorder. Nat Commun. 2014;5:3339.

12. Sklar P, Smoller JW, Fan J, Ferreira MA, Perlis RH, Chambert K, et al. Whole-genome association study of bipolar disorder. Mol Psychiatry. 2008;13:558–69.

13. Sklar P, Ripke S, Scott L, Andreassen O, Group PGCBDW, Psychiatric GWAS Consortium Bipolar Disorder Working Group. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat Genet. 2011;43:977–83.

14. Gershon ES, Alliey-Rodriguez N, Liu C. After GWAS: searching for genetic risk for schizophrenia and bipolar disorder. Am J Psychiatry. 2011;168:253–6.

15. Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry. 1978;35:837–44.

16. McGuffin P, Farmer A, Harvey I. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. Arch Gen Psychiatry. 1991;48:764–70.

17. Mannuzza S, Fyer AJ, Endicott JKD. Family Informant Schedule and Criteria (FISC). New York: Anxiety Di; 1985.

18. Spitzer RL. Research diagnostic criteria. Arch Gen Psychiatry. 1978;35:773.

19. American Psychiatric Association. Diagnostic and statistical manual of mental disorders DSM-IV-TR (Text Revision) (Diagnostic & statistical manual of mental disorders (DSM Hardcover)). American Psychiatric Publishing, Inc.; 2000.

20. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for Axis I DSM-IV disorders. Patient Ed (SCID-I/P, vs 20); 1994.

21. Hall RC. Global assessment of functioning. A modified scale. Psychosomatics. 1995;36:267–75.

22. Rosa AR, Sánchez-Moreno J, Martínez-Aran A, Salamero M, Torrent C, Reinares M, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin Pract Epidemiol Ment Health. 2007;3:5.

23. Chelminski I, Petros TV, Plaud JJ, Ferraro FR. Psychometric properties of the reduced Horne and Ostberg questionnaire. Pers Individ Dif. 2000;29:469–78.

24. Fangerau H, Ohlraun S, Granath RO, Nöthen MM, Rietschel M, Schulze TG. Computer-assisted phenotype characterization for genetic research in psychiatry. Hum Hered. 2004;58:122–30.

25. Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M, et al. Is response to prophylactic lithium a familial trait? J Clin Psychiatry. 2002;63:942–7.

26. Coccaro EF, Berman ME, Kavoussi RJ. Assessment of life history of aggression: development and psychometric characteristics. Psychiatry Res. 1997;73:147–57.

27. Parker G. The parental bonding instrument. Soc Psychiatry Psychiatr Epidemiol. 1990;25:281–2.

28. Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull. 1982;8:470–84.

29. Brown GW, Harris T. Social origins of depression: a study of psychiatric disorder in women. Abingdon, Oxfordshire; New York, NY: Routledge; 2012.

30. Holmes TH, Rahe RH. The social readjustment rating scale. J Psychosom Res. 1967;11:213–8.

31. Paykel ES, Prusoff BA, Myers JK. Suicide attempts and recent life events. A controlled comparison. Arch Gen Psychiatry. 1975;32:327–33.

32. Yeaworth RC, McNamee MJ, Pozehl B. The Adolescent Life Change Event Scale: its development and use. Adolescence. 1992;27:783–802.

33. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. Psychol Med. 1983;13:595–605.

34. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1:385–401.

35. Grabe HJ, Schulz A, Schmidt CO, Appel K, Driessen M, Wingenfeld K, et al. A brief instrument for the assessment of childhood abuse and neglect: the childhood trauma screener (CTS). Psychiatr Prax. 2012;39:109–15.

36. Rammstedt B, John OP. Measuring personality in one minute or less: a 10-item short version of the Big Five Inventory in English and German. J Res Pers. 2007;41:203–12.

37. Scandell DJ. Development and initial validation of validity scales for the NEO-Five Factor Inventory. Pers Individ Dif. 2000;29:1153–62.

38. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol. 1995;51:768–74.

39. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. AUDIT: The Alcohol Use Disorders Identification Test: guidelines for use in Primary Care. 2nd ed. World Health Organization; 2006.

40. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom K. The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict. 1991;86:1119–27.

41. Schwarzer R, Jerusalem M. Generalized self-efficacy scale. In: Weinman J, Wright S, Johnston M, editors. Measures in health psychology. A user's portfolio. Causal and control beliefs. Windsor, UK: Nfer-Nelson; 1995. p. 35–7.

42. Sahakian BJ, Owen AM. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. J R Soc Med. 1992;85:399.

43. Bowie CR, Harvey PD. Administration and interpretation of the Trail Making Test. Nat Protoc. 2006;1:2277–81.

44. Battery AIT. Manual of directions and scoring. Washington, DC: War Department, Adjutant General's Office; 1944.

45. Tewes U, Wechsler D. Hamburg-Wechsler-Intelligenztest für Erwachsene: HAWIE-R. Huber; 1991.

46. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test-Revised: normative data and analysis of inter-form and test–retest reliability. Clin Neuropsychol. 1998;12:43–55.

47. Gomar JJ, Ortiz-Gil J, McKenna PJ, Salvador R, Sans-Sansa B, Sarró S, et al. Validation of the Word Accentuation Test (TAP) as a means of estimating premorbid IQ in Spanish speakers. Schizophr Res. 2011;128:175–6.

48. Lucassen A, Parker M. Confidentiality and sharing genetic information with relatives. Lancet. 2010;375:1507–9.

49. Schumacher J, Kaneva R, Jamra RA, Orozco Diaz G, Ohlraun S, Milanova V, et al. Genomewide scan and fine-mapping linkage studies in four European samples with bipolar affective disorder suggest a new susceptibility locus on chromosome 1p35–p36 and provides further evidence of loci on chromosome 4q31 and 6q24. Am J Hum Genet. 2005;77:1102–11.

50. Flaquer A, Jamra RA, Etterer K, Díaz GO, Rivas F, Rietschel M, et al. A new susceptibility locus for bipolar affective disorder in PAR1 on Xp22.3/Yp11.3. Am J Med Genet Part B Neuropsychiatr Genet. 2010;153:1110–4.

51. Hamshere ML, Schulze TG, Schumacher J, Corvin A, Owen MJ, Jamra RA, et al. Mood-incongruent psychosis in bipolar disorder: conditional linkage analysis shows genome-wide suggestive linkage at 1q32.3, 7p13 and 20q13.31. Bipolar Disord. 2009;11:610–20.

52. Abou Jamra R, Fuerst R, Kaneva R, Orozco Diaz G, Rivas F, Mayoral F, et al. The first genomewide interaction and locus-heterogeneity linkage scan in bipolar affective disorder: strong evidence of epistatic effects between loci on chromosomes 2q and 6q. Am J Hum Genet. 2007;81:974–86.

53. Angst J, Gamma A, Bowden CL, Azorin JM, Perugi G, Vieta E, et al. Evidence-based definitions of bipolar-I and bipolar-II disorders among 5635 patients with major depressive episodes in the Bridge Study: validity and comorbidity. Eur Arch Psychiatry Clin Neurosci. 2013;263:663–73.

54. Moreno C, Hasin DS, Arango C, Oquendo MA, Vieta E, Liu S, et al. Depression in bipolar disorder versus major depressive disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Bipolar Disord. 2012;14:271–82.

55. Parker G, Fletcher K, McCraw S, Futeran S, Hong M. Identifying antecedent and illness course variables differentiating bipolar I, bipolar II and unipolar disorders. J Affect Disord. 2013;148:202–9.

56. Serretti A, Mandelli L, Lattuada E, Cusin C, Smeraldi E. Clinical and demographic features of mood disorder subtypes. Psychiatry Res. 2002;112:195–210, http://dx.doi.org/10.1016/S0165-1781(02)00227-5.

57. Tondo L, Visioli C, Preti A, Baldessarini RJ. Bipolar disorders following initial depression: modeling predictive clinical factors. J Affect Disord. 2014;167:44–9.

58. Xiang YT, Zhang L, Wang G, Hu C, Ungvari GS, Dickerson FB, et al. Sociodemographic and clinical features of bipolar disorder patients misdiagnosed with major depressive disorder in China. Bipolar Disord. 2013;15:199–205.

59. Bottlender R, Jäger M, Strauß A, Möller HJ. Suicidality in bipolar compared to unipolar depressed inpatients. Eur Arch Psychiatry Clin Neurosci. 2000;250:257–61.

60. Forty L, Smith D, Jones L, Jones I, Caesar S, Cooper C, et al. Clinical differences between bipolar and unipolar depression. Br J Psychiatry. 2008;192:388–9.

61. Mitchell PB, Wilhelm K, Parker G, Austin MP, Rutgers P, Malhi GS. The clinical features of bipolar depression: a comparison with matched major depressive disorder patients. J Clin Psychiatry. 2001;62:212–6.

62. Mitchell PB, Frankland A, Hadzi-Pavlovic D, Roberts G, Corry J, Wright A, et al. Comparison of depressive episodes in bipolar disorder and in major depressive disorder within bipolar disorder pedigrees. Br J Psychiatry. 2011;199:303–9.

63. Fears SC, Service SK, Kremeyer B, Araya C, Araya X, Bejarano J, et al. Multisystem component phenotypes of bipolar disorder for genetic investigations of extended pedigrees. JAMA Psychiatry. 2014;71:375–87.

64. Kember RL, Georgi B, Bailey-Wilson JE, Stambolian D, Paul SM, Bućan M. Copy number variants encompassing Mendelian disease genes in a large multigenerational family segregating bipolar disorder. BMC Genet. 2015;16:27.

65. Kim KH, Liu J, Galvin RJS, Dage JL, Egeland JA, Smith RC, et al. Transcriptomic analysis of induced pluripotent stem cells derived from patients with bipolar disorder from an old order Amish pedigree. PLoS One. 2015;10:e0142693.

66. Kremeyer B, García J, Muller H, Burley MW, Herzberg I, Parra MV, et al. Genome-wide linkage scan of bipolar disorder in a Colombian population isolate replicates loci on chromosomes 7p21–22, 1p31, 16p12 and 21q21–22 and identifies a novel locus on chromosome 12q. Hum Hered. 2011;70:255–68.

67. Goodwin S, McPherson JD, McCombie WR. Coming of age: ten years of next-generation sequencing technologies. Nat Rev Genet. 2016;17:333–51.

68. Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, et al., 1000 Genomes Project Consortium. An integrated map of genetic variation from 1,092 human genomes. Nature. 2013;491:56–65.

69. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010;167:748–51.

70. Falk A, Heine VM, Harwood AJ, Sullivan PF, Peitz M, Brüstle O, et al. Modeling psychiatric disorders: from genomic findings to cellular phenotypes. Mol Psychiatry. 2016;21:1167–79.